FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Ledipasvir/Sofosbuvir in Subjects with Genotype 1, 4, 5 and 6 Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease
Name of Test Drug:	Ledipasvir (LDV)/Sofosbuvir (SOF) Fixed Dose Combination (FDC)
Dose and Formulation:	LDV/SOF FDC (90/400 mg) tablet
Indication:	Hepatitis C Virus Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-337-4063
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	115268 2016-003489-25
ClinicalTrials.gov Identifier:	NCT03036839
Study Start Date:	27 June 2017 (First Subject Screened)
Study End Date:	22 November 2018 (Last Subject Last Observation for the Primary Endpoint) 14 February 2019 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Wan-Long Chuang, MD, PhD Affiliation: PPD
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Report Date:	14 May 2019
Previous Report Date:	10 December 2018

STUDY SYNOPSIS

Study GS-US-337-4063
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 Ledipasvir/Sofosbuvir in Subjects with Genotype 1, 4, 5 and 6 Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease

Investigators: Multicenter study

Study Centers: Subjects were enrolled across 21 sites in Taiwan, Italy, Germany, the United States, and Belgium.

Publications: Chuang W-L, Hu T-H, Buggisch P, et al. Ledipasvir/sofosbuvir for 8, 12, or 24 weeks is safe and effective in patients undergoing dialysis. J Hepatol 2019;70 (Suppl 1S):e225.

Study Period:

27 June 2017 (First Subject Screened)
22 November 2018 (Last Subject Last Observation for the Primary Endpoint)
14 February 2019 (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 ledipasvir/sofosbuvir (LDV/SOF) for 8, 12, or 24 weeks in subjects with chronic hepatitis C virus (HCV) infection who are on dialysis for end stage renal disease (ESRD), 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 attained SVR at 4 and 24 weeks after cessation of each study treatment regimen (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 LDV and SOF during treatment and after cessation of treatment

- To evaluate the steady-state pharmacokinetics (PK) of LDV and SOF and its metabolites in subjects who are on dialysis for 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 LDV/SOF on health-related quality of life in subjects on dialysis for ESRD

Methodology: This Phase 2, open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of 8, 12, or 24 weeks of LDV/SOF treatment in subjects with genotype 1, 2 (Taiwan only), 4, 5, or 6 HCV infection who were on dialysis for ESRD.

Approximately 100 subjects were planned to receive LDV/SOF fixed-dose combination (FDC) (90/400 mg) once daily with or without food for 8, 12, or 24 weeks, according to the following treatment group assignment:

Group 1: Treatment-naive genotype 1 subjects without cirrhosis were treated with LDV/SOF for 8 weeks

Group 2: Treatment-experienced genotype 1 subjects and treatment-naive or treatment-experienced genotype 2 (Taiwan only), 4, 5, and 6 subjects without cirrhosis were treated with LDV/SOF for 12 weeks

Group 3: Subjects with compensated cirrhosis were treated with LDV/SOF for 24 weeks

All subjects were to complete the posttreatment Week 4 and Week 12 visits regardless of their treatment duration. Subjects who achieved SVR12 were to complete the posttreatment Week 24 visit.

Subjects who provided separate and specific consent were eligible for participation in any or all of the following substudies:

- Intensive PK Substudy (target n=15): serial blood samples collected once at the Week 6, 8, or 12 (if applicable) on-treatment visit
- Hemodialysis PK Substudy (target n=10): blood samples collected within 10 minutes before initiation and approximately 1 hour before and within 10 minutes after conclusion of 1 hemodialysis session between Week 6 and Week 12, inclusive (as appropriate based on treatment regimen)
- Pharmacogenomics Substudy: blood sample collected at the baseline/Day 1 visit or at any time during the study

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 (10 December 2018).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 100 subjects
Analyzed: 95 subjects

- Enrolled Analysis Set: 95 subjects overall
  - Group 1 (8-week treatment group): 45 subjects
  - Group 2 (12-week treatment group): 31 subjects
  - Group 3 (24-week treatment group): 19 subjects
- All subjects from the Enrolled Analysis Set were also included in the Safety Analysis and Full Analysis Sets.
- PK Analysis Set: 94 subjects
  - Intensive PK Substudy Analysis Set: 2 subjects
  - Hemodialysis PK Substudy Analysis Set: 8 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/ nonlactating females ≥ 18 years of age, with chronic genotype 1, 2 (Taiwan only), 4, 5, or 6 HCV infection who were undergoing dialysis for ESRD; including subjects with HIV coinfection if they were suppressed on a stable, protocol-approved antiretroviral regimen for ≥ 8 weeks prior to screening.

Duration of Treatment: Treatment duration was 8, 12, and 24 weeks for Groups 1, 2, and 3, respectively, with up to 24 weeks of posttreatment follow-up for all groups.

Test Product, Dose, Mode of Administration, and Batch No.: LDV/SOF (1 × 90/400-mg tablet) was administered by mouth once daily with or without food for 8, 12, or 24 weeks.

The batch number of LDV/SOF administered in this study was DK1309B1.

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 as well as an update to the SVR12 data reported in the interim CSR. Efficacy analyses at all other scheduled assessment time points were described in the interim CSR (10 December 2018). The COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Virology: Baseline deep sequencing analysis of HCV nonstructural protein (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 were reported at a 15% assay cutoff.

Pharmacokinetics The interim CSR (10 December 2018) provided population PK analyses of LDV, SOF, and SOF metabolites GS-566500 and GS-331007. 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 final study analyses.

Safety: The interim CSR (10 December 2018) provided analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital signs 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 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 (10 December 2018) provided analyses of the quality of life questionnaires (Short Form-36 Health Survey [SF-36], Chronic Liver Disease Questionnaire-HCV [CLDQ-HCV], Functional Assessment of Chronic Illness Therapy-Fatigue Index [FACIT-F], and Work Productivity and Activity Impairment: Hepatitis C [WPAI: Hepatitis C]) 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 (10 December 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 Full Analysis Set. The SVR12 rate in each HCV genotype was calculated along with the 2-sided 95% exact confidence interval (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 was used to graphically present 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 LDV/SOF.

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

The 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 between SVR12 and SVR24 was performed for

subjects with an observed HCV RNA value within both the posttreatment Week 12 and 24 visit windows.

Pharmacokinetics: Population PK models for SOF, GS-331007, and LDV (previously developed for the Phase 2/3 LDV/SOF US 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 plasma 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 the posttreatment Week 12 time point.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: All 95 enrolled subjects received at least 1 dose of study drug and were included in the Safety and Full Analysis Sets. The majority of subjects (95.8%, 91 subjects) completed study treatment. Of the 95 enrolled and treated subjects, 4 subjects (4.2%) prematurely discontinued study treatment due to death. Of these, 3 were subjects with cirrhosis (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 exposures 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. A revision was made to the log provided in the interim report to correct a site and subject number from PPD to PPD. No new important protocol deviations were reported between the interim and final analyses.

Efficacy Results: Analysis of the primary efficacy endpoint (SVR12) is reported in Section 9 of the interim CSR (10 December 2018). The SVR12 rates reported in the interim analysis were revised for this final CSR to include Subject PPD (Group 3) who had discontinued the study between the posttreatment Week 4 and 12 visits due to an AE. This subject was able to

provide a sample for HCV RNA testing (within the subject's SVR12 visit window) after the data cutoff for the interim CSR. The sample was analyzed by the site's local lab using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 and was reported by the site in the General Comment eCRF (Listing 16.2.8.4).

For this final CSR, the SVR12 rates for Groups 1 and 2 were unchanged from those reported in the interim CSR. For Group 3, the SVR12 rate was revised from 78.9% (95% CI: 54.4% to 93.9%) to 84.2% (95% CI: 60.4% to 96.6%). The overall SVR12 rate was revised from 92.6% (95% CI: 85.4% to 97.0%) to 93.7% (95% CI: 86.8% to 97.6%) (Table 15.9.1). A total of 6 of 95 subjects (6.3%) did not achieve SVR12, all due to death (Listing 16.2.6.3). No subject had virologic failure (Table 15.9.2.1).

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

	Overall (N = 95)	**LDV/SOF 8 Weeks/Group 1 (N = 45)**	**LDV/SOF 12 Weeks/Group 2 (N = 31)**	**LDV/SOF 24 Weeks/Group 3 (N = 19)**
SVR4	91/95 (95.8%)	44/45 (97.8%)	31/31 (100.0%)	16/19 (84.2%)
95% CI	89.6% to 98.8%	88.2% to 99.9%	88.8% to 100.0%	60.4% to 96.6%
SVR12	89/95 (93.7%)	42/45 (93.3%)	31/31 (100.0%)	16/19 (84.2%)
95% CI	86.8% to 97.6%	81.7% to 98.6%	88.8% to 100.0%	60.4% to 96.6%
SVR24	89/95 (93.7%)	42/45 (93.3%)	31/31 (100.0%)	16/19 (84.2%)
95% CI	86.8% to 97.6%	81.7% to 98.6%	88.8% to 100.0%	60.4% to 96.6%

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

There was 100% concordance between SVR12 and SVR24 across treatment groups, as shown in the table below.

	Overall SVR24		**LDV/SOF 8 Weeks SVR24**		**LDV/SOF 12 Weeks SVR24**		**LDV/SOF 24 Weeks SVR24**	
	Yes (N=87)	**No (N=0)**	**Yes (N=42)**	**No (N=0)**	**Yes (N=31)**	**No (N=0)**	**Yes (N=14)**	**No (N=0)**
SVR12								
Yes	87	0	42	0	31	0	14	0
No	0	0	0	0	0	0	0	0
Positive predictive value	100%	—	100%	—	100%	—	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 (10 December 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 (10 December 2018). No additional PK analyses were performed between the interim and final study analyses. All PK analyses are provided in Tables 15.10.1.1 to 15.10.1.6 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 (10 December 2018).

Changes to AE data other than resolution dates between the interim and final analyses are provided in Listing 16.2.7.7. There were a few minor changes to reported and preferred terms and onset dates. No new treatment-emergent AEs were reported. Three new nontreatment-emergent SAEs were reported for 2 subjects:

- Subject PPD (LDV/SOF 24 Weeks) had Grade 2 events of worsening renal hyperparathyroidism and parathyroid hyperplasia on posttreatment Day 92, which resolved on posttreatment Day 160.
- Subject PPD (LDV/SOF 24 Weeks) had a Grade 2 event of cholangitis on posttreatment Day 84, which resolved on posttreatment Day 93. None of these events were considered by the investigator to be related to study treatment.

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. During this time, there were no AEs or SAEs that led to premature discontinuation of study drug (Listing 16.2.7.5). 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 the last dose) are discussed in Section 11.7 of the interim CSR (10 December 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 the last dose) are discussed in Section 11.8 of the interim CSR (10 December 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 (10 December 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 mean values for most parameters either showed improvement or did not significantly change from baseline to EOT and from baseline to posttreatment Week 12. All 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 final analysis of Study GS-US-337-4063 are as follows:

- Treatment with LDV/SOF for 8 weeks in subjects with HCV genotype 1 who were treatment-naive, without cirrhosis, and on dialysis for ESRD resulted in an SVR12 rate of 93.3%.
- Treatment with LDV/SOF for 12 weeks in subjects with HCV who were treatment-naive (genotype 2, 4, 5, or 6) or treatment-experienced (genotype 1, 2, 4, 5, or 6), without cirrhosis, and on dialysis for ESRD resulted in an SVR12 rate of 100.0%.
- Treatment with LDV/SOF for 24 weeks in subjects with HCV genotype 1, 2, 4, 5, or 6 who were treatment-naive or treatment-experienced, cirrhotic, and on dialysis for ESRD resulted in an SVR12 rate of 84.2% (revised from 78.9% at the interim analysis).
- The overall concordance between SVR12 and SVR24 was 100%. No subjects relapsed between posttreatment Weeks 12 and 24.
- Baseline NS5A and NS5B nucleoside inhibitor resistance associated variants did not have any impact on treatment response in treatment-naive or treatment-experienced subjects on dialysis for ESRD. There were no virologic failures.
- LDV/SOF once daily for 8, 12, or 24 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.