FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Global, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination for 8 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis
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)
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-367-1173 (POLARIS-3)
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	125751 2015-002996-12
ClinicalTrials.gov Identifier:	NCT02639338
Study Start Date:	23 December 2015 (First Subject Screened)
Study End Date:	02 January 2017 (Last Subject Last Observation)
Principal or Coordinating Investigator:	Name: Stuart Roberts, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	22 March 2017
Previous Report Date(s):	08 November 2016 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-367-1173

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

Title of Study: A Phase 3, Global, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination for 8 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis

Investigators: Multicenter study

Study Centers: Subjects were enrolled across 84 sites in the United States (US), Canada, the United Kingdom, France, Germany, Australia, and New Zealand.

Publications: Foster GR, Thompson AJ, Ruane PJ, Borgia SM, Dore G, Workowski K, et al. A Randomized Phase 3 Trial of Sofosbuvir/Velpatasvir/Voxilaprevir for 8 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks for Patients with Genotype 3 HCV Infection and Cirrhosis: The POLARIS-3 Study [Abstract 258]. J Hepatology 2016;63 (1S):135A.

Study Period:

23 December 2015 (First Subject Screened)
12 October 2016 (Last Subject Last Observation for the Primary Endpoint)
02 January 2017 (Last Subject Last Observation)

Phase of Development: Phase 3

Objectives:

The primary objective of this study was as follows:

- To determine the efficacy of treatment with sofosbuvir (SOF; GS-7977)/velpatasvir (VEL; GS-5816)/voxilaprevir (VOX; GS-9857) fixed-dose combination (FDC) for 8 weeks and of treatment with SOF/VEL 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 each treatment regimen

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attain sustained virologic response (SVR) at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure

- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF, VEL, and VOX 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 provide their separate and specific consent
- To assess the effect of treatment on health-related quality of life (QOL)

Methodology: This Phase 3, randomized, open-label, multicenter study evaluated the antiviral efficacy, safety, and tolerability of SOF/VEL/VOX for 8 weeks and SOF/VEL for 12 weeks in subjects with chronic genotype 3 HCV infection and cirrhosis who are naive to direct-acting antiviral (DAA) treatment (ie, DAA naive). Approximately 200 subjects were randomized (1:1) to 1 of the following 2 treatment groups:

- **SOF/VEL/VOX 8 Week group:** SOF/VEL/VOX (400/100/100 mg) once daily with food for 8 weeks
- **SOF/VEL 12 Week group:** SOF/VEL (400/100 mg) once daily without regard to food for 12 weeks

Randomization was stratified by treatment history (treatment naive or treatment experienced with an interferon (IFN)-based regimen).

All subjects were to complete the posttreatment Week 4 and 12 follow-up visits. Subjects who achieved SVR12 were to complete the posttreatment Week 24 follow-up visit.

After completing all required study visits, subjects were eligible to enroll into 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 of data collected throughout the course of the study, after all subjects had completed the posttreatment Week 24 visit or had prematurely discontinued from the study. Analysis of data collected for the primary efficacy endpoint (SVR12) was reported in the interim CSR (08 November 2016).

Number of Subjects (Planned and Analyzed):
Planned: 200 subjects
Analyzed: 220 subjects

- All Randomized Analysis Set: 220 subjects
- Full Analysis Set (FAS): 219 subjects
- Safety Analysis Set: 219 subjects
- Pharmacokinetic (PK) Analysis Set: 110 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were DAA-naive males and nonpregnant/nonlactating females ≥ 18 years of age, with chronic genotype 3 HCV infection and cirrhosis.

Duration of Treatment: Treatment duration was 8 or 12 weeks, with up to 24 weeks of posttreatment follow-up for both groups.

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

- **SOF/VEL/VOX FDC** (400/100/100 mg) tablets were administered once daily with food for 8 weeks.
- **SOF/VEL FDC** (400/100 mg) tablets were administered once daily without regard to food for 12 weeks.

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

The lot number of SOF/VEL administered in this study was DU1408B1.

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 (08 November 2016). The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study, with a lower limit of quantitation (LLOQ) of 15 IU/mL.

Virology: Baseline deep sequencing analysis of HCV nonstructural protein 3 (NS3), NS5A, and NS5B coding regions was performed for all subjects. For all subjects with virologic failure, deep sequencing was performed at the first time point after virologic failure if the plasma/serum sample was available and HCV RNA was > 1000 IU/mL. All data are reported at a 15% assay cutoff.

Pharmacokinetics: The interim CSR (08 November 2016) describes details on the collection of blood samples for PK analyses.

Safety: The interim CSR (08 November 2016) 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 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 is described in detail in Section 7.7 of the interim CSR (08 November 2016).

Efficacy: The primary efficacy endpoint was the proportion of subjects with HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs (SVR12) in the FAS. The SVR12 rate for the SOF/VEL/VOX 8 Week and SOF/VEL 12 Week groups were compared with the performance goal of 83% using a 2-sided exact 1-sample binomial test following a sequential testing procedure. If and only if the primary test for SVR12 rate in the SOF/VEL/VOX 8 Week group comparing with 83% was statistically significant at the 0.05 significance level, the SVR12 rate in SOF/VEL 12 Week group was compared to 83% at the 0.05 significance level. The 2-sided 95% exact CI based on the Clopper-Pearson method was provided for the SVR12 rate within each treatment group and also for each subgroup within each treatment group.

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

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

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: No PK assessments 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 data were analyzed by treatment group and included 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. All safety data, including data occurring > 30 days after the last dose of study drug, were listed. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0.

Quality of Life: The health-related QOL questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) were completed by subjects at baseline/Day 1, Weeks 4, 8 (SOF/VEL/VOX 8 Week group only), and 12 (SOF/VEL 12 Week group only) during treatment (or upon early

termination) and posttreatment Weeks 4, 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.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 219 subjects received at least 1 dose of study drug and were included in the Safety Analysis Set and the FAS (110 in the SOF/VEL/VOX 8 Week group and 109 in the SOF/VEL 12 Week group) (Table 15.8.1.2).

Full details on subject disposition, demographics, and baseline disease characteristics are reported in Section 8 of the interim CSR (08 November 2016), and subject disposition at posttreatment Week 24 is summarized in Table 15.8.1.2. 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 are presented in Tables 15.8.1.1 to 15.8.4, 15.11.1, and Figure 15.8.1, and Listings 16.2.1.1 to 16.2.5.2. In addition, an Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

Efficacy Results:

Primary Endpoint

The SVR12 rates for the SOF/VEL/VOX 8 Week and SOF/VEL 12 Week groups were both statistically superior relative to the prespecified SVR12 performance goal of 83% ($p < 0.001$ for both groups). The SVR12 rates were as follows (Table 15.9.1):

- **SOF/VEL/VOX 8 Week group**: 96.4% (95% CI: 91.0%-99.0%) of subjects (106 of 110) achieved SVR12
- **SOF/VEL 12 Week group**: 96.3% (95% CI: 90.9%-99.0%) of subjects (105 of 109) achieved SVR12

The results of the primary efficacy analysis presented in this report are the same as the results presented in the interim report.

Virologic Outcomes

A total of 8 of 219 subjects (3.7%) did not achieve SVR12; 4 of these 8 subjects had "other" virologic outcomes and were considered as treatment failures. In the SOF/VEL/VOX 8 Week group, 1 subject withdrew consent and 1 subject died on posttreatment Day 78 (described in Section 11.6 in the interim CSR). In the SOF/VEL 12 Week group, 1 subject was lost to follow up after completing study drug and 1 subject discontinued study due to an SAE (pelvic fracture) after 6 days of study drug (Table 15.9.2.1.1; Listings 16.2.6.3, 16.2.7.3, and 16.2.7.4).

Of the remaining 4 subjects who did not achieve SVR12, all 4 experienced virologic failure. In the SOF/VEL/VOX 8 Week group, 2 of 110 subjects (1.8%) had relapse determined at posttreatment Week 4. In the SOF/VEL 12 Week group, 2 of 109 subjects (1.8%) had virologic failure; 1 subject had on-treatment failure (rebound) that was determined at Week 8 and 1 subject

had relapse determined at posttreatment Week 4. Both subjects had PK data consistent with nonadherence from at least 1 on-treatment visit (Table 15.9.2.1.1; Listing 16.2.6.2; Appendix 16.1.10 of interim CSR [08 November 2016]). No subjects in either group relapsed between posttreatment Weeks 12 and 24 (Table 15.9.2.2 and Listings 16.2.6.1 and 16.2.6.4).

The high SVR12 rates and low numbers of subjects with virologic failure preclude meaningful subgroups analyses.

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 Listings 16.2.6.1 and 16.2.6.4).

	SOF/VEL/VOX 8 Weeks (N = 110)	**SOF/VEL 12 Weeks (N = 109)**
SVR4	107/110 (97.3%)	106/109 (97.2%)
95% CI	92.2% to 99.4%	92.2% to 99.4%
SVR12	106/110 (96.4%)	105/109 (96.3%)
95% CI	91.0% to 99.0%	90.9% to 99.0%
SVR24	106/110 (96.4%)	105/109 (96.3%)
95% CI	91.0% to 99.0%	90.9% to 99.0%

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 is based on the Clopper-Pearson method.
Source: Table 15.9.2.2

Concordance between SVR12 and SVR24

Among subjects in the SOF/VEL/VOX 8 Week group, 103 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100% concordance between SVR12 and SVR24. Among subjects in the SOF/VEL 12 Week group, 101 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100% concordance between SVR12 and SVR24.

	SOF/VEL/VOX 8 Weeks		**SOF/VEL 12 Weeks**		**Overall**	
	SVR24		**SVR24**		**SVR24**	
	Yes (N = 103)	**No (N = 0)**	**Yes (N = 101)**	**No (N = 0)**	**Yes (N = 204)**	**No (N = 0)**
SVR12						
Yes	103	0	101	0	204	0
No	0	0	0	0	0	0
Positive predictive value	100.0%		100.0%		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 who have both posttreatment Week 12 and posttreatment Week 24 data are included in the analysis.
Source: Table 15.9.2.3

All efficacy analyses are provided in Tables 15.9.1 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.

Full details on the resistance analysis are reported in Section 9.2.6 of the interim CSR (08 November 2016). No additional resistance analyses were performed since no subjects relapsed between posttreatment Week 12 and posttreatment Week 24.

Pharmacokinetics Results: No PK assessments 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 (08 November 2016).

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 included actions taken to treat the AE (ie, medication), change in onset or resolution dates, minor clarification of AE terms, and newly reported Grade 1 and 2 nontreatment-emergent AEs (Listings 16.2.7.1 and 16.2.7.7). One treatment-emergent Grade 3 AE (hypertensive crisis for Subject PPD initially recorded as related to study medication at the time of the interim CSR due to a data entry error was corrected to be not related to study drug; therefore, the number of subjects in the SOF/VEL 12 Week group who had a Grade 3 treatment-related AE was reduced from 2 subjects to 1 subject. These changes did not impact the overall interpretation or conclusions of the safety profile of SOF/VEL or 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 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 15.11.5.2 and Listings 16.2.7.1 to 16.2.7.7.

After the completion of the GS-US-367-1173 interim CSR (08 November 2016), it was noted that the study treatment received by Subject PPD who had died due to hypertension on posttreatment Day 78 was inconsistently described in the interim report. Typographical errors were made in the synopsis and Section 11.14 (Summary of Safety) indicating that this subject received SOF/VEL for 12 weeks rather than SOF/VEL/VOX for 8 weeks. In other sections, the treatment received was recorded correctly as SOF/VEL/VOX for 8 weeks. This error did not alter the overall assessment of safety for the study or the conclusions of the study.

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 15.11.6.1.1-15.11.6.3 and Listings 16.2.8.1.1, 16.2.8.1.3.1, and 16.2.8.1.5.1-16.2.8.1.9).

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 16.2.8.1.1 to 16.2.8.1.9.

Vital Sign Measurements and ECGs

Vital sign measurements (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) and ECGs were not collected at the posttreatment Week 24 visit. 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 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, 16.2.8.2.2, 16.2.8.2.3.1, and 16.2.8.2.3.2.

Quality of Life:

Complete details on the quality-of-life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) through posttreatment Week 12 are reported in Section 12 of the interim CSR (08 November 2016). No notable differences were observed in the quality-of-life questionnaires through posttreatment Week 12 between the interim analyses and the final analyses (Tables 15.12.1-15.12.4).

Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C questionnaires indicated that QOL parameters improved from baseline to posttreatment Week 24 following treatment with SOF/VEL/VOX or SOF/VEL 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 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.

CONCLUSIONS: The overall conclusions from this study are as follows:

- Both treatment groups met their primary efficacy endpoints, demonstrating statistically superior SVR12 rates to the prespecified 83% rate:
  - 8 weeks of treatment with SOF/VEL/VOX resulted in an SVR12 rate of 96.4% in DAA-naive subjects with genotype 3 HCV infection and cirrhosis
  - 12 weeks of treatment with SOF/VEL resulted in an SVR12 rate of 96.3% in DAA-naive subjects with genotype 3 HCV infection and cirrhosis
  - Baseline resistance-associated variants (RAVs) had no impact on virologic outcome in either treatment group; all subjects with baseline NS3 and/or NS5A RAVs achieved SVR12
- The overall concordance between SVR12 and SVR24 was 100.0%. No subjects relapsed between posttreatment Weeks 12 and 24.
- Treatment with SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks was generally well tolerated with similar incidence and severity of AEs. There were few Grade 3 or 4 AEs, SAEs, or discontinuations due to AEs; there were no treatment-emergent deaths; and no clinically meaningful laboratory abnormalities.