FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	An Open-Label Study of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Nosocomial Genotype 1 HCV Infection
Name of Test Drug:	Ledipasvir/Sofosbuvir fixed-dose combination (LDV/SOF FDC)
Dose and Formulation:	LDV/SOF 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-337-0125
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	115268 Not Applicable
Study Start Date:	29 July 2013 (First Subject Screened)
Study End Date:	18 August 2014 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Raymond T. Chung, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	10 November 2014

STUDY SYNOPSIS

Study GS-US-337-0125
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: An Open-Label Study of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Nosocomial Genotype 1 HCV Infection

Investigator: Raymond T. Chung, MD

Study Centers: One site in the United States (Boston, MA)

Publications: No publications at the time of this Clinical Study Report

Study Period:

29 July 2013 (First Subject Screened)
18 August 2014 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To determine the antiviral efficacy of combination treatment with ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) 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 the 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) 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 objectives of this study were as follows:

- To identify or validate genetic markers that may have been 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 investigate HCV viral diversity and evolution before, during, and after treatment

Methodology: This Phase 2, open-label study assessed the antiviral efficacy, safety, and tolerability of LDV/SOF FDC treatment for 12 weeks in subjects with nosocomial genotype 1 HCV infection.

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

Number of Subjects (Planned and Analyzed):
Planned: 35
Analyzed: 5

It was originally planned to enroll 35 subjects in the study; however, due to low enrollment, only 5 subjects were enrolled and analyzed.

Diagnosis and Main Criteria for Inclusion: Male and nonpregnant, nonlactating females, aged 18 years or older, with nosocomial acquisition of genotype 1 HCV infection within 36 months from the screening visit were enrolled. Subjects had body mass index (BMI) ≥ 18 kg/m^2 and HCV RNA $\geq 10^3$ IU/mL at screening. Subjects who had prior exposure to an HCV nonstructural protein (NS)5A inhibitor were excluded.

Duration of Treatment: Subjects were treated for 12 weeks.

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

LDV/SOF was administered orally at a dose of 90 mg/400 mg (1 FDC tablet once daily with or without food).

The lot number of LDV/SOF was DK1205B2.

Criteria for Evaluation:

Efficacy: Efficacy was evaluated using scheduled assessments of HCV RNA. Blood samples to determine serum HCV RNA levels were collected from subjects at screening; Day 1 (predose); Weeks 1, 4, 8, and 12; and posttreatment Weeks 4, 12, and 24. The COBAS® TaqMan® HCV Test, v2.0 for use with the High Pure System was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 25 IU/mL.

Viral RNA Sequencing/Phenotyping samples were collected at baseline/Day 1 and each visit for viral sequence analysis. Additionally, at any unscheduled visit initiated for the purpose of confirming virologic breakthrough, a viral sequence analysis plasma sample must have been collected.

Pharmacokinetics: No pharmacokinetic (PK) analyses were performed for this report.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, physical examinations, vital sign measurements, clinical laboratory tests, and 12-lead electrocardiograms (ECGs). Posttreatment assessments included monitoring of AEs and concomitant medications, vital sign measurements, and clinical laboratory tests.

Further details on study assessments are provided in the clinical study protocol (Appendix 16.1.1).

Statistical Methods:

All tables, figures, and listings produced for this study are provided in Section 15.1 and Appendix 16.2. Further details on statistical methods are provided in the statistical analysis plan (SAP) (Appendix 16.1.9).

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA <LLOQ 12 weeks after discontinuation of study drug) in the Full Analysis Set. The Full Analysis Set includes subjects who were enrolled into the study and received at least 1 dose of study drug. The point estimate of SVR12 rate and 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method were provided. No inferential statistics were provided for efficacy endpoints.

Secondary efficacy endpoints SVR4 and SVR24 rates were calculated using the same method as described for SVR12. On-treatment virologic failure and relapse were descriptively summarized. In addition, an analysis to assess the concordance of SVR12 with SVR24 was performed.

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

Pharmacokinetics: No PK analyses were performed for this report.

Safety: All subjects who were enrolled and 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, ECGs, and physical examinations. Safety data 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 17.

SUMMARY OF RESULTS:

Subject disposition, demographics, and baseline characteristics are provided in Section 15.1, Tables 1, 3, and 6.

Subject Disposition and Demographics: A total of 5 subjects received treatment in this study and were included in the Safety and Full Analysis Sets (Section 15.1, Table 1). Of the 5 subjects, 100% completed treatment and the 24-week follow-up.

All subjects were white (100.0%) and the majority were male (60.0%) (Section 15.1, Table 3). The mean age was 62 years (range: 54-76) (Section 15.1, Table 3). The overall mean (SD) baseline BMI was 28.9 (5.38) kg/m^2, with 2 subjects (40.0%) having a BMI $\geq$ 30 kg/m^2.

Subjects had acquired HCV infection at a mean of 89.1 weeks (range: 78.9-98.3) prior to enrollment, with a mean HCV RNA level of 5.9 $\log_{10}$ IU/mL (range: 5.3-6.5) (Section 15.1, Tables 3 and 6). All subjects had genotype 1b HCV infection. One subject had the IL28B CC genotype and 4 subjects had the IL28B non-CC genotype (3 with CT and 1 with TT) (Section 15.1, Table 3). Based on FibroTest**,** 2 subjects had no or minimal fibrosis, 1 had moderate fibrosis and 2 had severe fibrosis (Section 15.1, Table 3). All had significant co-morbidities and cardiac risk factors. All subjects had hypertension and hyperlipidemia, 4 had diabetes, 4 had coronary artery disease, and 1 had atherosclerotic cardiovascular disease

(Appendix 16.2.4, Listing 5). All subjects were taking multiple concomitant medications (range 5-25) including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and antithrombotic agents. Four subjects were on antidiabetic agents and 5 subjects were on lipid modifying agents (Appendix 16.2.4, Listing 7).

Four subjects had no prior HCV treatment, and 1 subject was a prior nonresponder to telaprevir in combination with pegylated interferon and ribavirin (Section 15.1, Table 3 and Appendix 16.2.4, Listing 7).

Efficacy Results: All 5 subjects demonstrated rapid and sustained declines in HCV RNA during treatment and all achieved SVR12, the primary efficacy endpoint. All 5 subjects achieved SVR4 and SVR24, the secondary efficacy endpoints (Section 15.1, Table 10).

All subjects had HCV RNA < LLOQ by Week 4 (Section 15.1, Table 12).

There were no subjects with virologic failure (Section 15.1, Table 9).

Baseline samples for all subjects were deep sequenced and no NS5A resistance associated variants, S282T or SOF treatment emergent variants were detected at baseline in any of the 5 subjects.

Pharmacokinetic Results: No PK analyses were performed for this report.

Safety Results: All AEs and laboratory abnormalities presented in this report were treatment emergent, unless specifically stated, and are referred to as AEs and laboratory abnormalities, respectively.

Treatment with LDV/SOF FDC was generally safe and well-tolerated. Four subjects experienced an AE; however, only 2 of these AEs were considered by the investigator to be related to study drug (influenza-like illness and dysgeusia) (Section 15.1, Table 17). Both of these AEs were Grade 1 in severity (Section 15.1, Table 15). The influenza-like illness resolved, however the dysgeusia was noted as still ongoing. No single AE was present in more than 1 subject. One subject, with a prior history of coronary artery disease and diabetes, experienced a serious adverse event (SAE) of acute myocardial infarction (non ST segment elevation); the subject was hospitalized, and underwent catheterization and successful angioplasty during which time there was an interruption of LDV/SOF FDC (Section 15.1, Table 23 and Appendix 16.2.7, Listing 9). This AE was not considered to be related to study drug by the investigator. In addition, 1 subject experienced a nontreatment emergent SAE of alcohol poisoning on Follow-up Day 173. This was resolved within 3 days. Narratives for these SAEs are provided in Section 15.2.

There were no clinically meaningful changes in clinical laboratory assessments, vital sign measurements, or other measured parameters in the study. No Grade 4 laboratory abnormalities were observed (Section 15.1, Table 29). One with diabetes mellitus had a Grade 3 laboratory abnormality of hyperglycemia (Appendix 16.2.8, Listing 17.4). This abnormality was not associated with any clinical signs or symptoms. Alanine aminotransferase normalization was observed in all subjects by Week 4 of treatment (Appendix 16.2.8, Listing 17.5).

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 (Appendix 16.2.7, Special Situations Report Listing).

There was 1 protocol deviation where 1 subject was administered <80% of the study drug between drug dispensing visits (Appendix 16.2.2, Important Protocol Deviation Log). This was not considered to have any impact on the study results by the investigator.

CONCLUSIONS:

The overall conclusions from this study are as follows:

- Treatment with LDV/SOF cured 5/5 HCV genotype 1b patients who had been infected nosocomially in the prior 2 years. Irrespective of baseline characteristics, all subjects achieved SVR12. No subjects experienced on-treatment virologic failure.
- Potent and rapid suppression of HCV RNA was observed and maintained through posttreatment Week 24.
- The SVR12 and SVR24 rates were the same, with a 100% positive predictive value between SVR12 and SVR24.
- Despite older age and significant cardiac co-morbidities, LDV/SOF was generally well-tolerated. There were no deaths, no permanent study drug discontinuations due to AEs, 1 SAE, no Grade 3 or 4 AEs, and 1 Grade 3 laboratory abnormality.