FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Randomized, Open-Label Study of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin in Subjects with Chronic Genotype 1 HCV Infection
Name of Test Drug:	Ledipasvir/Sofosbuvir Fixed-Dose Combination
Dose and Formulation:	Ledipasvir/Sofosbuvir FDC (90 mg/400 mg) Tablet
Indication:	Hepatitis C Virus Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-337-0118 (LONESTAR)
Phase of Development:	Phase 2
IND No.:	115268
EudraCT No.:	Not Applicable
Study Start Date:	22 October 2012 (First Subject Screened)
Study End Date:	13 January 2014 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Eric J. Lawitz, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Philip S. Pang, MD, PhD Telephone: PPD Fax: PPD
Report Date:	14 March 2014
Previous Report Date(s):	05 March 2014 (Interim Clinical Study Report Errata); 18 September 2013 (Interim Clinical Study Report)

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

Title of Study: A Phase 2, Randomized, Open-Label Study of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin in Subjects with Chronic Genotype 1 HCV Infection

Investigators: Eric J. Lawitz, MD

Study Centers: One site in the United States (San Antonio, TX)

Publications:

Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014;383 (9916):515-23.

Lawitz E, Poordad F, Hyland R, Ding X, Hebner C, Pang PS, et al. Once Daily Sofosbuvir/Ledipasvir Fixed Dose Combination with or without Ribavirin Resulted in ≥95% Sustained Virologic Response In Patients with HCV Genotype 1, Including Patients with Cirrhosis: the LONESTAR trial [Abstract 215]. Hepatology AASLD Abstracts 2013;58 (4):315A-6A.

Study Period:

22 October 2012 (First subject screened)
13 January 2014 (Last subject observation)

Phase of Development: Phase 2

Objectives:

The primary objective of this study were as follows:

- To evaluate the antiviral efficacy of combination therapy with ledipasvir/sofosbuvir (LDV/SOF; formerly SOF/LDV) fixed-dose combination (FDC) ± ribavirin (RBV) for 8 or 12 weeks in treatment-naive subjects and for 12 weeks in subjects who had previously received a protease-inhibitor (PI)-containing regimen, as measured by sustained virologic response at 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of LDV/SOF FDC ± RBV administered for 8 or 12 weeks as assessed by review of the accumulated safety data

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attain sustained virologic response at 2, 4, 8, and 24 weeks after discontinuation of therapy (SVR2, SVR4, SVR8, and SVR24)

- To evaluate the emergence of viral resistance to SOF and LDV during and after treatment discontinuation
- To characterize viral dynamics during and after treatment discontinuation
- To characterize steady-state pharmacokinetics (PK) of study drugs

The exploratory objective of this study was as follows:

- To identify or validate genetic markers that may be predictive of the natural history of disease, virologic response to therapy, and/or the tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics) in subjects who provide a separate and specific consent

Methodology: This Phase 2, randomized, open-label study assessed the safety, tolerability, and antiviral efficacy of LDV/SOF±RBV for 8 or 12 weeks. The study had 2 parallel cohorts: Cohort 1 consisted of noncirrhotic treatment-naive subjects (3 treatment groups) and Cohort 2 consisted of cirrhotic and noncirrhotic treatment-experienced subjects (2 treatment groups).

In Cohort 1, noncirrhotic treatment-naive subjects were randomized (1:1:1) to 1 of the following 3 treatment groups:

- **LDV/SOF 8 Week TN group (Group 1):** LDV/SOF 90 mg/400 mg (1 tablet) once daily for 8 weeks in treatment-naive subjects
- **LDV/SOF+RBV 8 Week TN group (Group 2):** LDV/SOF 90 mg/400 mg (1 tablet) once daily + RBV total daily dose of 1000 mg for subjects weighing < 75 kg (5 × 200-mg tablets) or 1200 mg for subjects weighing ≥ 75 kg (6 × 200-mg tablets) administered in a divided dose twice daily (BID) for 8 weeks in treatment-naive subjects
- **LDV/SOF 12 Week TN group (Group 3):** LDV/SOF 90 mg/400 mg (1 tablet) once daily for 12 weeks in treatment-naive subjects

In Cohort 2, cirrhotic and noncirrhotic treatment-experienced subjects were randomized (1:1) to 1 of the following 2 treatment groups:

- **LDV/SOF 12 Week TE group (Group 4):** LDV/SOF 90 mg/400 mg (1 tablet) once daily for 12 weeks in treatment-experienced subjects
- **LDV/SOF+RBV 12 Week TE group (Group 5):** LDV/SOF 90 mg/400 mg (1 tablet) once daily + RBV total daily dose of 1000 mg for subjects weighing < 75 kg (5 × 200-mg tablets) or 1200 mg for subjects weighing ≥ 75 kg (6 × 200-mg tablets) administered in a divided BID for 12 weeks in treatment-experienced subjects

Randomization was stratified by genotype (1a or 1b) in Cohort 1 and by genotype (1a or 1b) and the presence or absence of cirrhosis in Cohort 2. Enrollment into Cohort 2 was managed so that approximately 50% of the randomized subjects had cirrhosis. The treatment duration was 8 or 12 weeks. All subjects were required to complete posttreatment Week 2, 4, 8, and 12 visits regardless of their treatment duration. Subjects with hepatitis C virus (HCV) RNA < lower limit of quantitation (LLOQ) at the posttreatment Week 12 visit completed a posttreatment Week 24 visit unless viral relapse was determined. The end of study occurred at the posttreatment Week 24 visit. Subjects randomized to the 8-week treatment groups who experienced posttreatment virology failure were offered LDV/SOF+RBV for 24 weeks as rescue treatment

within the study.

After completing the current study, eligible subjects may have enrolled into 1 of 2 follow-on studies: the SVR Registry Study (Study GS-US-248-0122) or the Sequence Registry Study (Study GS-US-248-0123).

Number of Subjects (Planned and Analyzed):
Planned: 100 subjects (20 in each of the 5 treatment groups)
Analyzed: 100 subjects (20 in the LDV/SOF 8 Week TN group, 21 in the LDV/SOF+RBV 8 Week TN group, 19 in the LDV/SOF 12 Week TN group, 19 in the LDV/SOF 12 Week TE group, and 21 in the LDV/SOF+RBV 12 Week TE group)

Diagnosis and Main Criteria for Inclusion: Male and nonpregnant female subjects ≥ 18 years of age with chronic genotype 1 HCV infection and screening HCV RNA levels ≥ 10^4 IU/mL were enrolled. Subjects in Cohort 1 had no prior exposure to any interferon, RBV, or other approved or experimental HCV therapy and had documentation of absence of cirrhosis. Subjects in Cohort 2 had previously experienced virologic failure with an approved or investigational PI + pegylated interferon + RBV regimen and had documentation of the presence or absence of cirrhosis. All subjects had a body mass index ≥ 18 kg/m^2.

Duration of Treatment: The total time to complete all study visits was up to 42 weeks for subjects who did not require rescue treatment, including the following periods:

- Up to a 6-week screening period
- An 8- or 12-week treatment period
- Up to a 24-week posttreatment period

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

- **LDV/SOF** was administered orally at a dose of 90 mg/400 mg (1 tablet).
- **RBV** was administered orally at a total daily dose of 1000 or 1200 mg/day divided BID (5 or 6 × 200-mg tablets in a divided daily dose).

The lot numbers of study drugs administered in this study are provided in the interim clinical study report (CSR).

Criteria for Evaluation:

Efficacy: This CSR provides analyses of HCV RNA levels at posttreatment Week 24. The COBAS® TaqMan® HCV Test v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study.

Pharmacokinetics: The interim CSR describes details on collection of blood samples for PK analyses.

Safety: The interim CSR provides analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, physical examinations, vital signs measurements, and 12-lead electrocardiograms (ECGs). This final synoptic CSR summarizes any new treatment-emergent AEs or changes to previously reported treatment-emergent 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.

Statistical Methods:

All tables and 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.

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the full analysis set. The primary efficacy endpoint analysis was calculated for each treatment group along with the 2-sided 95% confidence interval (CI) based on the Clopper-Pearson method. No statistical hypothesis tests were performed. Point estimates and 95% exact CIs for the SVR12 rates were constructed for each demographic and baseline characteristic subgroup using the same methods described above.

SVR24 rates were calculated using the same method as described for SVR12. In addition, an ad hoc analysis to assess the concordance of SVR12 with SVR24 was performed.

Pharmacokinetics: 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 on-treatment visit. Results for all PK analyses are presented in the interim CSR. In addition, a population PK model was developed to characterize the PK of LDV, SOF, and SOF's major metabolite GS-331007. Results for all PK analyses are presented in separate Population Pharmacokinetics Reports.

Safety: All randomized 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, and physical examinations. Safety data were analyzed by treatment group and included all data collected on or after the first dose of study drug through the date of the last dose of study drug plus 30 days except for subjects who required rescue treatment for whom data were censored at the time that new therapy was started. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0.

SUMMARY – RESULTS:

Subject Disposition and Demographic Results:

A total of 100 randomized subjects received treatment in this study and all subjects were included in the full analysis set (Section 15.1, Table 3). Full details on subject disposition are reported in Section 8 of the interim CSR and subject disposition at posttreatment Week 24 is summarized in Section 15.1, Table 3.

No differences in demographic or baseline disease characteristics were observed between the interim analyses and the final analyses (Section 15.1, Table 4 and Appendix 16.2, Listing 4.1). There were a small number of additions and changes to concomitant medications which did not change the interpretation of the study (Section 15.1, Table 6 and Appendix 16.2, Listing 7.1). Full details on demographic and baseline disease characteristics are reported in Section 8 of the

interim CSR.

Two important protocol deviations based on not meeting an inclusion criterion were added to the clinical database following data finalization for the SVR12 analysis: 1 subject had mixed genotype 1a and 1b HCV infection (violation of inclusion criterion 6) and 1 had an exclusionary direct bilirubin value (violation of inclusion criterion 10) (Section 15.1, Table 3.1 and Appendix 16.2, Listing 2.2). Of note, further viral sequencing showed the subject with mixed genotype 1a and 1b HCV infection to have genotype 1a HCV infection (Appendix 16.2, Virology Listing 1 GS-US-337-0118).

Subject PPD a treatment-naive noncirrhotic subject with genotype 1a HCV infection who had relapsed following LDV/SOF treatment for 8 weeks, received rescue treatment with LDV/SOF+RBV for 24 weeks (Appendix 16.2, Listings 8.2 and 6.2). This subject completed study rescue treatment.

Analyses related to disposition, demographics, and exposure are presented in Section 15.1, Tables 1 through 7 and Figure 1 and Appendix 16.2, Listings 1 through 7.2. The Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

Efficacy Results:

Analysis of the primary efficacy endpoint is reported in Section 9 of the interim CSR. Results for SVR24, a secondary efficacy endpoint, are summarized in this final CSR.

The proportion of subjects with SVR12 and SVR24 is presented in the table below. The SVR12 and SVR24 rates were the same for all treatment groups, with a 100% positive predictive value between SVR12 and SVR24 (Section 15.1, Table 8 and Adhoc Table 1 and Appendix 16.2, Listing 8.1).

	Treatment-Naive			Treatment-Experienced	
	Group 1	Group 2	Group 3	Group 4	Group 5
	LDV/SOF 8 Weeks (N = 20)	LDV/SOF+RBV 8 Weeks (N = 21)	LDV/SOF 12 Weeks (N = 19)	LDV/SOF 12 Weeks (N = 19)	LDV/SOF+RBV 12 Weeks (N = 21)
SVR12	19/20 (95.0%)	21/21 (100.0%)	18/19 (94.7%)	18/19 (94.7%)	21/21 (100.0%)
95% CI	75.1% to 99.9%	83.9% to 100.0%	74.0% to 99.9%	74.0% to 99.9%	83.9% to 100.0%
SVR24	19/20 (95.0%)	21/21 (100.0%)	18/19 (94.7%)	18/19 (94.7%)	21/21 (100.0%)
95% CI	75.1% to 99.9%	83.9% to 100.0%	74.0% to 99.9%	74.0% to 99.9%	83.9% to 100.0%

TND = Target not detected.
Note: HCV RNA was analyzed using Roche TaqMan V 2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL.
Note: A missing SVR12 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 SVR12 value was imputed as a failure.
Note: The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Section 15.1, Table 10

Three subjects did not achieve SVR12 or SVR24: 1 withdrew consent before the posttreatment Week 12 visit and 2 relapsed. Subject PPD relapsed following initial treatment with LDV/SOF for 8 weeks (Appendix 16.2, Listing 8.1). Subsequently, this subject completed the rescue treatment of LDV/SOF+RBV for 24 weeks and achieved SVR24. Subject PPD who had received LDV/SOF for 12 weeks, withdrew consent and did not complete study

treatment (Appendix 16.2, Listing 3). This subject had HCV RNA < LLOQ, target not detected (TND) on posttreatment Day 66 (SVR8), but did not complete a posttreatment Week 12 visit and was considered a virologic failure due to lost to follow-up (Appendix 16.2, Listing 8.3). Subject PPD who had received LDV/SOF for 12 weeks, relapsed on posttreatment Day 17 after completing study treatment (Appendix 16.2, Listings 3 and 8.2).

No subjects relapsed between posttreatment Week 12 and 24, and all subjects who had achieved SVR12 also achieved SVR24 (Section 15.1, Adhoc Table 1 and Appendix 16.2, Listings 8.1 and 8.5).

All efficacy analyses are provided in the Section 15.1, Tables 8 through 15 and Figures 2 through 3.4 and Appendix 16.2, Listings 8.1 through 8.3 and 8.5.

Full details on the resistance analysis are reported in Section 9.2.5 of the interim CSR. No additional resistance analyses were performed since no subjects relapsed during the posttreatment Week 12 through Week 24.

Pharmacokinetics Results:

Full details on the PK analysis are reported in Section 10 of the interim CSR.

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.

AEs and SAEs

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 were associated with AE resolution dates (Appendix 16.2, Listing 9 and Adhoc Listing 6467). These changes did not impact the overall interpretation or conclusions of the safety profile of LDV+SOF with or without RBV in this study.

No additional nontreatment-emergent SAEs were reported (Appendix 16.2, Listing 12). Narratives for all SAEs from the first dose of study drug through the end of the study (ie, SVR24 visit) are provided in Section 15.2. No subject pregnancies or deaths were reported in this study (Appendix 16.2, Listings 13 and 14).

Subject PPD had no AEs during the rescue treatment with LDV/SOF+RBV for 24 weeks (Appendix 16.2, Listing 9).

All AE results are provided in Section15.1, Tables 16 through 30 and Appendix 16.2, Listings 9 through 12.

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

(Section 15.1, Tables 31.1 through 34 and Appendix 16.2, Listings 15 through 21.2).

Subject PPD had no Grade 3 or 4 laboratory abnormalities during the rescue treatment with LDV/SOF+RBV for 24 weeks (Appendix 16.2, Listing 10).

All laboratory results are provided in Section 15.1, Tables 31.1 through 34 and Figures 4.1 through 4.10 and Appendix 16.2, Listings 15 through 21.2.

Vital Sign Measurements and ECGs

Vital sign measurements (systolic and diastolic blood pressure and pulse) and height and weight were collected at the posttreatment Week 24 visit. No clinically meaningful changes in the vital sign measurements or height and weight were observed at the posttreatment Week 24 (Section 15.1, Tables 35.1 through 35.3 and Appendix 16.2, Listing 23).

All vital sign measurement and ECG results are provided in Section 15.1, Tables 35.1 through 35.3 and Appendix 16.2, Listings 22 and 23.

Special Situations

Special situations including medication error, misuse, overdose, and product complaints with associated AEs were collected during the study; no new safety concerns were identified from reports of special situations.

CONCLUSIONS:

The overall conclusions from this study are as follows:

- In treatment-naive subjects, high rates of SVR12 were achieved in all treatment groups, irrespective of treatment duration or the addition of RBV.
- Prior treatment failure with a PI-based regimen, the presence of cirrhosis, or the presence or absence of RBV had no significant impact on SVR12 rates.
- Potent and rapid suppression of HCV RNA was observed in all groups, irrespective of prior HCV treatment history, treatment (LDV/SOF±RBV), or treatment duration (8 or 12 weeks).
- No subjects experienced on-treatment virologic failure.
- The SVR12 and SVR24 rates were the same for all treatment groups, with a 100% positive predictive value between SVR12 and SVR24.
- The presence of nonstructural protein (NS) 5A resistance-associated variants did not predict whether a subject receiving LDV/SOF±RBV achieved SVR12. The treatment regimens in this study were equally effective in subjects with and without baseline NS3 PI resistance-associated variants and the NS3 Q80K variant.

  NS5A resistance-associated variants were detected in 2 subjects who had viral relapse, of whom 1 subject also had an S282T mutation. Despite the presence of NS5A LDV resistance-associated variants and low level of S282T, the 1 subject who relapsed following initial treatment with LDV/SOF for 8 weeks achieved SVR24 following rescue treatment with LDV/SOF+RBV for 24 weeks.
- The plasma exposures of SOF, its metabolites GS-566500 and GS-331007, and LDV were comparable in treatment-naive or treatment-experienced HCV-infected subjects irrespective

of treatment duration or presence/absence of RBV. In treatment-experienced subjects, with and without cirrhosis, similar PK profiles for SOF, its metabolites, and LDV were observed.

- Treatment with LDV/SOF±RBV was generally well tolerated in this study, with no deaths, no permanent study drug discontinuations due to AEs, few SAEs, and few Grade 3 or 4 AEs or laboratory abnormalities. Treatment duration (8 or 12 weeks) did not appear to affect the safety profile of the regimen in terms of overall frequency or severity of AEs or laboratory abnormalities.
- The safety profile of LDV/SOF+RBV treatment was similar to the expected safety profile of RBV.