FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination for 12 Weeks in Direct-Acting Antiviral-Experienced Subjects with Chronic HCV Infection
Name of Test Drug:	Sofosbuvir (SOF)/Velpatasvir (VEL)/Voxilaprevir (VOX; GS-9857) fixed-dose combination (FDC)
Dose and Formulation:	SOF/VEL/VOX FDC (400/100/100 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-367-1171 (POLARIS-1)
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	125751 2015-003455-21
ClinicalTrials.gov Identifier:	NCT02607735
Study Start Date:	11 November 2015 (First Subject Screened)
Study End Date:	21 June 2017 (Last Subject Last Observation)
Principal or Coordinating Investigator:	Name: Marc Bourlière, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa M. Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	14 September 2017
Previous Report Date(s):	10 November 2016 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-367-1171

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination for 12 Weeks in Direct-Acting Antiviral-Experienced Subjects with Chronic HCV Infection

Investigators: Multicenter study

Study Centers: In the primary study, subjects were enrolled across 108 study sites in the United States (US), France, Canada, the United Kingdom, Germany, Australia, and New Zealand.

In the deferred treatment substudy, subjects were enrolled across 73 study sites in the US, France, Canada, the United Kingdom, Germany, Australia, and New Zealand.

Publications: Bourlière M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, Ravendhran N, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. N Engl J Med. 2017 Jun 1;376(22):2134-2146.

Bourlière M, Gordon SC, Ramji A, Ravendhran N, Tran TT, Hyland RH, et al. Sofosbuvir/Velpatasvir/Voxilaprevir for 12 Weeks as a Salvage Regimen in NS5A Inhibitor-Experienced Patients with Genotype 1-6 Infection: The Phase 3 POLARIS-1 Study [Abstract 194]. J Hepatology 2016;63 (1S):102A.

Study Period:

11 November 2015 (First Subject Screened)
10 October 2016 (Last Subject Last Observation for the Primary Endpoint in the Primary Study)
18 April 2017 (Last Subject Last Observation for the Primary Endpoint in the Deferred Treatment Substudy)
21 June 2017 (Last Subject Last Observation)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To determine the efficacy of treatment with (SOF; GS-7977)/velpatasvir (VEL; GS-5816)/voxilaprevir (VOX; GS-9857) fixed-dose combination (FDC) for 12 weeks as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of treatment with SOF/VEL/VOX

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 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, VEL, and VOX during treatment and after cessation of treatment
- To characterize steady-state pharmacokinetics (PK) of the study drug
- To further evaluate efficacy and safety of SOF/VEL/VOX for 12 weeks in subjects who enter the deferred treatment substudy

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 provide their specific consent
- To assess the effect of treatment on health-related quality of life

Methodology:

This Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study assessed the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL/VOX treatment compared with 12 weeks of placebo treatment in direct-acting antiviral-experienced subjects with chronic HCV infection who have previously been treated with a nonstructural protein (NS)5A inhibitor.

Approximately 380 NS5A inhibitor-experienced subjects were planned to be randomized or enrolled to 1 of the following 2 treatment groups:

- **SOF/VEL/VOX 12 Week group:** SOF/VEL/VOX FDC (400/100/100 mg) tablet once daily with food for 12 weeks
- **Placebo 12 Week group:** SOF/VEL/VOX placebo tablet once daily with food for 12 weeks

Approximately 200 subjects with genotype 1 HCV infection (with a target of at least 30% with cirrhosis) were planned to be randomized in a 1:1 ratio in a double-blind manner into the SOF/VEL/VOX 12 Week group or Placebo 12 Week group. Randomization was stratified by the presence or absence of cirrhosis at screening.

Approximately 150 subjects with genotype 3 (n = 100) or 4 (n = 50) HCV infection (with a target of at least 30% with cirrhosis) were planned to be enrolled in the SOF/VEL/VOX 12 Week group.

Approximately 30 subjects with genotype 2, 5, or indeterminate with or without cirrhosis were also planned to be enrolled in the SOF/VEL/VOX 12 Week group.

Subjects in the SOF/VEL/VOX 12 Week group completed the posttreatment Week 4 and 12 visits. Subjects in the SOF/VEL/VOX 12 Week group who achieved SVR12 (HCV RNA less than the lower limit of quantitation [LLOQ] at the posttreatment Week 12 visit) also completed the posttreatment Week 24 visit.

Subjects in the Placebo 12 Week group who completed treatment and the posttreatment Week 4 visit were not required to complete posttreatment Week 12 and 24 visits. The subjects were offered the option to receive treatment with open-label SOF/VEL/VOX for 12 weeks in a deferred treatment substudy.

All subjects were eligible to participate in the PK substudy if consent was obtained. An intensive 24-hour PK sample collection was performed at the Week 2 or 4 visit of the primary study to determine the steady-state PK of SOF, SOF metabolites GS-566500 and GS-331007, VEL, and VOX.

After completing all required study visits, subjects were eligible to enroll into an SVR registry study or an SVR cirrhosis registry study if they achieved SVR or into a sequence registry study if they did not achieve SVR.

This final synoptic clinical study report (CSR) summarizes the results of the final analysis for the primary study, which was conducted after all subjects in the SOF/VEL/VOX 12 Week group completed the posttreatment Week 24 visit or had prematurely discontinued from the study. Analysis of data collected for the primary efficacy endpoint (SVR12) for the primary study was reported in the interim CSR (10 November 2016). An additional analysis summarizes the results of the deferred treatment substudy, which was conducted after all subjects in the deferred treatment substudy completed the posttreatment Week 24 visit or had prematurely discontinued from the substudy.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 380 subjects in the primary study

Analyzed: 416 subjects randomized/enrolled in the primary study

- All Randomized/Enrolled Analysis Set: 416 subjects
- Full Analysis Set: 415 subjects
- Safety Analysis Set: 415 subjects
- PK Analysis Set: 262 subjects
- PK Substudy Analysis Set: 37 subjects
- Deferred treatment substudy: 147 subjects enrolled
  - — Deferred Treatment Substudy Safety Analysis Set: 147 subjects
  - — Deferred Treatment Substudy Full Analysis Set: 147 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were NS5A inhibitor-experienced males or nonpregnant/nonlactating females of ≥ 18 years of age, with chronic HCV infection, with or without cirrhosis.

Duration of Treatment: In the primary study, treatment duration was 12 weeks, with up to 24 weeks of posttreatment follow-up.

In the deferred treatment substudy, treatment duration was 12 weeks, with up to 24 weeks of posttreatment follow-up.

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

- In the primary study, SOF/VEL/VOX FDC tablets were administered orally with food to subjects in the SOF/VEL/VOX 12 Week group at a dose of 400/100/100 mg (1 FDC tablet once daily).
- In the deferred treatment substudy, SOF/VEL/VOX FDC tablets were administered orally with food at a dose of 400/100/100 mg (1 FDC tablet once daily).

The lot numbers of SOF/VEL/VOX administered in this study were ER1501B2, ER1502B1, ER1503B1, and ER1509B1.

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

- In the primary study, SOF/VEL/VOX Placebo tablets matched the SOF/VEL/VOX FDC (400/100/100 mg) tablets and were administered orally with food to subjects in the Placebo 12 Week group (1 tablet once daily).

The lot number of SOF/VEL/VOX placebo administered in this study was ER1504B1.

Criteria for Evaluation:

Efficacy: This final synoptic CSR provides analyses of HCV RNA levels at posttreatment Week 24 in the primary study for subjects in the SOF/VEL/VOX 12 Week group and analyses of HCV RNA levels in the deferred treatment substudy for subjects enrolled into deferred treatment substudy. Efficacy analyses of the primary endpoint, SVR12, in the primary study were described in the interim CSR (10 November 2016). In the deferred treatment substudy, blood samples to determine HCV RNA levels were collected from subjects at Day 1 (predose), Weeks 1, 2, 4, 8, and 12 (or upon early termination), and posttreatment Weeks 4, 12, and 24 (if applicable). The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA. The LLOQ of this assay is 15 IU/mL.

Virology: Deep sequencing analysis of HCV NS3, NS5A, and NS5B coding regions was performed for all subjects at baseline in the primary study. For all subjects with virologic failure who received SOF/VEL/VOX in the primary study or in the deferred treatment substudy, 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 data are reported at a 15% assay cutoff.

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 VOX in the primary study.

In the deferred treatment substudy, a single PK blood sample was collected from all subjects at Weeks 1, 2, 4, 8, and 12 (or upon early termination).

Safety: The interim CSR (10 November 2016) provides analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital sign measurements, electrocardiogram (ECGs), and physical examinations collected during the primary study. This final synoptic CSR summarizes any new treatment-emergent AEs or changes to previously reported AEs for the primary study 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 primary study (posttreatment Week 24 of the primary study) are summarized. This final CSR also summarizes the analyses of the safety assessments collected in the deferred treatment substudy, which also included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital sign measurements, ECGs, and physical examinations. 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 collected during the primary study (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 primary study 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. Finally, this final CSR summarizes quality of life questionnaires collected during the deferred treatment substudy.

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 for the primary study is described in detail in Section 7.7 of the interim CSR (10 November 2016); Appendix 16.1.9 of this report provides the statistical analysis plans for the primary study and for the deferred treatment substudy.

Efficacy:

Primary Study

The primary efficacy endpoint of the primary study was the proportion of subjects with HCV RNA < LLOQ 12 weeks after discontinuation of the study drug (SVR12) in the SOF/VEL/VOX 12 Week group for the Full Analysis Set. The SVR12 rate in the SOF/VEL/VOX 12 Week group was compared with the performance goal of 85% using a 2-sided exact 1-sample binomial test at the 0.05 significance level.

A 2-sided 1-sample exact binomial test was used to test the statistical hypothesis. The point estimate and the 2-sided 95% exact confidence interval (CI) for SVR12 rate based on the Clopper-Pearson method was provided for the SOF/VEL/VOX 12 Week group. The point estimate and the 2-sided 95% exact CI for SVR4 rate based on Clopper-Pearson method was provided for the Placebo 12 Week group.

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

The SVR24 rate was calculated using the same method as described for SVR12. If a subject achieved SVR12 and had no further HCV RNA measurements, 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.

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 the number and percentage of subjects who met the endpoint definitions.

Deferred Treatment Substudy

In the deferred treatment substudy, SVR4, SVR12, and SVR24 rates were calculated using the same methods described for the primary study. No statistical hypothesis testing was performed for SVR12, which was the primary endpoint in the substudy. Point estimates and 2-sided 95% exact CIs for SVR4, SVR12, and SVR24 based on the Clopper-Pearson method were provided. The secondary efficacy endpoints for the substudy were the same as those provided in the primary study.

Pharmacokinetics: For the primary study, steady-state PK over a 24-hour dosing interval was determined in subjects who participated in the PK substudy at the Week 2 or 4 visit. Plasma concentrations of SOF, SOF metabolites GS-566500 and GS-331007, VEL, and VOX 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, %CV, median, Q1, Q3, minimum, maximum, and geometric mean and its 95% CI) were presented for PK concentration data and PK parameter data, as applicable, by cirrhosis status (presence, absence) and overall.

For the deferred treatment substudy, no PK assessments were performed for this report.

Safety: All randomized/enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Sets for both the primary study and the deferred treatment substudy. Safety data were analyzed by treatment group for the primary study and overall for the deferred treatment substudy. All data collected on or after the date of the first dose of study drug up to the date of the last dose of study drug plus 30 days in the study or substudy were included for both the primary study and the deferred treatment substudy. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0.

Quality of Life: In the primary study, the health-related QOL questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) were completed by subjects at baseline/Day 1, and Weeks 4 and 12 during treatment (or upon early termination), and posttreatment Week 4 (both treatment groups), and for the SOF/VEL/VOX 12 Week group only, posttreatment Weeks 12 and 24, as 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 postbaseline time points.

In the deferred treatment substudy, the health-related QOL questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) were completed by subjects at baseline/Day 1, and Weeks 4 and 12 during treatment (or upon early termination), and posttreatment Weeks 4, 12 and 24. 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.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

Primary Study

Of the 416 randomized or enrolled subjects in the primary study, 415 received at least 1 dose of study drug and were included in the Safety Analysis Set and the FAS (263 in the SOF/VEL/VOX 12 Week group and 152 in the Placebo 12 Week group) (Table 15.8.1.3). Full details on subject disposition, demographics, and baseline disease characteristics for the primary study are reported in Section 8 of the interim CSR (10 November 2016), 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 (Tables 15.8.3.1 and 15.8.3.2, 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 in the primary study are presented in Tables 15.8.1.1 to 15.8.4, 15.11.1; Figure 15.8.1, and Listings 16.1.6 to 16.2.5.2. In addition, an updated Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

Deferred Treatment Substudy

Of the 147 subjects who enrolled in the deferred treatment substudy, 147 received at least 1 dose of study drug (SOF/VEL/VOX for 12 weeks) and were included in the Deferred Treatment Substudy Safety Analysis and Full Analysis Sets (Substudy Table 15.8.1.2). All 147 subjects completed study drug, while 5 subjects (3.4%) did not complete the posttreatment Week 24 visit (4 subjects were lost to follow-up and 1 subject withdrew consent).

Overall, the majority of subjects were male (78.9%), white (82.3%), and not Hispanic or Latino (93.9%), with a mean age of 59 years (range: 29-80) (Substudy Table 15.8.3.1). The mean baseline body mass index (BMI) was 28.5 (range: 17.6-61.8) kg/m^2 and 33.3% of subjects had BMI $\geq$ 30 kg/m^2 (Substudy Table 15.8.3.2).

Most subjects had genotype 1 HCV infection (98.6% [1a = 76.9%, 1b = 20.4%, 1 other = 1.4%]) or genotype 6 HCV infection (1.4%), and most of the subjects (82.3%) had a non-CC IL28B genotype (CT = 60.5%, TT = 21.8%). Of the 147 subjects in the deferred treatment substudy, 49 (33.3%) had cirrhosis. The mean (SD) baseline HCV RNA was 6.3 (0.53) log_{10} IU/mL, and most subjects had baseline HCV RNA $\geq$ 800,000 IU/mL (79.6%) (Substudy Table 15.8.3.2).

In the deferred treatment substudy, all but 1 subject (0.7%, treated with SOF+SMV) had been previously treated with an NS5A inhibitor, as specified in the clinical study protocol. The most common NS5A inhibitors were ledipasvir (LDV) (61.9%, 91 of 147 subjects), daclatasvir (18.4%, 27 of 147 subjects) and ombitasvir (16.3%, 24 of 147 subjects): 51.7% of subjects had failed prior treatment with an NS5A+NS5B inhibitor (most common regimen was LDV+SOF,

72 subjects), 41.5% of subjects had failed prior treatment with an NS5A+NS3 inhibitor with or without an NS5B inhibitor, and 6.1% of subjects had failed prior treatment with an NS5A inhibitor with or without other direct-acting antivirals (DAAs) (Substudy Table 15.8.3.2 and Substudy Adhoc Table 22; Adhoc Listing 6).

Analyses related to disposition, demographics, and exposure in the deferred treatment substudy are presented in Substudy Tables 15.8.1.1 to 15.8.4, 15.11.1, and Substudy Adhoc Table 22; Substudy Figure 15.8.1; and Substudy Listings 16.1.6 to 16.2.5.2 and Substudy Adhoc Listings 6 and 7. In addition, an Important Protocol Deviations Log for the substudy is provided in Appendix 16.2.2.

Efficacy Results:

Primary Study

Primary Endpoint of the Primary Study

In the primary study, the SOF/VEL/VOX 12 Week group met the primary endpoint of an SVR12 rate that was statistically superior relative to the prespecified performance goal of 85% ($p < 0.001$). The SVR12 rate in the SOF/VEL/VOX 12 Week group was 96.2% (253 of 263 subjects; 95% CI: 93.1% to 98.2%) (Table 15.9.1.1).

No subjects in the Placebo 12 Week group achieved SVR4. The results of the primary efficacy analysis presented in this report are the same as the results presented in the interim report.

Virologic Outcomes in the Primary Study

A total of 10 of 263 subjects (3.8%) in the SOF/VEL/VOX 12 Week group did not achieve SVR12. One subject, with genotype 1a HCV infection, had on-treatment virologic failure (breakthrough) that was associated with low plasma concentrations of GS-331007 (the predominant SOF metabolite), VEL, and VOX at Weeks 8 and 12, consistent with nonadherence. Three subjects had relapse determined at posttreatment Week 4; all had genotype 3 HCV infection with cirrhosis. Three subjects (HCV genotypes 1a, 3, or 4, all with cirrhosis) achieved SVR4, but had relapse determined at the posttreatment Week 12 visit (Listings 16.2.6.2, 16.2.5.3, and 16.2.4.3.2). Three additional subjects did not achieve SVR12 (2 subjects withdrew consent, 1 subject was lost to follow-up) (Table 15.9.2.1.1; Listing 16.2.6.3).

No subjects in the SOF/VEL/VOX 12 Week group relapsed between posttreatment Weeks 12 and 24 (Table 15.9.2.2; Listings 16.2.6.1 and 16.2.6.4).

Comparison of SVR4, SVR12, and SVR24 in the Primary Study

Table 1 presents the proportion of subjects with SVR4, SVR12, and SVR24. The SVR rates reported in the interim analysis were maintained in the SVR24 analysis with no additional relapses (Tables 15.9.1.1, 15.9.2.2; Listings 16.2.6.1 and 16.2.6.4).

Table 1. GS-US-367-1171: SVR by Posttreatment Visit (Primary Study, Full Analysis Set)

	Placebo 12 Weeks (N = 152)	SOF/VEL/VOX 12 Weeks (N = 263)
SVR4	0/152	257/263 (97.7%)
95% CI	0.0% to 2.4%	95.1% to 99.2%
SVR12	0/152	253/263 (96.2%)
95% CI	0.0% to 2.4%	93.1% to 98.2%
SVR24	0/152	253/263 (96.2%)
95% CI	0.0% to 2.4%	93.1% to 98.2%

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.
Missing SVR24 will be imputed as success if SVR12 is achieved with no follow-up values or by bracketed success.
The exact 95% CI for the proportion within treatment group and genotype is based on the Clopper-Pearson method.
Source: Table 15.9.2.2

Concordance between SVR12 and SVR24 in the Primary Study

Among subjects in the SOF/VEL/VOX 12 Week group, 249 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100% concordance between SVR12 and SVR24 (Table 2).

Table 2. GS-US-367-1171: Concordance between SVR12 and SVR24 (Primary Study, Full Analysis Set)

	SOF/VEL/VOX 12 Weeks SVR24	
	Yes (N = 249)	No (N = 0)
SVR12		
Yes	249	0
No	0	0
Positive predictive value	100.0%	

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation 15 IU/mL.
Only subjects that have both Posttreatment Week 12 and Posttreatment Week 24 data are included in the analysis.
Source: Table 15.9.2.3

All efficacy analyses for the primary study are provided in Tables 15.9.1.1 to 15.9.3.3; Figures 15.9.1.1 to 15.9.2.5.4; and Listings 16.2.6.1 to 16.2.6.4.

Deferred Treatment Substudy

Table 3 presents the primary efficacy endpoint in the deferred treatment substudy, the proportion of subjects with SVR12. The SVR12 rate was 97.3% (95% CI: 93.2%-99.3%). A total of 4 of 147 subjects (2.7%) did not achieve SVR12; all had genotype 1a HCV infection. Two subjects (1 with cirrhosis and 1 without cirrhosis) had relapse determined at posttreatment Week 4. Two subjects (both without cirrhosis) achieved SVR4, but had relapse determined at the posttreatment Week 12 visit (Substudy Listing 16.2.6.2).

Table 3. GS-US-367-1171: SVR12 and Virologic Outcome (Deferred Treatment Substudy, Full Analysis Set)

	SOF/VEL/VOX 12 Weeks (N = 147)
SVR12	143/147 (97.3%)
95% CI	93.2% to 99.3%
Overall Virologic Failure	4/147 (2.7%)
Relapse	4/147 (2.7%)
Completed Study Treatment	4/147 (2.7%)
On-Treatment Virologic Failure	0/147
Other	0/147

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 within each genotype and overall is based on the Clopper-Pearson method.
Relapse = confirmed HCV RNA >=LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at last on-treatment visit.
On-Treatment Virologic Failure = Breakthrough (confirmed HCV RNA >= LLOQ after having previously had HCV RNA < LLOQ while on treatment), Rebound (confirmed >1 $\log_{10}$IU/mL increase in HCV RNA from nadir while on treatment), or Nonresponse (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment).
Other = subject who did not achieve SVR12 and did not meet virologic failure criteria.
Source: Substudy Tables 15.9.1 and 15.9.2.1.1

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly with similar decreases in HCV RNA observed across all HCV genotypes (Substudy Table 15.9.2.5). Consistent with the rapid and sustained decline in HCV RNA, 93.2% of subjects had HCV RNA < LLOQ at Week 4 (Substudy Table 15.9.2.4). Early viral response had no impact on SVR12 rates. A total of 10 subjects had HCV RNA > LLOQ at Week 4, of these, only 1 subject (Subject PPD did not achieve SVR12 (Substudy Table 15.9.3.2; Substudy Listing 16.2.6.2).

High SVR12 rates were achieved in all demographic and baseline characteristics subgroups (Substudy Table 15.9.3.1). The high overall SVR12 rates and low rate of virologic failure precluded meaningful subgroup analyses.

The SVR4 rate was 98.6% (95% CI: 95.2%-99.8%); 2 subjects achieved SVR4 who did not achieve SVR12 (Substudy Table 15.9.2.2). Of the 147 subjects in the deferred treatment substudy, 138 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100% concordance between SVR12 and SVR24 (Table 4).

Table 4. GS-US-367-1171: Concordance between SVR12 and SVR24 (Deferred Treatment Substudy, Full Analysis Set)

	SOF/VEL/VOX 12 Weeks SVR24	
	Yes (N = 138)	**No (N = 0)**
SVR12		
Yes	138	0
No	0	0
Positive predictive value	100.0%	

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation 15 IU/mL.
Only subjects that have both Posttreatment Week 12 and Posttreatment Week 24 data are included in the analysis.
Source: Substudy Table 15.9.2.3

All efficacy analyses for the deferred treatment substudy are provided in Substudy Tables 15.9.1 to 15.9.3.3; Substudy Figures 15.9.1.1 to 15.9.2.5.4; and Substudy Listings 16.2.6.1 to 16.2.6.4.

Virologic Resistance

Primary Study

Full details on the resistance analysis in the primary study are reported in Section 9.2.6 of the interim CSR (10 November 2016). No additional resistance analyses for the primary study were performed since no subjects relapsed between posttreatment Week 12 and posttreatment Week 24. After finalization of the interim CSR, there were additional data from the 1 subject with genotype 4d HCV infection who relapsed and who was found to have treatment-emergent Y93H in NS5A, so that, in the final analysis, 1 of the 6 subjects who relapsed developed treatment-emergent RAVs.

Deferred Treatment Substudy

Full details on the resistance analysis in the deferred treatment substudy are reported in Appendix 16.2.6 (Substudy Virology Resistance Analysis).

Overall, 89.1% of subjects had baseline NS3 and/or NS5A RAVs. Similar to the primary study, NS5A RAVs were the most common RAVs, observed in 82.3% of subjects. The presence of baseline RAVs did not impact the SVR12 rate, with an SVR12 rate of 96.9% for subjects with RAVs, compared with an SVR12 rate of 100% for subjects without RAVs.

Of the 4 subjects who had virologic failure, all of whom had genotype 1a and relapsed, 2 subjects developed treatment-emergent resistance. One subject had treatment-emergent NS3 Y56H, D168A/V, and NS5A L31M and the other subject had treatment-emergent NS3 V36V/A. No NS5B NI RAVs were observed at baseline or emerged in any of these subjects.

Pharmacokinetics Results:

Primary Study

In the primary study, the steady-state PK of SOF, GS-566500, GS-331007, VEL, and VOX for subjects receiving SOF/VEL/VOX (Tables 15.10.1.6-15.10.1.10) were similar to that observed in SOF/VEL+VOX Phase 2 studies (GS-US-337-1468 [LEPTON], GS-US-367-1168, and GS-US-367-1169).

Deferred Treatment Substudy

For the deferred treatment substudy, no PK assessments were performed for this report.

Plasma concentrations of SOF, GS-566500, GS-331007, VEL, and VOX were evaluated for 4 subjects in the deferred treatment substudy who had virologic failure and available PK samples (Appendix 16.1.10). Plasma concentration values of SOF, GS-331007, VEL, and VOX for these 4 subjects were consistent with those observed in the historic SOF/VEL/VOX Phase 2/3 population.

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 in the primary study were summarized in Section 11 of the interim CSR (10 November 2016).

Primary Study

Adverse Events and Serious Adverse Events in the Primary Study

A small number of updates were made to previously reported AE data in the primary study due to the ongoing nature of the study and data reconciliation. These changes included actions taken to treat the AE (ie, medication), change in onset or resolution dates, minor clarification to AE terms, newly reported Grade 1 and 2 treatment-emergent AEs, and newly reported nontreatment emergent AEs (Listings 16.2.7.1 and 16.2.7.7). These changes did not impact the overall interpretation or conclusions of the safety profile of SOF/VEL/VOX in this study. Listing 16.2.7.7 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 treatment-emergent deaths were reported (Listing 16.2.7.3). Narratives for all SAEs and AEs leading to discontinuation of study drug 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).

There was one new nontreatment emergent SAE that was attributed to study drug: Subject PPD experienced hepatocellular carcinoma 259 days after completing the study drug (Listings 16.2.7.1 and 16.2.7.7). There was 1 new nontreatment-emergent death. Subject PPD died on posttreatment Day 235 due to an intracranial bleed. The subject, a 75-year-old female, also had 2 new nontreatment-emergent SAEs: Grade 3 epilepsy that began

on posttreatment Day 167 and Grade 4 intracranial hemorrhage that began on posttreatment Day 209; neither event was considered by the investigator to be related to study drug (Listings 16.2.7.1, 16.2.7.3, and 16.2.7.7).

All AE results for the primary study are provided in Tables 15.11.2.1.1 to 15.11.5.2 and Adhoc Table 20; Listings 16.2.7.1 to 16.2.7.7.

Clinical Laboratory Results in the Primary Study

Blood samples for clinical laboratory analyses were not collected at the posttreatment Week 24 visit in the primary study. Overall, no clinically meaningful changes in the clinical laboratory results were observed (Tables 15.11.6.1.1-15.11.6.3 and Listings 16.2.8.1.1, 16.2.8.1.3.1-16.2.8.1.9).

All laboratory results for the primary study 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 16.2.8.1.1 to 16.2.8.1.9.

Vital Sign Measurements and ECGs in the Primary Study

Vital sign measurements (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) and ECGs were not collected at the posttreatment Week 24 visit of the primary study. Overall, no notable changes were observed (Tables 15.11.7.1-15.11.7.3. 15.11.9; and Listings 16.2.8.2.1, 16.2.8.2.3.1, and 16.2.8.2.3.2).

All vital sign measurements, height, weight, BMI, and ECG results for the primary study are provided in Tables 15.11.7.1 to 15.11.7.3 and 15.11.9, and Listings 16.2.8.2.1, 16.2.8.2.2, 16.2.8.2.3.1, and 16.2.8.2.3.2.

Deferred Treatment Substudy

Adverse Events and Serious Adverse Events in the Deferred Treatment Substudy

In the deferred treatment substudy, treatment with SOF/VEL/VOX for 12 weeks was generally well tolerated. Adverse events were reported for 76.2% of subjects (112 of 147). The most common AEs (ie, AEs reported in > 10% of subjects in either group) were fatigue, headache, diarrhea, and nausea (Substudy Table 15.11.2.1.3).

Most AEs were Grade 1 or Grade 2 in severity. Grade 3 AEs were reported for 4.8% of subjects (7 of 147) and no Grade 3 AE was reported in > 1 subject. No Grade 4 AEs were reported (Substudy Table 15.11.2.2.2).

Serious adverse events (SAEs) were reported for 4.1% of subjects (6 of 147). No trends in SAEs were observed; no SAE was reported in > 1 subject, and all SAEs were assessed as unrelated to study drug (Substudy Tables 15.11.4.2 and 15.11.4.3).

No subjects had AEs that led to discontinuation and 2 subjects had AEs that led to interruption of dosing (Substudy Table 15.11.2.4.2; Substudy Listings 16.2.5.1 and 16.2.7.6). A 73-year-old male subject had a serious generalized tonic-clonic seizure that was not considered related to study drug on Day 6 and study drug was interrupted the same day; this event resolved on Day 8, the same day that study drug resumed. The second subject, a 50-year-old male, had two Grade 2 events (abdominal pain and back pain) from Days 36 to 44, with study drug interrupted from Days 41 to 42; neither event was considered related to study drug (Substudy Table 15.11.2.4.2; Substudy Listings 16.2.5.1 and 16.2.7.6). No subjects died during the deferred treatment substudy.

Clinical Laboratory Results in the Deferred Treatment Substudy

Most laboratory abnormalities were Grade 1 or Grade 2 in severity (Substudy Table 15.11.6.2). The incidence of Grade 3 and 4 laboratory abnormalities was 8.8% and 2.0%, respectively; and the only Grade 3 or 4 hematologic abnormalities observed were decreased lymphocytes (1 subject [0.7%] for each grade) (Substudy Listing 16.2.8.1.3.1).

Subjects had Grade 3 or 4 chemistry abnormalities of elevated lipase (Grade 3, 8 subjects [5.4%]; Grade 4, 1 subject [0.7%]), elevated serum glucose (Grade 3, 3 subjects [2.0%]), elevated total bilirubin (Grade 3, 2 subjects [1.4%]), and elevated creatine kinase (Grade 4, 1 subject [0.7%]) (Substudy Table 15.11.6.2). All Grade 3 or 4 lipase elevations were asymptomatic with no cases of clinical pancreatitis. Of the 3 subjects with Grade 3 serum glucose elevations, 2 had a medical history of diabetes; the third had Grade 1 and 2 serum glucose elevations during placebo treatment in the primary study. Both subjects with Grade 3 elevated total bilirubin had cirrhosis and Grade 2 elevated total bilirubin at baseline (Listing 16.2.8.1.7.1; Substudy Listings 16.2.4.3.1 and 16.2.8.1.3.1). The Grade 4 creatine kinase elevation was an isolated event, attributed by the investigator to the subject's resumption of weight lifting (data on file).

All laboratory results for the deferred treatment substudy are provided in Substudy Tables 15.11.6.1.1 to 15.11.6.3 and Substudy Figures 15.11.6.1 to 15.11.6.10, and Substudy Listings 16.2.8.1.1 to 16.2.8.1.7.2.

Vital Sign Measurements and ECGs in the Deferred Treatment Substudy

No notable changes from baseline in vital signs were observed during the study (Substudy Tables 15.11.7.1-15.11.7.3. 15.11.9). No subjects had clinically significant postbaseline ECG abnormalities (Substudy Table 15.11.9; Substudy Listing 16.2.8.2.3.2).

All vital sign measurements and ECG results for the deferred treatment substudy are provided in Substudy Tables 15.11.7.1 to 15.11.7.3 and 15.11.9, and Substudy Listings 16.2.8.2.1, 16.2.8.2.2, 16.2.8.2.3.1, and 16.2.8.2.3.2.

Quality of Life:

Primary Study

Complete details on the quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) through posttreatment Week 12 of the primary study are reported in Section 12 of the interim CSR (10 November 2016).

Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C questionnaires administered in the primary study indicated that QOL parameters improved from baseline to posttreatment Week 24 following treatment with SOF/VEL/VOX for subjects with chronic HCV infection. Likewise, the mean scores for most scales improved from EOT to 24 weeks after the EOT (Tables 15.12.1-15.12.4). These results should be interpreted with caution as multiple endpoints were tested, and the study was not powered to test these exploratory endpoints.

All quality-of-life analyses for the primary study 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.

Deferred Treatment Substudy

Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C questionnaires administered in the deferred treatment substudy indicated that QOL parameters improved from baseline to posttreatment Week 24 following treatment with SOF/VEL/VOX for subjects with chronic HCV infection. Likewise, the mean scores for most scales improved from EOT to 24 weeks after the EOT (Substudy Tables 15.12.1-15.12.4). These results should be interpreted with caution as multiple endpoints were tested, and the study was not powered to test these exploratory endpoints.

All quality-of-life analyses for the deferred treatment substudy are provided in Substudy Tables 15.12.1 to 15.12.4, Substudy Figures 15.12.1 to 15.12.4, and Substudy Listings 16.2.6.5 to 16.2.6.8.

CONCLUSIONS:

The conclusions from the primary study are as follows:

- The study met its predefined primary efficacy endpoint: SOF/VEL/VOX for 12 weeks resulted in an SVR12 rate of 96.2%, which was statistically superior relative to the prespecified performance goal of 85% ($p < 0.001$).
- The overall concordance between SVR12 and SVR24 was 100.0%.
- The presence of baseline RAVs did not impact the treatment outcome in the SOF/VEL/VOX 12 Week group; treatment-emergent resistance was uncommon (observed in 1 of 6 subjects who relapsed).
- The steady-state PK of SOF, GS-566500, GS-331007, VEL, and VOX for subjects receiving SOF/VEL/VOX were similar to that observed in SOF/VEL+VOX Phase 2 studies.
- Treatment with SOF/VEL/VOX for 12 weeks was generally well tolerated with a safety profile generally similar to placebo. There was a low incidence of Grade 3 or 4 AEs, SAEs, and discontinuations due to AEs, and no clinically meaningful laboratory abnormalities.

The conclusions from the deferred treatment substudy are as follows:

- SOF/VEL/VOX for 12 weeks resulted in an SVR12 rate of 97.3% (95% CI: 93.2%-99.3%).
- The overall concordance between SVR12 and SVR24 was 100.0%.
- The presence of baseline RAVs did not impact treatment outcome; treatment-emergent resistance was observed in 2 of 4 subjects who relapsed.
- Treatment with SOF/VEL/VOX for 12 weeks was generally well tolerated. There was a low incidence of Grade 3 AEs and SAEs and no Grade 4 AEs, no discontinuations due to AEs, and no clinically meaningful laboratory abnormalities.