FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir for 12 Weeks in Subjects with Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease
Name of Test Drug:	Sofosbuvir (SOF)/Velpatasvir (VEL) Fixed-Dose Combination (FDC)
Dose and Formulation:	SOF/VEL 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-342-4062
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	118605 2016-003625-42
ClinicalTrials.gov Identifier:	NCT03036852
Study Start Date:	22 March 2017 (First Subject Screened)
Study End Date:	13 August 2018 (Last Subject Last Observation for the Primary Endpoint) 07 November 2018 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Sergio Borgia, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Marianne Camargo, MD, MSCR Telephone: PPD Fax: PPD
Report Date:	21 February 2019
Previous Report Date(s):	28 November 2018 (Interim Clinical Study Report)

STUDY SYNOPSIS
Study GS-US-342-4062
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir for 12 Weeks in Subjects with Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 22 sites in Canada, the United Kingdom, Spain, Israel, New Zealand, and Australia.

Publications: Borgia SM, Dearden J, Lurie Y, Shafran SD, Brown A, Hyland RH, et al. Sofosbuvir/Velpatasvir for 12 Weeks Is Safe and Effective in Patients Undergoing Dialysis. American Association for the Study of Liver Diseases (AASLD); 2018 09-13 November; San Francisco, CA.

Study Period:
22 March 2017 (First Subject Screened)
13 August 2018 (Last Subject Last Observation for the Primary Endpoint)
07 November 2018 (Last Subject Last Observation for this Report)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To evaluate the antiviral efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL) 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 the treatment regimen

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attained sustained virologic response (SVR) at 4 and 24 weeks after cessation of the study treatment regimen (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating hepatitis C virus (HCV) RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment
- To evaluate the steady-state pharmacokinetics (PK) of SOF and its metabolites and VEL in subjects who are on dialysis for end-stage renal disease (ESRD)

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 with SOF/VEL on health-related quality of life in subjects on dialysis for ESRD

Methodology: This Phase 2, open-label, global, multicenter study assessed the antiviral efficacy, safety, and tolerability of SOF/VEL for 12 weeks in subjects on dialysis for ESRD with chronic HCV infection of any genotype.

Approximately 100 subjects were planned to be enrolled to receive SOF/VEL fixed-dose combination (FDC) (400/100 mg) once daily with or without food for 12 weeks.

All subjects were to complete the posttreatment Week 4 and 12 visits. Subjects who achieved SVR12 (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.

A single PK blood sample was collected from all subjects at the Week 2, 4, 6, 8, and 12 visits and the early termination visit, as applicable, to determine plasma concentrations of SOF, SOF metabolites GS-566500 and GS-331007, and VEL.

Subjects were eligible to participate in either or both of 2 PK substudies if consent was obtained; participation in the hemodialysis substudy was limited to those subjects who were undergoing hemodialysis. For the intensive PK substudy, serial PK blood samples were collected once at the Week 6, 8, or 12 visit to determine the PK of SOF, SOF metabolites GS-566500 and GS-331007, and VEL. For the hemodialysis PK substudy, blood samples were collected at 1 hemodialysis session between Week 6 and 12, inclusive, to determine the plasma concentrations of SOF, SOF metabolites GS-566500 and GS-331007, and VEL, and to estimate the hemodialysis extraction ratio. Subjects who provided specific, additional informed consent may have provided blood samples for future biomarker and/or pharmacogenomics research.

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 who achieved SVR12 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 (28 November 2018).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 100 subjects
Analyzed: 59 subjects

- Enrolled Analysis Set: 59 subjects
- Full Analysis Set (FAS): 59 subjects
- Safety Analysis Set: 59 subjects

- PK Analysis Set: 59 subjects
  - Intensive PK Substudy Analysis Set: 1 subject
  - Hemodialysis PK Substudy Analysis Set: 2 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females of ≥ 18 years of age with chronic HCV infection with ESRD requiring peritoneal dialysis or hemodialysis. Subjects could be coinfected with HIV if they were suppressed on a stable, protocol-approved antiretroviral regimen for ≥ 8 weeks prior to screening.

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

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

SOF/VEL FDC (1 × 400/100 mg tablet) was administered by mouth once daily with or without food for 12 weeks.

The batch numbers of SOF/VEL FDC tablets administered in this study were DU1501B1 and DU1508B1.

Reference Therapy, Dose, Mode of Administration, and Batch 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 (28 November 2018). The COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The LLOQ of the assay was 15 IU/mL.

Virology: Baseline deep sequencing analysis of HCV nonstructural (NS)5A 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 (28 November 2018) provided population PK analyses of SOF, SOF metabolites GS-566500 and GS-331007, and VEL. Data were also provided for subjects who consented to participate in the hemodialysis PK substudy. No additional PK analyses were performed between the interim and the final study analyses.

Safety: The interim CSR (28 November 2018) provided analyses of adverse events (AEs), concomitant medications, clinical laboratory analyses, vital signs measurements, 12-lead 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 and final CSRs. 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 (28 November 2018) provided analyses of the quality of life questionnaires (Short Form-36 Health Survey [SF-36], Chronic Liver Disease Questionnaire-HCV [CLDQ-HCV], the Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F] questionnaire, and the Work Productivity and Activity Impairment: Hepatitis C [WPAI: Hep C] questionnaire) to assess the effect of treatment on health-related quality of life. This final synoptic CSR summarizes any changes to previously reported data between the data cuts for the interim and final CSRs.

Statistical Methods:

All tables, figures, and listings produced for this report 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 (28 November 2018).

Efficacy: The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after cessation of treatment, in the FAS. The SVR12 rate in each HCV genotype was calculated along with the 2-sided 95% exact CI based on the Clopper-Pearson method. The point estimates and 95% CIs of the SVR12 rates were displayed by genotype for key demographic and baseline characteristic subgroups. A Forest plot graphically presented estimates and 95% CIs in SVR12 rates for each of the subgroups.

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.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum). 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: Population PK models for SOF, GS-331007 and VEL, previously developed for the Phase 2/3 SOF/VEL United States new drug application population analyses, were applied to the data from all PK samples collected in this study. Details of the population PK analysis are provided in a separate population PK analysis plan.

The systemic concentration of study drug prior to and immediately following hemodialysis was summarized using descriptive summary statistics (sample size, mean, SD, coefficient of variation [%CV], median, Q1, Q3, minimum, maximum). For concentration values below the limit of quantitation (BLQ), the number of subjects with values of BLQ was presented.

In the Hemodialysis PK Substudy Analysis Set, estimates of the hemodialysis extraction ratio were summarized. In addition, a sensitivity analysis was conducted for the summary of hemodialysis extraction ratio by excluding negative hemodialysis extraction ratio values.

Safety: All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety data included all data collected on or after the first dose of 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 21.1.

Quality of Life: The health-related quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) were completed by subjects. 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: All 59 enrolled subjects received at least 1 dose of study drug and were included in the Safety Analysis Set and FAS. All but 1 subject completed study treatment (98.3%, 58 subjects). The 1 subject (1.7%) prematurely discontinued study treatment due to noncompliance with study drug (Table 15.8.1.2).

No 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 changes to concomitant medications and medical history that did not change the interpretation of the study results (Tables 15.8.3.3 and 15.11.7.4 and Listings 16.2.4.3.1 and 16.2.4.4). Analyses related to disposition, demographics, and exposure are presented in Tables 15.8.1.1 to 15.8.4, and 15.11.1; Figure 15.8.1; and Listings 16.2.1.1 to 16.2.5.2. An Important Protocol Deviations Log for the study is provided in Appendix 16.2.2. No additional important protocol deviations were reported between the interim and the final analyses.

Efficacy Results: Analysis of the primary efficacy endpoint is reported in Section 9 of the interim CSR (28 November 2018). Overall, 94.9% (95% CI: 85.9% to 98.9%) of subjects (56 of 59) achieved SVR12 (Table 15.9.1). One treatment-experienced subject, with genotype 3a HCV infection and cirrhosis, had relapse determined at posttreatment Week 4. One treatment-naive subject, with genotype 1b HCV infection without cirrhosis, had prematurely discontinued study drug after 11 weeks of treatment. This subject had 47.6% study drug adherence as measured by tablet counts and had low plasma concentrations of GS-331007 (the predominant SOF metabolite) and VEL at Weeks 8 and 12, consistent with noncompliance (Listings 16.2.5.3 and 16.2.6.2). One treatment-experienced subject, with genotype 1a HCV infection without cirrhosis, died of suicide between the posttreatment Week 4 and Week 12 visits (Listing 16.2.6.3). Of the 3 subjects who did not achieve SVR12, only 1 had completed treatment and then relapsed, precluding meaningful subgroup analyses.

The proportion of subjects with SVR4, SVR12, and SVR24 is presented in the table below. No subjects relapsed between posttreatment Weeks 12 and 24 (Listing 16.2.6.4).

	SOF/VEL 12 Weeks (N = 59)
SVR4	57/59 (96.6%)
95% CI	88.3% to 99.6%
SVR12	56/59 (94.9%)
95% CI	85.9% to 98.9%
SVR24	56/59 (94.9%)
95% CI	85.9% to 98.9%

HCV RNA was analyzed using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with a 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 was bracketed by values that were 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 15.9.2.3

The SVR12 rates reported in the interim analysis were maintained in the SVR24 analysis, with a 100% concordance between SVR12 and SVR24.

	SOF/VEL 12 Weeks SVR24	
	Yes (N = 52)	No (N = 0)
SVR12		
Yes	52	0
No	0	0
Positive predictive value	100%	

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 15.9.2.4

All efficacy analyses are provided in Tables 15.9.1 to 15.9.4.3, Figures 15.9.2.3 to 15.9.2.5.4, and Listings 16.2.6.1 to 16.2.6.4.

Virology Results: Full details regarding virologic resistance were reported in the interim CSR (28 November 2018). No additional resistance analyses were performed for this report since no subjects relapsed between posttreatment Week 12 and posttreatment Week 24.

Pharmacokinetics Results: Full details regarding PK assessments were provided in Section 10 of the interim CSR (28 November 2018). No additional PK analyses were performed between the interim and the final study analyses. All PK analyses are provided in Tables 15.10.1.1 to 15.10.1.5 and Listings 16.2.5.3 and 16.2.5.4.

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 drug were discussed in detail in Section 11 of the interim CSR (28 November 2018).

Coding of AEs for this report was performed using MedDRA Version 21.1, while Version 21.0 was used for the interim CSR. One change to a previously reported AE term resulted in a change to the preferred term from respiratory tract infection to lower respiratory tract infection viral. There were no other changes to AE data other than resolution dates between SVR12 and SVR24 (Listing 16.2.7.7).

No additional SAEs were reported between the data cuts taken at the posttreatment Week 12 and posttreatment Week 24 time points (Listing 16.2.7.4). Narratives for treatment-emergent SAEs and all deaths from the first dose of study drug through the end of the study are provided in Section 15.2. There were no SAEs or AEs that led to discontinuation or interruption of study drug from the first dose of study drug through the end of the study (Listings 16.2.7.5 and 16.2.7.6). No subject pregnancies were reported in this study (Listing 16.2.8.3).

All AE results for the study 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.

Safety-related clinical laboratory analyses up to the posttreatment Week 4 visit (up to 30 days after last dose) are discussed in Section 11.7 of the interim CSR (28 November 2018). No clinically meaningful changes in clinical laboratory results were observed between the interim and final analyses (Tables 15.11.6.1.1 to 15.11.6.3, Figures 15.11.6.1 to 15.11.6.11, and Listings 16.2.8.1.3 to 16.2.8.1.7.2).

Vital sign measurements (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) and ECG results up to the posttreatment Week 4 visit (up to 30 days after last dose) are discussed in Section 11.8 of the interim CSR (28 November 2018). No clinically meaningful changes in vital sign measurements or ECGs were observed between the interim and final analyses (Tables 15.11.7.1 to 15.11.7.3 and Listings 16.2.8.2.1 to 16.2.8.2.3).

Quality of Life Results: Full details on the quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) through posttreatment Week 12 were reported in Section 12 of the interim CSR (28 November 2018). No differences were observed in the quality of life questionnaire results between the interim and final analyses (Tables 15.12.1 to 15.12.4, Figures 15.12.1 to 15.12.4, and Listings 16.2.6.5 to 16.2.6.8).

Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C questionnaires indicated that quality of life parameters improved during treatment with SOF/VEL for 12 weeks in HCV-infected subjects with ESRD undergoing dialysis. The mean scores for most scales continued to improve from EOT to posttreatment Week 12. 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 conclusions from this study are as follows:

- Treatment with SOF/VEL for 12 weeks in subjects on dialysis for ESRD with HCV genotype 1 to 6 resulted in an SVR12 rate of 94.9%.
- The overall concordance between SVR12 and SVR24 was 100%. No subjects relapsed between posttreatment Weeks 12 and 24.
- NS5A and NS5B resistance-associated variants did not emerge in any subjects with virologic failure.
- The steady state exposures of SOF, GS-331007, and VEL were consistent with those observed in the dedicated Phase 1 renal impairment studies, as reflected in the Epclusa® (SOF/VEL) prescribing information.
- SOF/VEL once daily for 12 weeks was safe and well tolerated in HCV-infected subjects with ESRD undergoing dialysis. The AE and laboratory safety profile observed was consistent with that expected for HCV-infected subjects with ESRD undergoing dialysis. No new safety signals or toxicities were observed.