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 12 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks in Direct-Acting Antiviral-Experienced Subjects with Chronic HCV Infection who Have Not Received an NS5A Inhibitor
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-367-1170 (POLARIS-4)
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	125751 2015-003167-10
ClinicalTrials.gov Identifier:	NCT02639247
Study Start Date:	23 December 2015 (First Subject Screened)
Study End Date:	18 January 2017 (Last Subject Last Observation)
Principal or Coordinating Investigator:	Name: Stefan Zeuzem, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa M Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	28 March 2017
Previous Report Date(s):	10 November 2016 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-367-1170

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 12 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks in Direct-Acting Antiviral-Experienced Subjects with Chronic HCV Infection who Have Not Received an NS5A Inhibitor

Investigators: This study was multicenter.

Study Centers: Subjects were enrolled across 101 study sites in the United States, Canada, New Zealand, Australia, France, Germany, and the United Kingdom.

Publications: Zeuzem S, Flamm SL, Tong MJ, Vierling JM, Pianko S, Buggisch P, et al. A Randomized, Controlled, Phase 3 Trial of Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir/Velpatasvir for 12 Weeks in Direct Acting Antiviral-Experienced Patients with Genotype 1-6 HCV Infection: The POLARIS-4 Study [Abstract 109]. J Hepatology 2016;63 (1S):59A.

Study Period:

23 December 2015 (First Subject Screened)
05 October 2016 (Last Subject Last Observation for the Primary Endpoint)
18 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 12 weeks and SOF/VEL FDC for 12 weeks as measured by the proportion of subjects with sustained virologic 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 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

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 (QOL)

Methodology: This Phase 3, randomized, open-label, multicenter, international study evaluated the safety and efficacy of SOF/VEL/VOX treatment for 12 weeks and SOF/VEL treatment for 12 weeks in direct-acting antiviral (DAA)-experienced subjects with chronic HCV infection who have not previously been treated with an nonstructural protein (NS) 5A inhibitor. Subjects who had DAA exposure to a NS3/4A protease inhibitor (PI) only were excluded.

Overall, approximately 380 non-NS5A inhibitor DAA-experienced subjects were planned to be randomized or enrolled into 1 of the following 2 treatment groups:

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

Approximately 350 subjects with genotype 1, 2, or 3 HCV infection (with a target of at least 30% with cirrhosis) were randomized in a 1:1 ratio into the SOF/VEL/VOX 12 Week or SOF/VEL 12 Week group. Randomization was stratified by HCV genotype (1, 2, or 3) and cirrhosis status (presence or absence). The target enrollments for subjects with genotype 1, 2, and 3 HCV infection were 200, 50, and 100 subjects, respectively.

The 30 additional subjects with genotype 4, 5, or indeterminate HCV infection (including those with genotype 6 HCV infection due to the inability of the assay to distinguish this HCV genotype at screening), regardless of cirrhosis status, were enrolled in the SOF/VEL/VOX 12 Week group only.

All subjects completed the posttreatment Week 4 and 12 visits. All subjects who achieved SVR12, defined as HCV RNA less than the lower limit of quantitation (< LLOQ) at posttreatment Week 12, completed the posttreatment Week 24 visit.

After completing all required study visits, subjects were eligible to enroll into a sustained virologic response (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 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 (10 November 2016).

Number of Subjects (Planned and Analyzed):
Planned: Approximately 380 subjects
Analyzed: 333 subjects

- All Randomized/Enrolled Analysis Set: 333 subjects
- Full Analysis Set: 333 subjects
- Safety Analysis Set: 333 subjects
- Pharmacokinetic Analysis Set: 182 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were non-NS5A inhibitor DAA-experienced males or nonpregnant/nonlactating females of ≥ 18 years of age with chronic HCV infection with or without cirrhosis. Subjects who only had DAA exposure to a NS3/4A PI were excluded.

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

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 12 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, ER1502B1, 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 (10 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: No pharmacokinetic (PK) analyses were performed for this report.

Safety: The interim CSR (10 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 QOL 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 QOL. 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 (10 November 2016).

Efficacy: The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after cessation of treatment, in the Full Analysis Set. The SVR12 rate for the SOF/VEL/VOX 12 Week and SOF/VEL 12 Week groups were compared with the performance goal of 85% using a 2-sided exact 1-sample binomial test at the 0.025 significance level. The 2-sided 95% exact CI based on the Clopper-Pearson method was provided for the SVR12 rate for each treatment group.

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

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

Safety: All randomized or enrolled 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 sign 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. 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 and 12, early termination (if applicable), and posttreatment Weeks 4, 12, and 24 (if applicable). A Wilcoxon signed-rank test explored within treatment group changes from baseline to each of the time points and from EOT to each posttreatment time point. A Wilcoxon rank-sum test explored between treatment group differences in change from baseline to each of the posttreatment time points.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 333 subjects were randomized or enrolled into the study. All randomized or enrolled subjects received at least 1 dose of study drug and were included in the Full Analysis Set and Safety Analysis Set (182 in the SOF/VEL/VOX 12 Week group and 151 in the SOF/VEL 12 Week group) (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 16.1.6 to 16.2.5.2. In addition, an updated Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

Efficacy Results: The SVR12 rates for the SOF/VEL/VOX 12 Week and SOF/VEL 12 Week groups were as follows (Table 15.9.1):

- SOF/VEL/VOX 12 Week group: 97.8% (95% CI: 94.5% to 99.4%) of subjects (178 of 182) achieved SVR12.
- SOF/VEL 12 Week group: 90.1% (95% CI: 84.1% to 94.3%) of subjects (136 of 151) achieved SVR12.

The SVR12 rate for the SOF/VEL/VOX 12 Week group was statistically superior relative to the pre-specified SVR12 performance goal of 85% at the significance level of 0.025 ($p < 0.001$), and the SVR12 rate for the SOF/VEL 12 Week group was not statistically superior relative to the pre-specified SVR12 performance goal of 85% at the significance level of 0.025.

The SVR12 rate for the SOF/VEL/VOX 12 Week group was updated in the final analysis from that reported in the interim analysis due to 1 subject achieving SVR12 by imputation. Subject PPD with genotype 3a with cirrhosis missed the posttreatment Week 12 visit and was listed as “visit pending” at the time of the interim data cut. This subject returned for the posttreatment Week 24 visit, had HCV RNA < LLOQ and therefore achieved SVR24, and was imputed as a success for SVR12 (Listings 16.2.4.2.1 and 16.2.6.1).

Virologic Outcomes

In the SOF/VEL/VOX 12 Week group, 4 of 182 subjects (2.2%) did not achieve SVR12. Of these, no subjects had on-treatment virologic failure, 1 subject relapsed, and 3 subjects did not

achieve SVR12 for reasons other than virologic failure. In the SOF/VEL 12 Week group, 15 of 151 subjects (9.9%) did not achieve SVR12. Of these, 1 subject had on-treatment virologic failure and 14 subjects relapsed (Table 15.9.2.1.1 and Listing 16.2.6.1).

Comparison of SVR4, SVR12, and SVR24

The proportion of subjects with SVR4, SVR12, and SVR24 is presented by treatment group in the table below. The SVR4 and SVR12 rates for the SOF/VEL 12 Week group reported in the interim analysis were maintained in the SVR24 analysis. The SVR4 and SVR12 rates for the SOF/VEL/VOX 12 Week group reported in the interim analysis were updated in the final analysis due to achievement of SVR24 by 1 subject who had missed the posttreatment Week 4 and 12 visits at the time of the interim analysis. The SVR12 and SVR24 rates were the same for both treatment groups as no subjects relapsed between posttreatment Week 12 and posttreatment Week 24 (Tables 15.9.1 and 15.9.2.2, and Listings 16.2.6.1).

	SOF/VEL/VOX 12 Weeks (N = 182)	**SOF/VEL 12 Weeks (N = 151)**
SVR4	179/182 (98.4%)	138/151 (91.4%)
95% CI	95.3% to 99.7%	85.7% to 95.3%
SVR12	178/182 (97.8%)	136/151 (90.1%)
95% CI	94.5% to 99.4%	84.1% to 94.3%
SVR24	178/182 (97.8%)	136/151 (90.1%)
95% CI	94.5% to 99.4%	84.1% to 94.3%

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 12 Week group, 174 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100.0% concordance between SVR12 and SVR24. Among subjects in the SOF/VEL 12 Week group, 133 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100.0% concordance between SVR12 and SVR24.

	SOF/VEL/VOX 12 Weeks		**SOF/VEL 12 Weeks**		**Overall**	
	SVR24		**SVR24**		**SVR24**	
	Yes (N = 174)	**No (N = 0)**	**Yes (N = 133)**	**No (N = 0)**	**Yes (N = 307)**	**No (N = 0)**
SVR12						
Yes	174	0	133	0	307	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

Virologic Resistance

Full details on the virologic resistance analysis are reported in Section 9.2.5 of the interim CSR (10 November 2016). No additional resistance analyses were performed since no subjects relapsed between posttreatment Week 12 and posttreatment Week 24.

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.

Pharmacokinetics Results: No PK analyses were performed for this report.

Safety Results: All AEs and laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as AEs and laboratory abnormalities in this report, unless otherwise specified. Evaluations of safety data through 30 days after the last dose of study drugs were summarized in Section 11 of the interim CSR (10 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 nontreatment-emergent AEs (Listings 16.2.7.1 and 16.2.7.7). One Grade 4 AE, illicit drug overdose, that was reported in a subject in the SOF/VEL/VOX 12 week group was further specified to be combined heroin and fentanyl toxicity; the AE occurred 2 days after dosing was completed, was considered serious, not related to study drug, and led to death (Listings 16.2.7.3, 16.2.7.4 and 16.2.7.7). One additional, nontreatment-emergent Grade 4 AE, cerebral hemorrhage was reported in a subject in the SOF/VEL/VOX 12 week group; the AE occurred 133 days after dosing was completed, was considered serious, not related to study drug, and led to death (Listings 16.2.7.3, 16.2.7.4 and 16.2.7.7). Therefore, the number of subjects in the SOF/VEL/VOX 12 Week group who died increased from 1 subject to 2 subjects (Table 15.11.2.1.1 and Listing 16.2.7.7).

No additional treatment-emergent SAEs were reported (Listing 16.2.7.4). No additional treatment-emergent 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. The most common AEs (SOF/VEL/VOX 12 Week vs SOF/VEL 12 Week group) were headache (27.5% vs 28.5%), fatigue (23.6% vs 28.5%), diarrhea (19.8% vs 4.6%), and nausea (12.1% vs 7.9%) (Table 15.11.2.1.3).

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, and pulse) 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 Results:

Complete details on the QOL questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) through posttreatment Week 12 are reported in Section 12 of the interim CSR (10 November 2016). No notable differences were observed in the QOL 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 posttreatment Week 24 (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 QOL 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:

- Treatment with SOF/VEL/VOX resulted in an SVR12 rate of 97.8%, which was statistically superior to the performance goal of 85% at the pre-specified 0.025 significance level ($p < 0.001$), meeting the primary efficacy endpoint.
- Treatment with SOF/VEL for 12 weeks resulted in an SVR12 rate of 90.1%, which was not statistically superior to the performance goal of 85% at the pre-specified 0.025 significance level.
- The presence of NS3, NS5A, and NS5B NI RAVs at baseline did not impact the treatment outcome; no treatment-emergent RAVs were detected in the subject who relapsed in the SOF/VEL/VOX 12 Week group.
- The overall concordance between SVR12 and SVR24 was 100.0%. No subjects relapsed between posttreatment Weeks 12 and 24.
- Treatment with SOF/VEL/VOX or SOF/VEL for 12 weeks was generally well tolerated with similar incidence and severity of AEs. Few Grade 3 or 4 AEs, SAEs, deaths, or discontinuations due to AEs were reported, and no clinically meaningful laboratory abnormalities were observed.