FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naïve and Treatment-Experienced Subjects with Chronic Genotype 4 or 5 HCV Infection
Name of Test Drug:	Ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC)
Dose and Formulation:	LDV/SOF (90 mg/400 mg) FDC tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-337-1119
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	Not Applicable 2013-003978-27
ClinicalTrials.gov Identifier:	NCT02081079
Study Start Date:	07 March 2014 (First Subject Screened)
Study End Date:	17 February 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Armando Abergel, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Phil Pang, MD, PhD Telephone: PPD Fax: PPD
Report Date:	26 May 2015
Previous Report Date(s):	18 March 2015 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-337-1119
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naïve and Treatment-Experienced Subjects with Chronic Genotype 4 or 5 HCV Infection

Investigators: This was a multicenter study.

Study Centers: 5 sites in France

Publications:

Abergel A, Loustaud-Ratti V, Metivier S, Jiang D, Kersey K, Knox SJ, et al. Ledipasvir/Sofosbuvir Treatment Results in High SVR Rates in Patients with Chronic Genotype 4 and 5 HCV Infection [Abstract 0056]. Presented at: 50th Annual Meeting of the European Associated for the Study of the Liver (EASL); 2015 April 22-26. Vienna, Austria. J Hepatol 2015;62:S219.

Study Period:

07 March 2014 (First Subject Screened)
25 November 2014 (Last Subject Observation for the Primary Endpoint)
17 February 2015 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study are as follows:

- To determine the antiviral efficacy of treatment with sofosbuvir (SOF)/ledipasvir (LDV) fixed-dose combination (FDC) in subjects with chronic hepatitis C virus (HCV) infection, as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12, defined as HCV RNA < lower limit of quantification [LLOQ] 12 weeks posttreatment)
- To evaluate the safety and tolerability of LDV/SOF FDC as assessed by review of the accumulated safety data

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)

- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

The exploratory objective of this study is as follows:

- To identify or validate genetic markers that may be predictive of virologic response to therapy and/or tolerability of therapy through genetic discovery research (ie, pharmacogenomics), in subjects who provide their separate and specific consent

Methodology: This Phase 2, multicenter, open-label study evaluated antiviral efficacy and safety of treatment with LDV/SOF FDC (90 mg/400 mg) once daily for 12 weeks in treatment-naive and treatment-experienced subjects with genotype 4 or 5 HCV infection.

Approximately 80 eligible subjects were planned for enrollment, with approximately 20 subjects in each of 4 treatment groups defined by HCV genotype (genotype 4 or 5) and prior HCV treatment status (naive or experienced). Up to 50% of subjects may have had compensated cirrhosis at screening.

This final synoptic clinical study report (CSR) summarizes the results of the final analysis of the data collected throughout the study. Analysis of data collected for the primary efficacy endpoint (SVR) has previously been reported in the interim CSR (dated 18 March 2015).

Number of Subjects (Planned and Analyzed):
Planned: 80 subjects
Analyzed: 85 subjects (44 genotype 4, 41 genotype 5) were included in the Full Analysis Set and the Safety Analysis Set.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were treatment-naive and treatment-experienced males and nonpregnant, nonnursing females ≥ 18 years old with genotype 4 or 5 HCV infection; screening HCV RNA ≥ 10^4 IU/mL; and body mass index (BMI) ≥ 18 kg/m^2.

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

Test Product, Dose, Mode of Administration, and Lot No.: LDV/SOF was administered orally once daily at a dose of 90/400 mg (1 × 90/400 mg FDC tablet).

The lot number of LDV/SOF used in this study was DK1302B1.

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 and any resultant updates to SVR12 data. Efficacy analyses at all other scheduled assessment time points were described in the interim CSR (SVR12). The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study, with an LLOQ of 15 IU/mL.

Pharmacokinetics: No pharmacokinetic (PK) analyses were conducted for this study.

Safety: The interim CSR provided analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, and physical examinations. 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, 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 the proportion of subjects with HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after discontinuation of study treatment (SVR12) for the Full Analysis Set. The proportion of subjects who achieved SVR12 by genotype and prior HCV treatment status was estimated; exact 2-sided 95% confidence intervals (CIs) were constructed using the Clopper-Pearson method.

The primary efficacy endpoint was also analyzed for select demographic, baseline, and disease characteristics subgroups. Point estimates and 95% exact CIs for SVR12 rates for each subgroup were calculated as described above.

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 {24697}. If a subject achieved SVR24 and did not have HCV RNA data at SVR12 time point, the subject was assumed to have achieved SVR12. In addition, an analysis to assess the concordance of SVR12 with SVR24 was performed.

Pharmacokinetics: No PK analyses were conducted for this study.

Safety: All randomized subjects who received at least 1 dose of study drug were included in the safety analysis. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, and physical examinations. Safety data were analyzed by genotype and overall 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. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.1.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 85 subjects were enrolled into the study (44 genotype 4, 41 genotype 5). All of the enrolled subjects completed 12 weeks of treatment with LDV/SOF, and were included in the Safety and Full Analysis Sets. 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 2.1.

There were no differences in demographics between the interim SVR12 analyses and the final SVR24 analyses (Section 15.1, Table 3 and Appendix 16.2, Listing 4.1). There were a small number of changes to concomitant medications that did not change the interpretation of the study results (Section 15.1, Table 5 and Appendix 16.2, Listing 7).

Analyses related to disposition, demographics, and exposure are presented in Section 15.1, Tables 1 through 6 and Figure 1, and Appendix 16.2, Listings 1 through 7. In addition, an 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. Updated SVR12 results are reported in this final 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. At the final analysis, there was 100% concordance between SVR12 and SVR24 for all treatment groups (Section 15.1, Tables 7, 9.1, and 9.2, and Appendix 16.2, Listing 8.1). At the interim analysis, 1 treatment-naive subject with genotype 5 HCV infection (Subject PPD) had missing HCV RNA at posttreatment Week 12 and was considered to have not achieved SVR12 for the interim CSR; for the final analysis, this subject achieved SVR24 and was therefore imputed to have achieved SVR12 (Appendix 16.2, Listing 8.1). Therefore, among subjects with genotype 5 HCV infection who were treatment naive, the proportion of subjects who achieved SVR12 at the final analysis increased from 90.5% (19 of 21) to 95.2% (20 of 21) and the overall SVR12 rate for subjects with genotype 5 HCV infection increased from 92.7% (38 of 41) to 95.1% (39 of 41).

	Group 1 GT 4 TN (N = 22)	Group 2 GT 4 TE (N = 22)	Total GT 4 (N = 44)	Group 3 GT 5 TN (N = 21)	Group 4 GT 5 TE (N = 20)	Total GT 5 (N = 41)
SVR12	21/22 (95.5%)	20/22 (90.9%)	41/44 (93.2%)	20/21 (95.2%)	19/20 (95.0%)	39/41 (95.1%)
95% CI	77.2% to 99.9%	70.8% to 98.9%	81.3% to 98.6%	76.2% to 99.9%	75.1% to 99.9%	83.5% to 99.4%
SVR24	21/22 (95.5%)	20/22 (90.9%)	41/44 (93.2%)	20/21 (95.2%)	19/20 (95.0%)	39/41 (95.1%)
95% CI	77.2% to 99.9%	70.8% to 98.9%	81.3% to 98.6%	76.2% to 99.9%	75.1% to 99.9%	83.5% to 99.4%

GT = genotype; TE = treatment experienced; TN = treatment naive
HCV RNA analyzed using Roche TaqMan V 2.0 assay for use with the Ampliprep 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.
The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.
Source: Section 15.1. Table 9.2

No subject in any group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse) (Section 15.1, Table 8, and Appendix 16.2, Listing 8.2)

A total of 3 of 44 subjects (6.8%) with genotype 4 HCV infection (1 treatment naive, 2 treatment experienced) and 2 of 41 subjects (4.9%) with genotype 5 HCV infection (1 treatment naive, 1 treatment experienced) did not achieve SVR12. All 5 subjects had virologic relapse at the posttreatment Week 4 visit after achieving HCV RNA < LLOQ at their last on-treatment visit. All efficacy analyses are provided in Section 15.1, Tables 7 through 13, Figures 2 through 4.4, and Appendix 16.2, Listings 8.1 through 8.3, and Listing 8.5.

Full details on the virologic resistance analyses are reported in Section 9.2.1 of the interim CSR. No additional resistance analyses were performed since no subjects relapsed after posttreatment Week 12 through posttreatment Week 24.

Pharmacokinetic Results: No PK analyses were conducted for this study.

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. Evaluation of safety through 30 days after the last dose of study drugs were summarized in Section 11 of the interim CSR.

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 were primarily associated with AE resolution dates or minor clarification to AE terms (Appendix 16.2, Listing 9 and Ad Hoc Listing 7272). These changes did not impact the overall interpretation or conclusion of the safety profile of LDV/SOF in this study. Ad Hoc Listing 7272 provides a detailed listing of AEs that had changes in reported or preferred term and onset or resolution date between the data cuts taken at the posttreatment Week 12 and posttreatment Week 24 time points.

There were no additional treatment-emergent or nontreatment-emergent SAEs (Appendix 16.2, Listing 12 and Ad Hoc Listing 7272). A narrative for the 1 subject who had the only SAE in this study (from first dose of study drug through the end of the study [ie, the SVR24 visit]) is provided in Section 15.2. No subject pregnancies or deaths were reported in this study (Appendix 16.2, Listings 13 and Listing 14).

All AE results are provided in Section 15.1, Table 15 through Table 29, and Appendix 16.2, Listing 9 through Listing 14.

Clinical Laboratory Results

Blood samples for clinical laboratory analyses were not collected at the posttreatment Week 24 visit.

All laboratory results are provided in Section 15.1, Tables 30.1 through 32, Figures 5.1 through 5.10, and Appendix 16.2, Listings 8.4 and 16 through 21.2.

Vital Sign Measurements and Electrocardiograms (ECGs)

Vital sign measurements (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) were collected at the posttreatment Week 24 visit. No notable changes were observed (Appendix 16.2, Listing 23.1).

All vital sign measurements and ECG results are provided in Section 15.1, Tables 33.1 through 33.3, and Appendix 16.2, Listings 22 through 23.2.

CONCLUSIONS:

- High rates of SVR12 were achieved following treatment with LDV/SOF in subjects with genotype 4 (93.2%) or genotype 5 (95.1%) HCV infection. SVR12 rates were similar for treatment-naive and treatment-experienced subjects and those with or without cirrhosis.
- Concordance between SVR12 and SVR24 was 100%.
- No subjects experienced on-treatment virologic failure.
- High SVR rates were achieved despite the presence of nonstructural (NS)5A resistance-associated polymorphisms (RAPs). Virologic relapse was associated with retained NS5A and NS5B RAPs and the emergence of NS5A Y93C (n = 1), NS5B S282T (n = 2) or M289I (n = 1).
- LDV/SOF FDC was well tolerated with low rates of SAEs and clinical laboratory abnormalities, and no discontinuations due to AEs, pregnancies, or death.