FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 2 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-337-1903
Phase of Development:	Phase 3b
IND No.: **EudraCT No.:**	Not Applicable Not Applicable
ClinicalTrials.gov Identifier:	NCT02738333
Study Start Date:	12 April 2016 (First Subject Screened)
Study End Date:	11 May 2017 (Last Subject Last Observation)
Principal or Coordinating Investigator:	Name: Nobuyuki Enomoto, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Benedetta Massetto, MD Telephone: PPD Fax: PPD
Report Date:	18 August 2017
Previous Report Date(s):	05 April 2017 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-337-1903

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

Title of Study: A Phase 3b, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 2 HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 40 sites in Japan.

Publications: At the time of this report, the results of this study have not been presented or published.

Study Period:

12 April 2016 (First Subject Screened)
14 February 2017 (Last Subject Last Observation for the Primary Endpoint)
11 May 2017 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3b

Objectives:

The primary objectives of this study were as follows:

- To evaluate the antiviral efficacy of therapy with ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) as measured by sustained virologic response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of each 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 cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating hepatitis C virus (HCV) ribonucleic acid (RNA) during treatment and after cessation of each treatment regimen
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after cessation of treatment

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, virologic response to therapy and/or the tolerability of medical therapies through genetic discovery research (eg, genomics), in subjects who provide a separate and specific consent
- To assess the effect of treatment with LDV/SOF on Health-Related Quality of Life (HRQoL)

Methodology: This Phase 3b, randomized, open-label, multicenter study in Japan assessed the antiviral efficacy, safety, and tolerability of LDV/SOF administered for 12 weeks in treatment-naive and treatment-experienced adults with chronic genotype 2 HCV infection.

Cohort 1: Approximately 200 subjects were to be randomized in a 1:1 ratio to one of the following 2 treatment groups:

- LDV/SOF 12 Week group: LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks
- SOF+RBV 12 Week group: SOF tablet (400 mg) once daily and ribavirin (RBV) (600-1000 mg divided twice daily) for 12 weeks

Randomization was stratified by cirrhosis status (presence/absence) and prior treatment experience (treatment naive/treatment experienced). At least 20 subjects were to have Child-Pugh-A compensated cirrhosis. Approximately 50% of subjects were to be treatment naive and 50% were to be treatment experienced.

Cohort 2: LDV/SOF RBV-ineligible/intolerant 12 Week group: Up to 25 subjects who were ineligible for or intolerant of RBV therapy were to receive an LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks. Approximately 2 subjects were to have Child-Pugh-A compensated cirrhosis.

All subjects were to complete the posttreatment Week 4, 12, and 24 visits regardless of their treatment duration.

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 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 (05 April 2017).

Number of Subjects (Planned and Analyzed):

Planned:

Cohort 1: approximately 200 subjects
Cohort 2: approximately 25 subjects

Analyzed:

Cohort 1: 214 subjects
Cohort 2: 25 subjects

- Full Analysis Set: 239 subjects (Cohort 1, LDV/SOF: 106 subjects; Cohort 1, SOF+RBV: 108 subjects; Cohort 2, LDV/SOF [RBV-ineligible/intolerant]: 25 subjects)
- Safety Analysis Set: 239 subjects (Cohort 1, LDV/SOF: 106 subjects; Cohort 1, SOF+RBV: 108 subjects; Cohort 2, LDV/SOF [RBV-ineligible/intolerant]: 25 subjects)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females ≥ 20 years of age, with chronic (≥ 6 months) genotype 2 HCV infection who were HCV treatment naive or treatment experienced, had documentation of the presence or absence of cirrhosis, and had a body weight ≥ 40 kg. In Cohort 2, subjects must have been ineligible for or intolerant of RBV.

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

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

- LDV/SOF was administered orally to subjects at a dose of 90 mg/400 mg (1 FDC tablet once daily).
- SOF was administered orally to subjects at a dose of 400 mg (1 tablet once daily).
- RBV (Rebetol®) was administered orally to subjects at a dose of 600-1000 mg/day (divided twice daily), depending on the subject's weight.

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

- LDV/SOF: DK1309B1
- SOF: DC1307B1
- RBV: A002D

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

Criteria for Evaluation:

Efficacy: Blood samples to determine serum HCV RNA levels were collected from subjects at screening, Day 1 (predose), Weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12 during treatment (or upon early termination), and posttreatment Weeks 4, 12, and 24. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to determine HCV RNA results in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics/Pharmacodynamics: Pharmacokinetics and pharmacodynamics were not evaluated in this study.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital signs measurements, electrocardiograms (ECGs), and physical examinations.

Other: Health-related quality of life (HRQoL) was assessed with the 36-Item Short Form Health Survey (SF-36), the Chronic Liver Disease Questionnaire (CLDQ-HCV), the Fatigue Index (FACIT-F), and the Work Productivity and Activity Impairment Questionnaire: Hepatitis C, v2.0 (WPAI: Hep C).

Statistical Methods:

Efficacy: For efficacy analyses, data were analyzed by treatment group (LDV/SOF 12 Weeks, SOF+RBV 12 Weeks, and LDV/SOF RBV-ineligible/intolerant 12 Weeks) using the Full Analysis Set. The primary efficacy endpoint was the proportion of subjects with SVR12 (HCV RNA < LLOQ 12 weeks after cessation of treatment) in the Full Analysis Set. Point estimates and 2-sided 95% exact CIs for SVR12 based on the Clopper-Pearson method were provided for each treatment group. The primary analyses consisted of a noninferiority test of the 2 treatments in Cohort 1: LDV/SOF for 12 weeks versus SOF+RBV for 12 weeks at the 0.05 significance level (2-sided). A clinically meaningful noninferiority margin of 10% was applied. The 2-sided 95% CI for the difference in SVR12 rates between the 2 treatment groups was constructed based on stratum-adjusted Mantel-Haenszel proportions for the assessment of noninferiority. In the primary efficacy analysis of Cohort 2 (RBV-ineligible/intolerant), no statistical hypothesis testing was performed.

Secondary efficacy endpoints included SVR4, SVR24, proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through end of treatment (EOT), proportion of subjects with virologic failure, and characterization of HCV drug resistance substitutions.

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

Pharmacokinetics/Pharmacodynamics: Pharmacokinetics and pharmacodynamics were not evaluated in this study.

Safety: All randomized/enrolled 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. For safety analyses, data were analyzed by treatment group (LDV/SOF 12 Weeks, SOF+RBV 12 Weeks, and LDV/SOF RBV-ineligible/intolerant 12 Weeks) unless otherwise specified (eg, AEs by treatment and age group [< 65 years and ≥ 65 years]), and included all data collected on or after the first dose of any 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 20. MedDRA, Version 19.1, was used for coding adverse events for the interim CSR (05 April 2017).

Other: The HRQoL questionnaires were completed by subjects at Day 1 (baseline), Weeks 4, 8, 12, EOT, and posttreatment Weeks 4, 12, and 24. A Wilcoxon signed rank test explored within-treatment-group changes in status from baseline to each of the timepoints, and from EOT to posttreatment time points. A Wilcoxon rank sum test was used to explore differences between Cohort 1 treatment groups (LDV/SOF 12 Weeks and SOF+RBV 12 Weeks) in change in status from baseline to each of the postbaseline timepoints.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 239 subjects were enrolled in the study and received at least 1 dose of study drug. A total of 214 subjects were randomized in Cohort 1: 106 subjects to the LDV/SOF 12 Week group and 108 subjects to the SOF+RBV 12 Week group. A total of 25 subjects were enrolled in the LDV/SOF RBV-ineligible/intolerant 12 Week group (Cohort 2). All enrolled subjects received at least 1 dose of study drug and were included in the Full Analysis Set and Safety Analysis Set (Table 15.8.1.3).

No notable differences in demographic or baseline disease characteristics were observed between the interim analyses and the final analyses (Table 15.8.3 and Listings 16.2.4.1 and 16.2.4.2.1). There were a small number of additions and changes to concomitant medications that did not change the interpretation of the study results (Table 15.11.7.4 and Listing 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 16.1.2 to 16.2.5.2. In addition, an updated Important Protocol Deviations Log for the study is provided in Appendix 16.2.2. No new important protocol deviations were reported.

Efficacy Results:

Analysis of the primary efficacy endpoint is reported in Section 9 of the interim CSR (05 April 2017).

The LDV/SOF 12 Week group of Cohort 1 met the primary endpoint of an SVR12 rate that was noninferior to the SVR12 rate in the SOF+RBV 12 Week group:

- LDV/SOF 12 Week group: 96.2% (95% CI: 90.6% to 99.0%) of subjects (102 of 106) achieved SVR12
- SOF+RBV 12 Week group: 95.4% (95% CI: 89.5% to 98.5%) of subjects (103 of 108) achieved SVR12

In Cohort 2, the LDV/SOF RBV-ineligible/intolerant 12 Week group, the SVR12 rate was comparable to the rates in both treatment groups of Cohort 1:

- LDV/SOF RBV-ineligible/intolerant 12 Week group: 96.0% (95% CI: 79.6% to 99.9%) of subjects (24 of 25) achieved SVR12

A comparison of the results for SVR12 and SVR24, a secondary efficacy endpoint, is presented in the table below. The SVR12 rates reported in the interim analysis were maintained in the SVR24 analysis, with a 100% concordance between SVR12 and SVR24 (Table 15.9.2.3).

No subjects relapsed between posttreatment Weeks 12 and 24 (Listing 16.2.6.4).

	Cohort 1: LDV/SOF 12 Weeks (N = 106)	Cohort 1: SOF+RBV 12 Weeks (N = 108)	Cohort 2: LDV/SOF 12 Weeks (N = 25)
SVR12	102/106 (96.2%)	103/108 (95.4%)	24/25 (96.0%)
95% CI	90.6% to 99.0%	89.5% to 98.5%	79.6% to 99.9%
SVR24	102/106 (96.2%)	103/108 (95.4%)	24/25 (96.0%)
95% CI	90.6% to 99.0%	89.5% to 98.5%	79.6% to 99.9%

Cohort 2 included patients who were ineligible or intolerant for RBV therapy.
HCV RNA was analyzed using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with an LLOQ of 15 IU/mL.
SVRx is sustained virologic response (HCV RNA < LLOQ) x weeks after stopping study treatment.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
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.
Source: Table 15.9.2.2

Virologic Resistance Results:

Full details on the resistance analysis were reported in Section 9.3.1 of the interim CSR (05 April 2017). No additional resistance analyses were performed since no subjects relapsed during posttreatment Week 12 through posttreatment Week 24.

Pharmacokinetics/Pharmacodynamics Results: Pharmacokinetics and pharmacodynamics were not evaluated in 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. Evaluations of safety data through 30 days after the last dose of study drugs were summarized in Section 11 of the interim CSR (05 April 2017).

Adverse Events and Serious Adverse Events

A small number of minor updates were made to previously reported AE data due to the ongoing nature of the study and data reconciliation. The updates were primarily due to a change in the coding of AEs during the study period due to the up-versioning of MedDRA 19.1 to MedDRA 20. The Preferred Term for the Reported Term “cold” or “common cold” was coded in MedDRA 19.1 as “nasopharyngitis” and was changed in MedDRA 20 to “viral upper respiratory tract infection”. One additional treatment-emergent Grade 2 AE of anemia was reported in a subject in the SOF+RBV group (Subject PPD The AE had an onset of Day 9 and was resolved on posttreatment Day 85. It was considered to be related to study drug by the investigator and RBV was discontinued (Listing 16.2.7.7).

No additional treatment-emergent Grade 3 or 4 AEs, AEs that led to study drug discontinuation or serious adverse events (SAEs) were reported (Listing 16.2.7.7). No additional deaths were reported (Listing 16.2.7.3). Narratives for all SAEs, AEs leading to discontinuation of study drug, and deaths 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 were reported in this study (Listing 16.2.8.3).

All AE results are provided in Tables 15.11.2.1.1 to 15.11.5.4 and Listings 16.2.7.1 to 16.2.7.7. The most commonly reported AEs in Cohort 1 by treatment group (ie, AEs reported in ≥ 5% of subjects) were viral upper respiratory tract infection (11.3%, 12 subjects) and headache (9.4%,

10 subjects) in the LDV/SOF 12 Week group; and anemia (23.1%, 25 subjects), viral upper respiratory tract infection (21.3%, 23 subjects), and headache (8.3%, 9 subjects) in the SOF+RBV 12 Week group (Table 15.11.2.1.4). The most commonly reported AEs in Cohort 1 changed between the SVR12 analysis and the SVR24 analysis due to the change in Preferred Term from "nasopharyngitis" to "viral upper respiratory tract infection" between MedDRA 19.1 and MedDRA 20. In Cohort 2, the LDV/SOF RBV-ineligible/intolerant 12 Week group, the most commonly reported AEs were headache, stomatitis, and pyrexia (each 8.0%, 2 subjects).

These changes did not impact the overall interpretation or conclusions of the safety profile of LDV/SOF or SOF+RBV in this study, as described in the interim CSR (05 April 2017).

Clinical Laboratory Results

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

All laboratory results are provided in Tables 15.11.6.1.1 to 15.11.6.3, Figures 15.11.6.1 to 15.11.6.12, and Listings 16.2.8.1.1 to 16.2.8.1.9.

Vital Sign Measurements and ECGs

ECGs were not collected at the posttreatment Week 24 visit. Overall, no notable changes were observed in vital sign measurements (diastolic and systolic blood pressure, and pulse) (Tables 15.11.7.1 to 15.11.7.3, and 15.11.8, and Listings 16.2.8.2.1, 16.2.8.2.3.1, and 16.2.8.2.3.2).

Quality of Life Results:

Complete details on the QOL questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) through posttreatment Week 12 are reported in Section 12 of the interim CSR (05 April 2017). No notable differences were observed in the QOL questionnaires between the interim analyses and the final analyses at posttreatment Week 24 (Tables 15.12.1 to 15.12.4).

All QOL analyses are provided in 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.

CONCLUSIONS: The overall conclusions from this study are as follows:

- The study met its predefined primary efficacy in Japanese subjects with chronic genotype 2 HCV infection, demonstrating that the SVR12 rate of 96.2% in the LDV/SOF 12 Week group was noninferior to the SVR12 rate of 95.4% in the SOF+RBV 12 Week group.
- High SVR rates were achieved despite the presence of baseline nonstructural protein (NS)5A and NS5B resistance-associated variants.
- The overall concordance between SVR12 and SVR24 was 100.0%. No subjects relapsed between posttreatment Weeks 12 and 24.
- LDV/SOF for 12 weeks was generally well tolerated and, compared with SOF+RBV for 12 weeks, lacked toxicities associated with RBV. No treatment-emergent deaths, Grade 4 AEs, or treatment-related SAEs were observed.
- The single tablet regimen of LDV/SOF for 12 weeks provides high efficacy and a favorable safety and tolerability profile in both RBV-eligible and RBV-ineligible/intolerant genotype 2 HCV-infected subjects, including those with compensated cirrhosis and prior interferon treatment failure.