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 in Subjects with Chronic HCV Infection and Child-Pugh Class B Cirrhosis
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-342-1137 (ASTRAL-4)
Phase of Development:	Phase 3
IND No.:	118605
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02201901
Study Start Date:	31 July 2014 (First Subject Screened)
Study End Date:	25 November 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Michael Charlton, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Anu Osinusi, MD, MPH Telephone: PPD Fax: PPD
Report Date:	14 March 2016
Previous Report Date(s):	13 October 2015 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-342-1137
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 in Subjects with Chronic HCV Infection and Child-Pugh Class B Cirrhosis

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 47 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.

Charlton MR, O'Leary JG, Bzowej NH, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir/Velapatasvir Fixed Dose Combination for the Treatment of HCV in Patients with Decompensated Liver Disease: The Phase 3 ASTRAL-4 Study. Hepatology 2015; 62 (6): 1387A–1388A.

Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and Velapatasvir for HCV in Patients with Decompensated Cirrhosis. N Eng J Med 2015; 373 (27):2618-2628.

Study Period:

31 July 2014 (First Subject Screened)
25 November 2015 (Last Subject Observation)
25 August 2015 (Last Subject Observation for the Primary Endpoint)

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) fixed-dose combination (FDC) with and without ribavirin (RBV) for 12 weeks and SOF/VEL FDC for 24 weeks in subjects with chronic hepatitis C virus (HCV) infection and Child-Pugh-Turcotte (CPT) class B cirrhosis 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 attain 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 CPT score and Model for End-Stage Liver Disease (MELD) score
- To evaluate the kinetics of circulating 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
- To characterize steady-state pharmacokinetics (PK) of study drugs

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 SOF/VEL±RBV for 12 weeks and SOF/VEL for 24 weeks in subjects with chronic HCV infection and CPT class B cirrhosis.

Approximately 225 subjects were randomized (1:1:1) to 1 of the following 3 treatment groups:

- **SOF/VEL 12 Week group (Group 1):** SOF/VEL FDC (400/100 mg) tablet once daily for 12 weeks
- **SOF/VEL+RBV 12 Week group (Group 2):** SOF/VEL FDC tablet once daily + RBV (1000 or 1200 mg/day divided twice daily) tablets for 12 weeks
- **SOF/VEL 24 Week group (Group 3):** SOF/VEL FDC tablet once daily for 24 weeks

Randomization was stratified by HCV genotype (1, 2, 3, 4, 5, 6, and indeterminate).

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, all subjects could enroll into the Cirrhosis SVR Registry Study if SVR was achieved or into the Sequence Registry Study if SVR was not achieved.

All subjects, with a target of up to 15 participants per group, were eligible to participate in the PK substudy if written consent was obtained. An intensive 24-hour PK sample collection was performed at the on-treatment Week 2 or 4 visit to determine the steady-state PK of SOF, SOF metabolites GS-566500 and GS-331007, VEL, and RBV (if appropriate).

This final synoptic clinical study report (CSR) summarizes the results of the final analysis of the 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 (13 October 2015).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 225 subjects

Analyzed:

- Full Analysis Set (FAS): 267 subjects
- Safety Analysis Set: 267 subjects
- PK Analysis Set: 267 subjects
- PK Substudy Analysis Set: 37 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females of ≥ 18 years of age with chronic HCV infection and CPT class B cirrhosis who had not undergone liver transplantation.

Duration of Treatment: Treatment duration was 12 weeks (SOF/VEL 12 Week and SOF/VEL+RBV 12 Week groups) or 24 weeks (SOF/VEL 24 Week group), with up to 24 weeks of posttreatment follow-up.

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

- **SOF/VEL** FDC tablets were administered orally to all subjects at a dose of 400/100 mg (1 FDC tablet once daily)
- **RBV** was administered orally to subjects in the SOF/VEL+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 lot numbers of study drugs administered in this study were as follows:

- **SOF/VEL**: DU1403B1 and DU1402B1
- **RBV:** AA6551Z and AA2773Z

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

Criteria for Evaluation:

Efficacy: This final synoptic CSR provides analyses of HCV RNA levels at posttreatment Week 24. Efficacy analyses at all other scheduled assessment time points were described in the interim CSR (13 October 2015). The COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study, with an LLOQ of 15 IU/mL. Assessments to determine MELD and CPT scores were performed at screening and all study visits.

Pharmacokinetics: The interim CSR describes details on the collection of blood samples for PK analyses of SOF, its metabolites GS-566500 and GS-331007, VEL, and RBV (if appropriate).

Safety: The interim CSR (13 October 2015) provides analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital sign measurements, electrocardiogram (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 provides 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 Week 24 and any changes to data that were previously reported in the interim between the data cutoffs 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 (13 October 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 FAS. The SVR12 rate of each treatment group was compared to the assumed spontaneous rate of 1% by using the 2-sided exact 1-sample binomial test at the 0.0167 significance level. The null (H0) and alternative (H1) hypotheses used to assess the superiority of SOF/VEL relative to the spontaneous rate of 1% were as follows:

H0: SVR12 rate = 1%

H1: SVR12 rate ≠ 1%

A 2-sided 1-sample binomial test was used to test the statistical hypothesis. The 2-sided 95% exact confidence intervals (CIs) based on the Clopper-Pearson method were provided for the SVR12 rate for all treatment groups.

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), change in CPT and MELD scores in subjects who did and did not achieve SVR12, and proportion of subjects with virologic failure.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, standard deviation [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 visit windows.

Pharmacokinetics: Steady-state PK over a 24-hour dosing interval was determined in subjects who participated in the PK substudy at the on-treatment Week 2 or 4 visit. Concentrations of SOF, GS-566500, GS-331007, VEL, and RBV (if appropriate) in plasma were determined using validated bioanalytical assays. The PK parameters for these analytes were computed for all subjects with evaluable PK profiles. Descriptive statistics (sample size, mean, SD, coefficient of variation [%CV], median, Q1, Q3, minimum, maximum, and geometric mean and its 95% CI) were presented for PK concentration data and PK parameter data.

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: Hep C) were completed at baseline/Day 1, Weeks 4, 8, and 12 (all treatment groups) and Weeks 16, 20, and 24 (SOF/VEL 24 Week group only) during treatment (or upon early termination), 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:

Of the 268 randomized subjects, 267 received at least 1 dose of study drug and were included in the Safety Analysis Set and FAS (Table 15.8.1.3.1). Full details on subject disposition, demographics, and baseline disease characteristics are reported in Section 8 of the interim CSR (13 October 2015), and subject disposition at posttreatment Week 24 is summarized in Table 15.8.1.3.1.

No notable differences in demographic or baseline disease 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). There were a small number of additions and changes to concomitant medications that did not change the interpretation of the study results (Table 15.11.8.1 and Listing 16.2.4.4.1). Analyses related to disposition, demographics, and exposure are presented in Tables 15.8.1.1 to 15.8.4, 15.11.1.1, and 15.11.1.2, 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 SVR12 rates were as follows (Table 15.9.1):

- SOF/VEL 12 Week group: 83.3% (95% CI: 74.0% to 90.4%) of subjects (75 of 90) achieved SVR12
- SOF/VEL+RBV 12 Week group: 94.3% (95% CI: 87.1% to 98.1%) of subjects (82 of 87) achieved SVR12
- SOF/VEL 24 Week group: 87.8% (95% CI: 79.2% to 93.7%) of subjects (79 of 90) achieved SVR12

The SVR12 rate for the SOF/VEL 24 Week group was updated in the final analysis from that reported in the interim analysis due to achievement of SVR12 by 2 subjects (1 subject with genotype 1a and 1 subject with genotype 1b HCV infection) who had missed the posttreatment Week 12 visit and were listed as "visit pending" at the time of the interim data cut. These subjects (Subjects PPD and PPD returned for the posttreatment Week 24 visit and had HCV RNA < LLOQ (Listing 16.2.6.1). These subjects therefore achieved SVR24 and were imputed as successes for SVR12.

The final SVR12 and virologic outcome by HCV genotype are shown in the table below.

	Genotype							
	Total (All Genotypes)	**GT-1a**	**GT-1b**	**GT-1 Total**	**GT-2**	**GT-3**	**GT-4**	**GT-6**
SOF/VEL 12 Week Group, n	90	50	18	68	4	14	4	0
SVR12	75/90 (83.3%)	44/50 (88.0%)	16/18 (88.9%)	60/68 (88.2%)	4/4 (100.0%)	7/14 (50.0%)	4/4 (100.0%)	0
Overall Virologic Failure	11/90 (12.2%)	3/50 (6.0%)	2/18 (11.1%)	5/68 (7.4%)	0/4	6/14 (42.9%)	0/4	0
Other	4/90 (4.4%)	3/50 (6.0%)	0/18	3/68 (4.4%)	0/4	1/14 (7.1%)	0/4	0
SOF/VEL+RBV 12 Week Group, n	87	54	14	68	4	13	2	0
SVR12	82/87 (94.3%)	51/54 (94.4%)	14/14 (100.0%)	65/68 (95.6%)	4/4 (100.0%)	11/13 (84.6%)	2/2 (100.0%)	0
Overall Virologic Failure	3/87 (3.4%)	1/54 (1.9%)	0/14	1/68 (1.5%)	0/4	2/13 (15.4%)	0/2	0
Other	2/87 (2.3%)	2/54 (3.7%)	0/14	2/68 (2.9%)	0/4	0/13	0/2	0
SOF/VEL 24 Week Group, n	90	55	16	71	4	12	2	1
SVR12	79/90 (87.8%)	52/55 (94.5%)	15/16 (93.8%)	67/71 (94.4%)	3/4 (75.0%)	6/12 (50.0%)	2/2 (100.0%)	1/1 (100.0%)
Overall Virologic Failure	8/90 (8.9%)	2/55 (3.6%)	1/16 (6.3%)	3/71 (4.2%)	0/4	5/12 (41.7%)	0/2	0/1
Other	3/90 (3.3%)	1/55 (1.8%)	0/16	1/71 (1.4%)	1/4 (25.0%)	1/12 (8.3%)	0/2	0/1

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation of 15 IU/mL.
Other = subject who did not achieve SVR12 and did not meet virologic failure criteria.
Source: Table 15.9.2.1.1

All 3 treatment groups met their primary efficacy endpoints with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%. The p-value was < 0.001 for the comparison with the SVR12 for each treatment group (Table 15.9.1).

Among subjects with genotype 1 HCV infection, the SVR12 rate was higher for those in the SOF/VEL+RBV 12 Week group (95.6%, 65 of 68) compared with the SOF/VEL 12 Week group (88.2%, 60 of 68) or the SOF/VEL 24 Week group (94.4%, 67 of 71) (Table 15.9.2.2). Across treatment groups, the higher SVR rates were observed in subjects with genotype 1a HCV infection in the SOF/VEL+RBV 12 Week group (94.4%, 51 of 54) and the SOF/VEL 24 Week group (94.5%, 52 of 55) compared with the SOF/VEL 12 Week group (88.0%, 44 of 50). In subjects with genotype 1b HCV infection, the SVR12 rate in the SOF/VEL+RBV 12 Week group was 100.0% (14 of 14) compared with 88.9% (16 of 18) and 93.8% (15 of 16) in the SOF/VEL 12 Week and SOF/VEL 24 Week groups, respectively. In subjects with genotype 3 HCV infection; the SVR12 rate was higher for those in the SOF/VEL+RBV 12 Week group (84.6%, 11 of 13) compared with the SOF/VEL 12 Week group (50.0%, 7 of 14) or the SOF/VEL 24 Week group (50.0%, 6 of 12).

All subjects with genotype 2, 4, or 6 HCV infection achieved SVR12 across all treatment groups with the exception of 1 subject with genotype 2 HCV infection in the SOF/VEL 24 Week group who discontinued study drug after 28 days of treatment due to an SAE of incarcerated umbilical hernia assessed as unrelated to SOF/VEL by the investigator, and subsequently died 39 days later (Listings 16.2.7.3 and 16.2.7.5).

Virologic Outcomes:

A total of 31 of 267 subjects (11.6%) did not achieve SVR12 or SVR24; 9 of these 31 subjects had "other" virologic outcomes and were considered as treatment failures (Listing 16.2.6.3). Specifically, 7 subjects died and 2 subjects were lost to follow up. Details on the 7 subjects who died are described in Section 11.4 in the interim CSR. Of the 2 other subjects who did not achieve SVR12 or SVR24 (categorized as "other"), 1 subject was in the SOF/VEL 12 Week group and 1 subject was in the SOF/VEL 24 Week group. The subject in the SOF/VEL 12 Week group completed treatment but was subsequently lost to follow up. The subject in the SOF/VEL 24 Week group was noncompliant, discontinued study treatment at Week 10, and was subsequently lost to follow up.

A small number of subjects experienced virologic failure: 11 of 90 subjects (12.2%) in the SOF/VEL 12 Week group, 3 of 87 subjects (3.4%) in the SOF/VEL+RBV 12 Week group, and 8 of 90 subjects (8.9%) in the SOF/VEL 24 Week group (Table 15.9.2.1.1). All virologic failures were due to relapse with the exception of 2 subjects. One subject with genotype 3 HCV infection in the SOF/VEL+RBV 12 Week group had on-treatment breakthrough with PK data showing undetectable plasma drug levels consistent with non-adherence to study drug and 1 subject with genotype 3 HCV infection in the SOF/VEL 24 Week group had on-treatment breakthrough (Listing 16.2.6.2). No subjects relapsed between posttreatment Weeks 12 and 24 (Table 15.9.2.3, and Listings 16.2.6.1 and 16.2.6.4).

Among subjects with genotype 1 HCV infection, there was 1 subject with virologic failure (1.5%) in subjects treated with SOF/VEL+RBV for 12 weeks compared with 5 (7.4%) in the SOF/VEL 12 Week group and 3 (4.2%) in the SOF/VEL 24 Week group (Table 15.9.2.1.4). The rates of virologic failure observed in subjects with genotype 1b HCV infection were numerically higher than in subjects with genotype 1a HCV infection in the SOF/VEL 12 Week and 24 Week groups. The extension of treatment duration of SOF/VEL from 12 to 24 weeks in subjects with genotype 1 HCV infection was associated with slightly lower virologic failure rates. All genotype 1 virologic failures were due to relapse.

Among subjects with genotype 3 HCV infection, virologic failure rates were lowest in the SOF/VEL+RBV 12 Week group (15.4%) compared with 42.9% in the SOF/VEL 12 Week group and 41.7% in the SOF/VEL 24 Week group (Table 15.9.2.1.4). In the SOF/VEL+RBV 12 Week group, 1 subject had PK data consistent with non-adherence to study drug at the time of virologic failure and the other subject with virologic failure had discontinued RBV due to anemia at Week 4. Extension of treatment duration of SOF/VEL from 12 to 24 weeks in subjects with genotype 3 HCV infection was not associated with improved virologic outcomes. All genotype 3 virologic failures were due to relapse with the exception of 2 subjects; 1 subject in the SOF/VEL+RBV 12 Week group with breakthrough associated with non-adherence to study drug and 1 subject in the SOF/VEL 24 Week group with on-treatment breakthrough.

There were no virologic failures in subjects with genotype 2, 4, or 6 HCV infection, regardless of treatment regimen.

Comparison of SVR4, SVR12, and SVR24:

The proportion of subjects with SVR4, SVR12, and SVR24 is presented by treatment group and genotype in the table below. The SVR rates for the SOF/VEL 12 Week and SOF/VEL+RBV 12 Week groups reported in the interim analysis were maintained in the SVR24 analysis with no additional relapses. The SVR12 rate for the SOF/VEL 24 Week group was updated in the SVR24 analysis due to achievement of SVR12 by 2 subjects who had missed the posttreatment Week 12 visit and were listed as "visit pending" at the time of the interim analysis. At the final analysis, all treatment groups maintained the same SVR12 and SVR24 rates (Tables 15.9.1, 15.9.2.2, and Listing 16.2.6.1).

	Genotype							
	Total (All Genotypes)	**GT-1a**	**GT-1b**	**GT-1 Total**	**GT-2**	**GT-3**	**GT-4**	**GT-6**
SOF/VEL 12 Week Group, n	90	50	18	68	4	14	4	0
SVR4	83/90 (92.2%)	48/50 (96.0%)	17/18 (94.4%)	65/68 (95.6%)	4/4 (100.0%)	10/14 (71.4%)	4/4 (100.0%)	0
95% CI	84.6% to 96.8%	86.3% to 99.5%	72.7% to 99.9%	87.6% to 99.1%	39.8% to 100.0%	41.9% to 91.6%	39.8% to 100.0%	–
SVR12	75/90 (83.3%)	44/50 (88.0%)	16/18 (88.9%)	60/68 (88.2%)	4/4 (100.0%)	7/14 (50.0%)	4/4 (100.0%)	0
95% CI	74.0% to 90.4%	75.7% to 95.5%	65.3% to 98.6%	78.1% to 94.8%	39.8% to 100.0%	23.0% to 77.0%	39.8% to 100.0%	–
SVR24	75/90 (83.3%)	44/50 (88.0%)	16/18 (88.9%)	60/68 (88.2%)	4/4 (100.0%)	7/14 (50.0%)	4/4 (100.0%)	0
95% CI	74.0% to 90.4%	75.7% to 95.5%	65.3% to 98.6%	78.1% to 94.8%	39.8% to 100.0%	23.0% to 77.0%	39.8% to 100.0%	–
SOF/VEL+RBV 12 Week Group, n	87	54	14	68	4	13	2	0
SVR4	83/87 (95.4%)	52/54 (96.3%)	14/14 (100.0%)	66/68 (97.1%)	4/4 (100.0%)	11/13 (84.6%)	2/2 (100.0%)	0
95% CI	88.6% to 98.7%	87.3% to 99.5%	76.8% to 100.0%	89.8% to 99.6%	39.8% to 100.0%	54.6% to 98.1%	15.8% to 100.0%	–
SVR12	82/87 (94.3%)	51/54 (94.4%)	14/14 (100.0%)	65/68 (95.6%)	4/4 (100.0%)	11/13 (84.6%)	2/2 (100.0%)	0
95% CI	87.1% to 98.1%	84.6% to 98.8%	76.8% to 100.0%	87.6% to 99.1%	39.8% to 100.0%	54.6% to 98.1%	15.8% to 100.0%	–
SVR24	82/87 (94.3%)	51/54 (94.4%)	14/14 (100.0%)	65/68 (95.6%)	4/4 (100.0%)	11/13 (84.6%)	2/2 (100.0%)	0
95% CI	87.1% to 98.1%	84.6% to 98.8%	76.8% to 100.0%	87.6% to 99.1%	39.8% to 100.0%	54.6% to 98.1%	15.8% to 100.0%	–

	Genotype							
	Total (All Genotypes)	**GT-1a**	**GT-1b**	**GT-1 Total**	**GT-2**	**GT-3**	**GT-4**	**GT-6**
SOF/VEL 24 Week Group, n	90	55	16	71	4	12	2	1
SVR4	81/90 (90.0%)	53/55 (96.4%)	16/16 (100.0%)	69/71 (97.2%)	3/4 (75.0%)	6/12 (50.0%)	2/2 (100.0%)	1/1 (100.0%)
95% CI	81.9% to 95.3%	87.5% to 99.6%	79.4% to 100.0%	90.2% to 99.7%	19.4% to 99.4%	21.1% to 78.9%	15.8% to 100.0%	2.5% to 100.0%
SVR12	79/90 (87.8%)	52/55 (94.5%)	15/16 (93.8%)	67/71 (94.4%)	3/4 (75.0%)	6/12 (50.0%)	2/2 (100.0%)	1/1 (100.0%)
95% CI	79.2% to 93.7%	84.9% to 98.9%	69.8% to 99.8%	86.2% to 98.4%	19.4% to 99.4%	21.1% to 78.9%	15.8% to 100.0%	2.5% to 100.0%
SVR24	79/90 (87.8%)	52/55 (94.5%)	15/16 (93.8%)	67/71 (94.4%)	3/4 (75.0%)	6/12 (50.0%)	2/2 (100.0%)	1/1 (100.0%)
95% CI	79.2% to 93.7%	84.9% to 98.9%	69.8% to 99.8%	86.2% to 98.4%	19.4% to 99.4%	21.1% to 78.9%	15.8% to 100.0%	2.5% to 100.0%

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation 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 is bracketed by values that are 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.
Source: Table 15.9.2.2

Concordance between SVR12 and SVR24:

Among subjects in the SOF/VEL 12 Week group, 74 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100% concordance between SVR12 and SVR24. Among subjects in the SOF/VEL+RBV 12 Week group, 77 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100% concordance between SVR12 and SVR24. Among subjects in the SOF/VEL 24 Week group, 74 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100% concordance between SVR12 and SVR24.

	SOF/VEL 12 Weeks SVR24		**SOF/VEL+RBV 12 Weeks SVR24**		**SOF/VEL 24 Weeks SVR24**		**Overall SVR24**	
	Yes (N = 71)	No (N = 3)	Yes (N = 76)	No (N = 1)	Yes (N = 73)	No (N = 1)	Yes (N=220)	No (N = 5)
SVR12								
Yes	71	0	76	0	73	0	220	0
No	0	3	0	1	0	1	0	5
Positive Predictive Value	100%		100%		100%		100%	

HCV RNA was analyzed using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with a limit of quantitation 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

Changes in Hepatic Function:

Analyses of CPT and MELD scores for subjects who achieved SVR12 are presented in Section 9.2.6 of the interim CSR and presented below for subjects who achieved SVR24.

The table below presents the CPT score at baseline versus decrease (improvement), no change, or increase (worsening) in CPT score at posttreatment Week 24 for subjects who achieved SVR24. Overall, 115 subjects (54.0%) had an improvement in CPT score while 77 subjects (36.2%) had no change. A higher proportion of subjects had an improvement in CPT scores at SVR24 compared to SVR12, likely reflecting the longer time of observation following HCV clearance.

A minority of subjects (9.9%, 21 subjects) experienced an increase (worsening) in CPT score from baseline to posttreatment Week 24. A higher percentage of subjects receiving SOF/VEL for 24 weeks (63.8%) compared with subjects receiving SOF/VEL±RBV for 12 weeks (44.9% to 53.3%) had improvements in CPT score from baseline to posttreatment Week 24; this difference likely reflects the longer time of observation.

	SOF/VEL 12 Weeks (N = 75)	**SOF/VEL +RBV 12 Weeks (N = 82)**	**SOF/VEL 24 Weeks (N = 79)**	**Overall (N = 236)**
CPT Score Between Baseline and Posttreatment Week 24				
Decrease (Improvement)	31/69 (44.9%)	40/75 (53.3%)	44/69 (63.8%)	115/213 (54.0%)
No Change	30/69 (43.5%)	28/75 (37.3%)	19/69 (27.5%)	77/213 (36.2%)
Increase (Worsening)	8/69 (11.6%)	7/75 (9.3%)	6/69 (8.7%)	21/213 (9.9%)
No Assessment	6	7	10	23

Baseline value was the last available value on or prior to first dose date of any study drug.
No change was assigned for differences (posttreatment visits minus baseline score) of 0, decrease was assigned for differences that were less than 0, and increase was assigned for values that were greater than 0.
Source: Table 15.9.5.3.2

The instances where the numerical change in CPT score observed resulted in a change in CPT class are presented in the shift table below.

Overall, among the 191 subjects who had CPT class B cirrhosis at baseline and achieved SVR24, 138 subjects (72.3%) remained CPT class B at posttreatment Week 24, 50 subjects (26.2%) improved to CPT class A, and 3 subjects (1.6%) worsened to CPT class C.

Among the 13 subjects who had CPT class A cirrhosis at baseline and achieved SVR24, 12 subjects (92.3%) remained CPT class A at posttreatment Week 24. Of the 9 subjects who had CPT class C cirrhosis at baseline and achieved SVR24, 2 subjects (22.2%) improved to CPT class A, 5 subjects (55.6%) improved to CPT class B, and 2 subjects (22.2%) remained at CPT class C. Notably, there were improvements in CPT class from baseline to posttreatment Week 24 in all 5 subjects (100.0%) with CPT class C cirrhosis who achieved SVR24 and received SOF/VEL for 24 weeks; this difference likely reflects the longer time of observation with HCV RNA suppression.

Among all subjects who received SOF/VEL+RBV for 12 weeks and achieved SVR24, only 1 of 75 subjects (1.3%) had a worsening CPT class from B to C.

Baseline CPT Class	Posttreatment Week 24 CPT Class			
	CPT A (5-6)	CPT B (7-9)	CPT C (10-15)	No Assessment
SOF/VEL 12 Week Group				
CPT A (5-6)	1/1 (100.0%)	0/1	0/1	2
CPT B (7-9)	14/67 (20.9%)	52/67 (77.6%)	1/67 (1.5%)	4
CPT C (10-12)	1/1 (100.0%)	0/1	0/1	0
SOF/VEL+RBV 12 Week Group				
CPT A (5-6)	6/6 (100.0%)	0/6	0/6	0
CPT B (7-9)	15/66 (22.7%)	50/66 (75.8%)	1/66 (1.5%)	6
CPT C (10-12)	0/3	1/3 (33.3%)	2/3 (66.7%)	1
SOF/VEL 24 Week Group				
CPT A (5-6)	5/6 (83.3%)	1/6 (16.7%)	0/6	1
CPT B (7-9)	21/58 (36.2%)	36/58 (62.1%)	1/58 (1.7%)	9
CPT C (10-12)	1/5 (20.0%)	4/5 (80.0%)	0/5	0
Overall				
CPT A (5-6)	12/13 (92.3%)	1/13 (7.7%)	0/13	3
CPT B (7-9)	50/191 (26.2%)	138/191 (72.3%)	3/191 (1.6%)	19
CPT C (10-12)	2/9 (22.2%)	5/9 (55.6%)	2/9 (22.2%)	1

Baseline value was the last available value on or prior to first dose date of any study drug.
Source: Table 15.9.5.5

All subjects who achieved SVR24 and had an improvement in CPT score were further analyzed to determine which component of the CPT score (albumin, bilirubin, INR, ascites, or encephalopathy) had improved, remained the same, or worsened (Table 15.9.5.17). Of the 115 subjects who achieved SVR24 and had improvements in CPT score, 79 subjects (68.7%), 29 subjects (25.2%), and 30 subjects (26.1%) showed improvements in total albumin, bilirubin, and ascites, respectively. Changes in INR were minimal. In addition, 20 subjects (17.4%) had improvements in encephalopathy. A higher proportion of subjects had improvements in the clinical parameters (ascites and encephalopathy) at the SVR24 time point compared with SVR12.

Of the 40 subjects who achieved SVR24 and had improvements in CPT score in the SOF/VEL+RBV 12 Week group, 75.0%, 17.5%, and 17.5% of subjects had improvements in albumin, bilirubin, and ascites, respectively, while 12.5% of subjects had improvements in encephalopathy and 5.0% had improvements in INR.

The table below presents the proportion of subjects with a decrease, no change, or increase in MELD score between baseline and posttreatment Week 24 in subjects who achieved SVR24. Overall, the majority of subjects who achieved SVR24 had a decrease (improvement) (51.6%, 110 of 213 subjects) in MELD score between baseline and posttreatment Week 24. Among subjects who received SOF/VEL+RBV for 12 weeks and achieved SVR24, 49.3% (37 of 75 subjects) had a decrease (improvement) in MELD score.

	SOF/VEL 12 Weeks (N = 75)	SOF/VEL+RBV 12 Weeks (N = 82)	SOF/VEL 24 Weeks (N = 79)	Overall (N = 236)
MELD Score Between Baseline and Posttreatment Week 24				
Decrease (Improvement)	38/69 (55.1%)	37/75 (49.3%)	35/69 (50.7%)	110/213 (51.6%)
No Change	14/69 (20.3%)	19/75 (25.3%)	15/69 (21.7%)	48/213 (22.5%)
Increase (Worsening)	17/69 (24.6%)	19/75 (25.3%)	19/69 (27.5%)	55/213 (25.8%)
No Assessment	6	7	10	23

Baseline value was the last available value on or prior to first dose date of any study drug.
No change was assigned for differences (posttreatment visits minus baseline score) of 0, decrease was assigned for differences that were less than 0, and increase was assigned for values that were greater than 0.
Source: Table 15.9.5.9

Improvements in MELD score were a result of improvements in total bilirubin; changes in creatinine and INR were minimal (Table 15.9.5.19).

All efficacy analyses are provided in Tables 15.9.1 to 15.9.5.19, Figures 15.9.2.4.1 to 15.9.2.5.4.3, and Listings 16.2.6.1 to 16.2.6.7.

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

Pharmacokinetic Results:

Full details on the PK analysis are reported in Section 10 of the interim CSR.

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 data through 30 days after the last dose of study drugs were summarized in Section 11 of the interim CSR (13 October 2015). Table 2 provides a detailed table 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.

Adverse Events

Several updates were made to previously reported AE data due to the ongoing nature of the study and data reconciliation in this population with advanced cirrhosis. 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 Table 2).

Adverse Events Leading to Discontinuation

For Subject PPD in the SOF/VEL+RBV 12 Week group, the initial case report form (CRF) showed that the Grade 3 AEs of nausea, vomiting, chills, and asthenia and SAEs of device related infection, sepsis, hyponatremia, seizure, and syncope led to interruption of RBV dosing. These AEs were updated by the investigator to show that they led to permanent discontinuation of RBV (Table 2).

For Subject PPD in the SOF/VEL 24 Week group, the initial CRF showed that the AE leading to discontinuation was hyperbilirubinemia. This was updated by the investigator to Grade 3 AEs of nausea and vomiting leading to study drug discontinuation, instead of hyperbilirubinemia (Table 2). No other additional treatment-emergent Grade 3 or 4 AEs were reported.

Serious Adverse Events and Deaths

No additional treatment-emergent SAEs were reported (Listing 16.2.7.4). One additional death was reported; Subject PPD in the SOF/VEL 24 Week group died of decompensated cirrhosis on posttreatment Day 169 (Listing 16.2.7.3). This subject had a history of HCV infection, hepatic cirrhosis, hyperlipidaemia, hypertension, thrombocytopenia, type 2 diabetes mellitus, coronary artery disease, hepatic encephalopathy, and ascites. The subject completed 24 weeks of treatment with SOF/VEL. On posttreatment Day 34, the subject was diagnosed with an SAE of decompensated cirrhosis from hepatocellular carcinoma and portal vein thrombosis (reported in the interim CSR) that eventually culminated in his death on posttreatment Day 169. The investigator assessed the death as due to decompensated cirrhosis from hepatocellular carcinoma and portal vein thrombosis. These events were assessed as unrelated to SOF/VEL by the investigator.

In addition, Subject PPD in the SOF/VEL 12 Week group, with a medical history of HCV infection, hepatic cirrhosis with evidence of ascites and hepatic encephalopathy, chronic obstructive pulmonary disease, and osteomyelitis, had several non-treatment-emergent SAEs reported during the posttreatment period. These included bacterial peritonitis (posttreatment Days 89−140), osteomyelitis (posttreatment Days 96−140), and respiratory distress (posttreatment Days 109−117). Additional details are provided in Section 15.2.

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 15.11.2.1.1.1 to 15.11.5.11 and Listings 16.2.7.1 to 16.2.7.11.

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 15.11.6.4.5, 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 15.11.6.4.5, Figures 15.11.6.1 to 15.11.6.11, 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.

These changes did not impact the overall interpretation or conclusions of the safety profile of SOF/VEL or SOF/VEL+RBV in this study.

Quality of Life:

Complete details on the quality of life survey (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) through posttreatment Week 12 are reported in Section 12 of the interim CSR. 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 16.2.6.9 to 16.2.6.12.

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 16.2.6.9 to 16.2.6.12). These results indicated that that no on-treatment decrements in quality of life in subjects in the SOF/VEL 12 Week or SOF/VEL 24 Week groups occurred. Within the SOF/VEL+RBV 12 Week group, during the treatment period, decreases (worsening) from baseline were generally observed in 4 of 8 domain scores of the SF-36 (domains of vitality, social functioning, role emotional, and mental health) and the mental component score. Both increases (improvement) and decreases (worsening) from baseline were observed for the domains of physical functioning, role physical, and bodily pain.

The mean scores for most scales improved from EOT to 24 weeks after the EOT. 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:

- Treatment with SOF/VEL±RBV for 12 weeks or SOF/VEL for 24 weeks in subjects with decompensated cirrhosis resulted in high SVR12 rates:
  - In the SOF/VEL 12 Week group, the SVR12 rate was 83.3% (75 of 90 subjects).
  - In the SOF/VEL+RBV 12 Week group, the SVR12 rate was 94.3% (82 of 87 subjects).
  - In the SOF/VEL 24 Week group, the SVR12 rate was 87.8% (79 of 90 subjects).
- The SVR12 rates were highest in subjects treated with SOF/VEL+RBV for 12 weeks with few virologic failures:
  - In subjects with genotype 1 HCV infection, the virologic failure rate was 1.5% (1 of 68 subjects).
  - In subjects with genotype 3 HCV infection, the virologic failure rate was 15.4% (2 of 13 subjects), of which 1 subject had on-treatment breakthrough with PK data showing undetectable plasma drug levels consistent with non-adherence to study drug.
- Overall, there were no virologic failures in subjects with genotype 2, 4, or 6 HCV infection.
- The presence of pretreatment NS5A and NS5B RAVs did not impact treatment outcome with SOF/VEL+RBV for 12 weeks.
- No subjects relapsed between posttreatment Weeks 12 and 24.

- Approximately half of subjects who achieved SVR24 experienced an early improvement in CPT and MELD scores, primarily related to improvements in synthetic function (albumin) and decreases in bilirubin.
- Pharmacokinetic exposures among subjects with decompensated cirrhosis in this study as compared to subjects with compensated liver disease in other studies did not reveal clinically meaningful differences.
- SOF/VEL was generally well tolerated in these subjects with decompensated liver disease, as evidenced by low rates of study treatment discontinuation and the majority of Grade 3 and 4 AEs, SAEs, and laboratory abnormalities being consistent with clinical sequelae of advanced liver disease and RBV toxicity.