FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection
Name of Test Drug:	Ledipasvir/sofosbuvir fixed-dose combination (FDC)
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-337-0109 (ION-2)
Phase of Development:	Phase 3
IND No.:	115268
EudraCT No.:	Not applicable
Study Start Date:	03 January 2013 (First Subject Screened)
Study End Date:	20 February 2014 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Nezam H. Afdhal, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Philip S. Pang, MD, PhD Telephone: PPD Fax: PPD
Report Date:	09 June 2014
Previous Report Date(s):	05 March 2014 (Interim Clinical Study Report Errata); 09 January 2014 (Interim Clinical Study Report)

STUDY SYNOPSIS
Study GS-US-337-0109:
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 64 sites in the United States (US).

Publications:

Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection. NEJM 2014; 370:1483-1493.

Afdhal N, Reddy KR, Pockros P, DiBisceglie AM, Arora S, Yang JC, et al. All oral fixed-dose combination sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-experienced genotype 1 HCV-infected patients: the phase 3 ION-2 study. J Hepatol 2014; 60 (1): S45.

Study Period:

03 January 2013 (First Subject Screened)
20 February 2014 (Last Subject Observation)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To determine the antiviral efficacy of combination treatment with ledipasvir/sofosbuvir (LDV/SOF; formerly SOF/LDV) fixed-dose combination (FDC) ± ribavirin (RBV) as measured by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of each treatment regimen 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 attained SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)
- To evaluate the kinetics of circulating hepatitis C virus (HCV) ribonucleic acid (RNA) during treatment and after treatment discontinuation
- To evaluate the emergence of viral resistance to LDV and SOF during treatment and after treatment discontinuation
- To characterize the steady-state pharmacokinetics (PK) of study drugs

The exploratory objectives of this study were as follows:

- To identify or validate genetic markers that may have been predictive of the natural history of disease, virologic response to therapy, and/or tolerability of medical therapy through genetic discovery research (eg, pharmacogenomics) in subjects who provided their separate and specific consent
- To assess the effect of treatment on health-related quality of life

Methodology: This Phase 3, randomized, open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF±RBV treatment in treatment-experienced subjects with chronic genotype 1 HCV infection who were virologic failures to prior treatment with a regimen containing pegylated interferon (Peg-IFN)+RBV.

Approximately 400 eligible subjects were randomized in a 1:1:1:1 ratio to 1 of the following 4 treatment groups:

- **LDV/SOF 24 Week group (Group 1):** LDV/SOF FDC (90 mg/400 mg) tablet once daily for 24 weeks
- **LDV/SOF+RBV 24 Week group (Group 2):** LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided twice daily [BID]) for 24 weeks
- **LDV/SOF 12 Week group (Group 3):** LDV/SOF FDC (90 mg/400 mg) tablet once daily for 12 weeks
- **LDV/SOF+RBV 12 Week group (Group 4):** LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

Randomization was stratified by HCV genotype (1a or 1b; subjects with mixed genotype 1a/1b were stratified as 1a), the presence or absence of cirrhosis at screening, and response to prior HCV therapy (relapse/breakthrough or nonresponse) at screening. Enrollment was managed so that approximately 20% of randomized subjects had compensated cirrhosis and approximately 50% of randomized subjects had failed prior treatment with a protease inhibitor (PI)+Peg-IFN+RBV regimen.

The treatment duration was to be 24 weeks for Groups 1, 2, and 3 (per protocol Amendment 1) and 12 weeks for Group 4. The treatment duration for all subjects randomized to Group 3 was subsequently shortened from 24 weeks to 12 weeks when the protocol-prespecified criterion was met (Section 7.2 of the interim clinical study report [CSR]).

All subjects were to complete the posttreatment Week 4 and 12 visits regardless of their treatment duration or response. Subjects who had HCV RNA less than the lower limit of quantitation (LLOQ) at the posttreatment Week 12 visit were to complete the posttreatment Week 24 visit, unless a confirmed viral relapse occurred.

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

This final synoptic CSR summarizes the results of the final analysis of data collected throughout the course of the study. Analysis of data collected for the primary efficacy endpoint (SVR12) was also reported in the interim CSR (dated 09 January 2014).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 400 subjects (100 in each treatment group)

Analyzed:

- Full analysis set: 440 subjects
- Safety analysis set: 440 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females ≥ 18 years of age, with chronic genotype 1 HCV infection, who had screening HCV RNA levels ≥ 10^4 IU/mL; had documentation of the presence or absence of cirrhosis; had virologic failure to prior treatment with a Peg-IFN+RBV regimen (including regimens containing nonstructural protein 3/4A [NS3/4A] PIs); and had a body mass index (BMI) ≥ 18 kg/m^2.

Duration of Treatment: Treatment duration was 24 weeks for Groups 1 and 2 and 12 weeks for Groups 3 and 4.

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

- **LDV/SOF** was administered orally to all subjects at a dose of 90 mg/400 mg (1 FDC tablet once daily).
- **RBV** was administered orally to subjects in Groups 2 and 4 at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided BID).

The lot numbers of study drugs administered in this study were as follows:

- **LDV/SOF**: DK1204B2 and DK1206B2
- **RBV**: A77418Z

Reference Therapy, Dose, Mode of Administration, and Lot No.: None

Criteria for Evaluation:

Efficacy: This 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. The COBAS® TaqMan® HCV Test v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study, with an LLOQ of 25 IU/mL.

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.

Quality of Life: The interim CSR provided analyses of the quality of life 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 quality of life. This final CSR summarizes additional data at posttreatment Weeks 12 and 24 and any changes to data that were previously reported in the interim between the data cut offs 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.

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the full analysis set. In the primary efficacy analysis, the SVR12 rates in each of the 4 treatment groups were compared with the adjusted historical SVR null rate of 25% using a 2-sided, 1-sample, binomial test. The basis for the 25% SVR null rate is described in the interim CSR. The Hochberg procedure was used to strongly control the family-wise type I error rate at the 0.05 level. The 2-sided 95% exact confidence intervals (CIs) based on the Clopper-Pearson method were also provided for the SVR12 rates in each of the 4 treatment groups. Secondary efficacy endpoints included SVR4 and SVR24.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum) by treatment group (and treatment duration when appropriate). All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definition.

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}. In addition, an 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 PK 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 signs, ECGs, and physical examinations. Safety data were analyzed by treatment group and included all data collected on or after the date of the first dose of any study drug through the date of the last dose of study drug plus 30 days. Additionally, SAEs were collected on or after the first dose of study drug through the end of the study. Adverse events were coded using the Medical Dictionary for Regulatory Activities, Version 16.0.

Quality of Life: The health related quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) were completed at Day 1 (baseline), Weeks 2, 4, 8, 12, and 24 (if applicable), 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 end of treatment to each posttreatment time point. A Wilcoxon rank sum test explored between treatment group differences in change from baseline to each of the time points.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 440 randomized subjects received treatment in this study and were included in the safety and full analysis sets (Section 15.1, Table 3). Full details on subject disposition, demographics, and baseline disease characteristics 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 notable 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 that did not change the interpretation of the study results (Section 15.1, Table 6, and Appendix 16.2, Listing 7). 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 7.1. In addition, an updated 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, Tables 8, 10.1, and 10.2, and Appendix 16.2, Listing 8.1).

	LDV/SOF 12 Weeks (N = 109)	**LDV/SOF+RBV 12 Weeks (N = 111)**	**LDV/SOF 24 Weeks (N = 109)**	**LDV/SOF+RBV 24 Weeks (N = 111)**
SVR12	102/109 (93.6%)	107/111 (96.4%)	108/109 (99.1%)	110/111 (99.1%)
95% CI	87.2% to 97.4%	91.0% to 99.0%	95.0% to 100.0%	95.1% to 100.0%
SVR24	102/109 (93.6%)	107/111 (96.4%)	108/109 (99.1%)	110/111 (99.1%)
95% CI	87.2% to 97.4%	91.0% to 99.0%	95.0% to 100.0%	95.1% to 100.0%

TND = target not detected
Note: HCV RNA was analyzed using Roche TaqMan v2.0 assay for use with the High Pure System assay with an LLOQ of 25 IU/mL.
Note: SVR12 and SVR24 were sustained virologic response (HCV RNA < LLOQ) 12 and 24 weeks after stopping study treatment, respectively.
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'); a missing SVR24 was imputed as a success if SVR12 was a success; otherwise, the missing SVR 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, Tables 8 and 10.2

Thirteen of 440 subjects (3%) did not achieve SVR12 or SVR24: 1 withdrew consent before the posttreatment Week 12 visit, 11 subjects relapsed, and 1 subject had on-treatment virologic failure (rebound) associated with documented study drug noncompliance, as reported in Section 9 of the interim CSR. This subject was randomized to the LDV/SOF+RBV 24 Week group and completed 6 weeks of study treatment. The subject never achieved HCV RNA

< LLOQ and met the on-treatment virologic stopping criteria of rebound (confirmed HCV RNA > 1 $\log_{10}$ IU/mL increase from nadir) at Week 4.

All relapses occurred in the 12-week treatment groups, and all, except 1, occurred by the posttreatment Week 4 visit (Appendix 16.2, Listing 8.2). In the LDV/SOF 12 Week group, 6 subjects relapsed by posttreatment Week 4, and 1 subject relapsed between posttreatment Weeks 4 and 12. In the LDV/SOF+RBV 12 Week group, 4 subjects relapsed by posttreatment Week 4. No subjects relapsed between posttreatment Weeks 12 and 24, and all subjects who had achieved SVR12 also achieved SVR24 (Section 15.1, Table 10.1, and Appendix 16.2, Listings 8.1 and 8.5). Four subjects who achieved SVR12 and did not have HCV RNA measurements at the posttreatment Week 24 visit were imputed to achieve SVR24 based on bracketed success (achieving SVR12 and having observed HCV RNA values < LLOQ obtained after the posttreatment Week 24 visit window) (Section 15.1, Table 11, and Appendix 16.2, Listing 8.1).

All efficacy analyses are provided in Section 15.1, Tables 8 through 15 and Figures 2.1 through 4.4, and Appendix 16.2, Listings 8.1 through 8.3 and 8.5.

Full details on the resistance analysis are reported in Section 9.3.2 of the interim CSR. No additional resistance analyses were performed since no subjects relapsed during the posttreatment Week 12 through Week 24.

Pharmacokinetic 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.

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 clarifications to AE terms and newly reported Grade 1 or 2 AEs (Appendix 16.2, Listing 10 and Adhoc Listing 1). No additional Grade 3 or 4 AEs were reported. These changes did not impact the overall interpretation or conclusions of the safety profile of LDV/SOF with or without RBV in this study. Adhoc Listing 1 provides a detailed listing of any newly reported AEs and AEs that had changes in reported or preferred term, onset date, severity, relationship to study drug, or action(s) taken between the data cuts taken at the posttreatment Week 12 and posttreatment Week 24 time points.

No additional nontreatment-emergent SAEs were reported (Appendix 16.2, Listing 13). Narratives for all SAEs 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 or deaths were reported in this study (Appendix 16.2, Listings 14 and 15).

All AE results are provided in Section15.1, Tables 16 through 30, and Appendix 16.2, Listings 10 through 15.

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 to 31.12 and 32 to 34, and Appendix 16.2, Listings 16 through 22.2).

All laboratory results are provided in Section 15.1, Tables 31.1 through 34 and Figures 5.1 through 5.10, and Appendix 16.2, Listings 16 through 22.2.

Vital Signs Measurements and ECGs

Vital signs measurements (systolic and diastolic blood pressure and pulse) and weight were collected at the posttreatment Week 24 visit. No notable changes were observed (Section 15.1, Tables 36.1 through 36.4, and Appendix 16.2, Listings 24.1 and 24.2).

All vital signs measurement and ECG results are provided in Section 15.1, Tables 35 through 36.4, and Appendix 16.2, Listings 23 through 24.2.

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.

Quality of Life:

Full details on the quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) through posttreatment Week 4 are reported in Section 12 of the interim CSR. All quality-of-life analyses are provided in Section 15.1, Tables 37.1 through 37.4, Figures 6.1 through 6.4, and Appendix 16.2, Listings 9.1 through 9.4.

Overall, results from the quality-of-life surveys remained consistent between posttreatment Week 4 and posttreatment Week 24 (Section 15.1, Tables 37.1 through 37.4, Figures 6.1 through 6.4, and Appendix 16.2, Listings 9.1 through 9.4). These results indicated that, in contrast to the RBV-free (LDV/SOF) groups, which had no on-treatment decrements in quality of life, the RBV-containing (LDV/SOF+RBV) groups had statistically significant ($p < 0.05$) worsening in health-related quality of life between baseline and end-of-treatment responses for the SF-36 (domains of physical functioning, role physical, vitality, social functioning [24 Week group only], role emotional, and mental component [24 Week group only]) and the FACIT-F trial outcome index (24 Week group only). The mean scores for most scales improved from end of treatment to 24 weeks after the end of treatment, with the greatest improvement generally occurring between end of treatment and posttreatment Week 4. 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 overall conclusions from this study are as follows:

- LDV/SOF, administered once daily with or without food as an FDC tablet for 12 weeks to treatment-experienced subjects, including those who had failed the current standard of care, resulted in high SVR12 rates.
- The addition of RBV to a 12-week treatment course of LDV/SOF or extending treatment duration to 24 weeks did not appreciably enhance the observed SVR12 rates.
- No subjects relapsed between posttreatment Weeks 12 and 24.

- Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, high BMI, genotype 1a, high viral load, or non-CC IL28B allele) had no impact on SVR12 rates.
- Logistic regression analysis identified 1 factor associated with relapse in a limited number of subjects after 12 weeks of therapy: the presence of cirrhosis. However, this negative risk factor is of limited clinical utility. Although the SVR12 rate was numerically lower among subjects with cirrhosis than those without cirrhosis, the majority of subjects with cirrhosis achieved SVR12 after a 12-week duration of therapy.
- In general, the PK of SOF, GS-566500, GS-331007, and LDV in the LDV/SOF±RBV groups was similar. Compensated cirrhosis had no clinically meaningful impact on LDV or SOF PK.
- Overall, the virologic failure rate was low (12 of 440 subjects, 2.7%). No genotypic or phenotypic resistance to SOF was detected in virologic failure subjects. Virologic failure was associated with single class LDV resistance.
- High SVR12 rates were achieved in subjects with baseline NS5A resistance-associated variants. Baseline NS3 resistance-associated variants and the Q80 polymorphism had no appreciable effect on SVR12 rates.
- Treatment with LDV/SOF±RBV was generally well tolerated in this study, with no deaths, no permanent discontinuations of study drug due to AEs, few SAEs, few Grade 3 AEs and only 1 Grade 4 AE, and few Grade 3 or 4 laboratory abnormalities.
- Inclusion of RBV in the LDV/SOF treatment regimen contributed substantially to the incidence of AEs (eg, anemia) and clinically significant laboratory abnormalities experienced by subjects; this is also indirectly reflected in the on-treatment decreases in quality of life observed for the RBV-containing groups, as measured by patient-reported outcomes.
- The percentage of subjects experiencing AEs was higher in the 24-week treatment groups compared with the 12-week treatment groups.
- Considering both the efficacy and safety profiles of these regimens, LDV/SOF for 12 weeks should be recommended for treatment-experienced patients with genotype 1 HCV infection.