FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2 Open- Label Study to Evaluate The Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed Dose Combination Tablet With Ribavirin for 12 Weeks in Treatment-naïve Patients With Chronic HCV Genotype 3 Infection
Name of Test Drug:	Ledipasvir/sofosbuvir fixed-dose combination (FDC)
Dose and Formulation:	Ledipasvir/sofosbuvir FDC (90/400 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-337-1701
Phase of Development:	Phase 2
IND No.:	Not applicable
EudraCT No.:	Not applicable
ClinicalTrials.gov Identifier:	NCT02413593
Study Start Date:	15 April 2015 (First Subject Screened)
Study End Date:	08 January 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Jordan Feld, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Chohee Yun, MD Telephone: PPD Fax: PPD
Report Date:	17 May 2016

STUDY SYNOPSIS
Study GS-US-337-1701
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2 Open- Label Study to Evaluate The Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed Dose Combination Tablet With Ribavirin for 12 Weeks in Treatment-naïve Patients With Chronic HCV Genotype 3 Infection

Investigators: Multicenter study

Study Centers: 15 sites in Canada

Publications:

Feld JJ, Ramji A, Shafran S, Willems B, Marotta P, Huchet E, et al. Ledipasvir/Sofosbuvir with ribavirin for 12 Weeks is effective and safe in treatment-naïve genotype 3 HCV-infected patients in Canada [Abstract SAT-183]. Presented at: The 51st Annual Congress of the European Association for the Study of Liver: The International Liver Congress (EASL); 2016 April 13-17; Barcelona, Spain.

Study Period:

15 April 2015 (First Subject Screened)
08 January 2016 (Last Subject Observation)
23 December 2015 (Last Subject Observation for the Primary Endpoint)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To determine the antiviral efficacy of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) tablet with ribavirin (RBV) as measured by the proportion of subjects who attained a sustained viral response (SVR) at 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of this treatment regimen as assessed by review of the accumulated safety data

The secondary objectives of this study were as follows:

- To evaluate the kinetics of circulating hepatitis C virus (HCV) RNA during treatment and after treatment discontinuation
- To determine the proportion of subjects who attained SVR at 4 weeks after discontinuation of therapy (SVR4)

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

The exploratory objectives of this study was as follows:

- To identify or validate genetic markers that may be 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

Methodology: This Phase 2, open-label, multicenter study was conducted to evaluate the antiviral efficacy, safety, and tolerability of LDV/SOF+RBV for 12 weeks in treatment-naive subjects with genotype 3 HCV infection. Approximately 100 subjects were to be enrolled to receive LDV/SOF FDC (90/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided twice a day) for 12 weeks. Up to 40% of the subjects may have had compensated cirrhosis. All subjects were to complete the posttreatment Weeks 4 and 12 visits following the last dose of study drug, regardless of their treatment duration.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 100 subjects
Analyzed:

- All enrolled subjects: 111 subjects
- Full Analysis Set (FAS): 111 subjects
- Safety Analysis Set: 111 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were HCV treatment-naive males and nonpregnant/nonlactating females, aged 18 years or older, with chronic genotype 3 HCV infection, had documentation of the presence or absence of cirrhosis, and had a body mass index (BMI) ≥ 18 kg/m^2.

Duration of Treatment: Treatment duration was 12 weeks with a 12-week posttreatment follow-up period.

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

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

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

- **LDV/SOF**: DK1304B1
- **RBV**: AA2773Z

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

Criteria for Evaluation:

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

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

Safety: Safety assessments including monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital sign measurements, and physical examinations.

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.

Efficacy: The primary efficacy endpoint was the proportion of subjects with HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs (SVR12) for the FAS. Point estimates and 2-sided 95% exact confidence intervals (CIs) for SVR12 based on the Clopper-Pearson method were provided. Subgroup analyses were performed to assess the relationship between SVR12 and baseline demographic and disease characteristics. Point estimates and 95% exact CIs of the SVR12 rates were calculated for each subgroup.

Secondary efficacy endpoints included SVR4, proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through the end of treatment, and proportion of subjects with virologic failure.

Pharmacokinetics: No PK assessments were performed for this report.

Safety: All 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 sign measurements, and physical examinations. Safety data included all data collected on or after the first dose of any study drug up to the last dose of study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1. All AEs and laboratory abnormalities presented in this report were treatment emergent and are referred to as AEs and laboratory abnormalities, respectively, in this report.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 111 subjects were enrolled and received at least 1 dose of study drug (Table 15.8.1.2). Of the 111 enrolled and treated subjects, 2 subjects (1.8%) prematurely discontinued study treatment: 1 subject (0.9%) due to an AE and 1 subject (0.9%) was lost to follow-up.

The majority of subjects were male (61.3%), white (70.3%), of non-Hispanic or non-Latino ethnicity (100.0%), with a mean age of 48 years (range: 26-75) (Table 15.8.3). The mean (SD) baseline BMI for subjects was 27.0 (6.45) kg/m^2, and 24.3% of subjects had a BMI $\geq$ 30 kg/m^2.

All subjects had genotype 3 HCV infection. The majority of subjects in the Safety Analysis Set had genotype 3a HCV infection (94.6%), non-CC (CT or TT) IL28B alleles (62.2%), and HCV RNA ≥ 800,000 IU/mL (68.5%), with a mean (SD) HCV RNA value of 6.2 (0.66) $\log_{10}$ IU/mL. A total of 39 subjects (35.1%) had cirrhosis at screening. The mean (SD) baseline alanine aminotransferase (ALT) value was 98 (63.9) U/L, and 64.9% of subjects had baseline ALT values > 1.5 × ULN. Overall, the mean (SD) baseline estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation was 122.6 (40.13) mL/min.

Efficacy Results: The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs, in the FAS. Table 1 presents the proportion of subjects with SVR12. The SVR12 rate was 89.2% (99 of 111 subjects). Overall, 12 subjects (10.8%) did not achieve SVR12. Of these, 8 subjects (7.2%) relapsed, 3 subjects (2.7%) were lost to follow-up, and 1 subject (0.9%) died (Listing 16.2.6.3). No subjects had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse).

The SVR4 rate was 91.9% (102 of 111 subjects) (Table 15.9.2.2). Of the 3 subjects who achieved SVR4 but did not achieve SVR12, 2 subjects relapsed and 1 subject was lost to follow-up (Listings 16.2.6.1 and 16.2.6.3).

Table 1. GS-US-337-1701: Proportion of Subjects with SVR12 and Virologic Outcomes (Full Analysis Set)

	LDV/SOF+RBV 12 Weeks (N = 111)
SVR12	99/111 (89.2%)
Overall Virologic Failure	8/111 (7.2%)
Relapse	8/111 (7.2%)
Completed Study Treatment	8/109 (7.3%)
Discontinued Study Treatment	0/2
On-Treatment Virologic Failure	0/111
Other	4/111 (3.6%)

HCV RNA was analyzed using COBAS® Ampliprep/COBAS® Taqman® HCV Quantitative Test, v2.0 with limit of quantitation 15 IU/mL.
Relapse = confirmed HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at last on-treatment visit.
On-Treatment Virologic Failure = Breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), Rebound (confirmed > 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment), or Non-response (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment). Other = subject who did not achieve SVR12 and did not meet virologic failure criteria.
Source: Table 15.9.2.1.1

Prespecified analyses of subgroups indicated that the SVR12 rates were generally consistent with those observed in the overall population, with high SVR12 rates observed in most subgroups (Table 15.9.3.1). Among subjects with cirrhosis, the SVR12 rates were lower (31 of 39 subjects, 79.5%, 95% CI: 63.5% to 90.7%) compared with subjects without cirrhosis (66 of 70 subjects, 94.3%, 95% CI: 86.0% to 98.4%).

HCV RNA levels (log_{10} IU/mL) declined rapidly (Table 15.9.2.4). After 1 week of treatment, the median change from baseline was −4.30 log_{10} IU/mL. At on-treatment Week 4, 97.3% of subjects had HCV RNA < LLOQ (Table 15.9.2.3).

All efficacy analyses are provided in Tables 15.9.1 to 15.9.3.3, Figures 15.9.2.3 to 15.9.2.5.4, and Listings 16.2.6.1 to 16.2.6.3.

Virologic Resistance Analysis:

Sequencing for the HCV nonstructural protein 5A (NS5A), and NS5B regions was attempted for all enrolled subjects at baseline and subjects with virologic failure at the failure time point by deep sequencing with a 1% cut-off. HCV consensus sequences were generated for all successfully deep sequenced samples.

The NS5A variants were considered as associated with resistance to NS5A inhibitors as follows: S24G/N/R, M28A/G/T, A30E/G/H/K/R, L31I/F/M/V, P32L, S38F, P58D/G, E92T, and Y93C/F/H/N/S. The following variants were defined as NS5B nucleoside inhibitor (NI) resistance-associated variants (RAVs): S96T, N142T, L159F, E237G, S282any, C289I/L, L320F/I/V, and V321A/I.

Baseline analyses were performed for subjects who completed treatment and had a virologic outcome (N = 107) and did not include 4 subjects who were in the "other" virologic outcome category.

NS5A deep sequencing results were obtained for 106 of 107 subjects; NS5A amplification failed in 1 subject (Appendix 16.2, Virology Listing 1). NS5B deep sequencing results were obtained for 104 subjects, short fragment population sequencing was obtained for 2 additional subjects, and NS5B amplification failed in 1 subject (Appendix 16.2, Virology Listing 2). Baseline sequencing results were used for basic local alignment search tool (BLAST) analysis to determine HCV subtypes and showed that 100 subjects had genotype 3a HCV infection, 2 subjects had genotype 3b HCV infection, 3 subjects had genotype 3g HCV infection, 1 subject had genotype 3h HCV infection, and 1 subject had genotype 3i HCV infection (Appendix 16.2, Virology Listing 5).

Baseline NS5A RAVs were detected in 15 of 106 subjects (14.2%) with successful NS5A deep sequencing (Table 2). Of these, 13 of 15 subjects (86.7%) with baseline NS5A RAVs achieved SVR12. NS5B NI RAVs were detected in 10 of 104 subjects (9.6%) with successful NS5B deep sequencing. All subjects with baseline NS5B NI RAVs achieved SVR.

Table 2. GS-US-337-1701: Number of Subjects with Baseline NS5A RAVs and Virologic Outcome

	LDV/SOF+RBV 12 Weeks (N = 111)
Subjects with NS5A sequencing data and virologic outcome	106/111 (89.2%)
With NS5A baseline RAVs (1% cut-off)	15/106 (14.2%)
SVR rate in subjects with baseline NS5A RAVs	13/15 (86.7%)
SVR rate in subjects without baseline NS5A RAVs	85/91 (93.4%)

Source: Appendix 16.2, Virology Listing 1

No on-treatment breakthrough was observed in this study. A total of 8 subjects experienced viral relapse. NS5A and NS5B were successfully deep sequenced from all 8 subjects at baseline and virologic failure time points (Table 3). Two of the 8 subjects with virologic relapse had Y93H at baseline (1.0% and 18.1% of viral population). Y93H was no longer detectable at virologic failure in both subjects. No other NS5A RAVs or NS5B NI RAVs were detected in subjects with relapse at baseline or virologic failure.

Table 3. GS-US-337-1701: NS5A RAVs and NS5B NI RAVs in Subjects with Virologic Failure

Subject ID	Genotype	NS5A RAVs		NS5B NI RAVs	
		Baseline	Relapse	Baseline	Relapse
PPD	3a	Y93H (18.1%)	None	None	None
PPD	3a	Y93H (1.0%)	None	None	None
PPD PPD PPD PPD PPD PPD	3a	None	None	None	None

Source: Appendix 16.2, Virology Listings 3 and 4.

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

Safety Results:

The mean (SD) duration of exposure to study regimen was 12.1 (0.42) weeks (Table 15.11.1). The proportion of subjects with ≥ 80% adherence to LDV/SOF was 98.2% and with ≥ 80% adherence to RBV was 95.5% (Table 15.8.4).

Adverse Events and Serious Adverse Events

The majority of subjects (84.7%, 94 of 111 subjects) experienced at least 1 AE (Table 15.11.2.1.3). The most frequently reported AEs were fatigue (51.4%, 57 subjects), headache (36.0%, 40 subjects), and nausea (22.5%, 25 subjects).

Most AEs reported in the study were Grade 1 or Grade 2 in severity (Listings 16.2.7.1 and 16.2.7.2). Three Grade 4 AEs (hepatic cancer, homicidal ideation, and suicidal ideation) were reported in 2 subjects (1.8%) (Table 15.11.2.2.1). These AEs were considered serious and not related to study drug (Listing 16.2.7.4). Subject PPD had an AE of hepatic cancer that led to premature discontinuation of study treatment (Listing 16.2.7.2). Subject PPD discontinued study treatment after 57 days and experienced AEs of homicidal ideation and suicidal ideation 18 days after the last dose of study drugs; this subject was lost to follow-up (Listing 16.2.1.2). Grade 3 AEs were reported in 6 subjects (5.4%) (Table 15.11.2.2.1). One Grade 3 AE (hypertensive crisis) on Day 43, considered serious but considered not related to study drug, led to study treatment interruption; the AE resolved after 2 days and the subject resumed study treatment on Day 57 (Listings 16.2.5.1 and 16.2.7.2). In addition, 1 Grade 3 AE (migraine) was considered related to study drug by the investigator but did not require modification of study treatment; this AE resolved 2 days after the completion of study treatment.

A total of 4 subjects (3.6%) experienced at least 1 serious adverse event (SAE) (hypertensive crisis, hyponatremia, intervertebral disc protrusion, homicidal ideation, suicidal ideation, and hepatic cancer); none were considered related to study drug (Table 15.11.4.1 and

Listing 16.2.7.4). No 1 SAE was reported in more than 1 subject. The SAEs of hypertensive crisis and hyponatremia in 1 subject led to study drug interruption.

The subject with an SAE of hepatic cancer (Subject PPD who also had Grade 2 AEs of melena and splenic varices, was the only subject who had an AE leading to premature discontinuation of study drug (Listing 16.2.7.5). This subject died 22 days after the last dose of study treatment (Listing 16.2.7.3).

Though no pregnancies were reported during the study (Listing 16.2.8.3), 1 pregnancy was reported after the subject completed study treatment and the posttreatment Week 12 visit and 1 partner pregnancy was reported.

Narratives for SAEs, pregnancies, and the 1 death during this study are provided in Section 15.2. All AE results are provided in Tables 15.11.1 to 15.11.5.5, and Listings 16.2.7.1 to 16.2.7.6, and 16.2.8.3.

Clinical Laboratory Results

Two subjects (1.8%) had a Grade 4 laboratory abnormality (Table 15.11.6.4.2). One Grade 4 laboratory abnormality was reported at Week 8 (elevated aspartate aminotransferase [AST]) for a subject who had graded AST abnormalities at baseline (Listing 16.2.8.1.3). One Grade 4 laboratory abnormality was reported at the posttreatment Week 4 visit (elevated lipase); this isolated abnormality resolved by posttreatment Day 30.

Thirteen subjects (11.7%) had a Grade 3 laboratory abnormality (Table 15.11.6.4.2 and Listing 16.2.8.1.3). There were 8 subjects (7.2%) with Grade 3 hematology abnormalities of decreased hemoglobin during treatment that resolved or were resolving after treatment. A summary of hemoglobin values showed that 9 subjects (8.1%) had postbaseline hemoglobin values < 10 g/dL (Table 15.11.6.1.1.2). No subjects had postbaseline hemoglobin values < 8.5 g/dL. Two subjects (1.8%) with either a history of diabetes or elevated serum glucose prior to starting study treatment had Grade 3 laboratory abnormalities of increased serum glucose (Listing 16.2.4.3.1). One subject (0.9%) had a Grade 3 coagulation abnormality of elevated prothrombin time at Week 12 that resolved at the posttreatment Week 4 visit. In addition, Grade 3 chemistry abnormalities were reported in 1 subject each (0.9%) for elevated creatine kinase (isolated abnormality at Week 2), decreased serum sodium (in a subject with a medical history of hyponatremia), and elevated total bilirubin (in a subject with elevated levels at baseline and throughout the study).

All laboratory results are provided in Tables 15.11.6.1.1.1 to 15.11.6.4.2, Figures 15.11.6.1.1 to 15.11.6.2.4, and Listings 16.2.8.1.1 to 16.2.8.1.9.

Vital Sign Measurements

No clinically relevant changes in vital sign measurements were reported (Tables 15.11.7.1.1 to 15.11.7.1.3, Listings 16.2.8.2.1 to 16.2.8.2.2).

CONCLUSIONS: The conclusions from Study GS-US-337-1701 are as follows:

- In treatment-naive subjects with genotype 3 HCV infection, treatment with LDV/SOF+RBV for 12 weeks provided a high virologic response rate; the SVR12 rate was 89.2% (99 of 111 subjects). The SVR12 rate was lower in subjects with cirrhosis (79.5%) than those without cirrhosis (94.3%).
- Treatment with LDV/SOF+RBV resulted in rapid and sustained viral suppression. No subjects experienced on-treatment virologic failure.
- Presence of baseline NS5A or NS5B NI RAVs did not impact treatment outcome. No NS5A or NS5B RAVs were detected at virologic failure.
- Treatment with LDV/SOF+RBV was well tolerated in this study. The safety profile observed was consistent with that reported for treatment with LDV/SOF+RBV. There was no new safety signal or toxicity observed in this study.