FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks with Ribavirin or for 24 Weeks Without Ribavirin in Treatment-Experienced Cirrhotic Subjects with Chronic Genotype 1 HCV Infection
Name of Test Drug:	Ledipasvir (LDV)/Sofosbuvir (SOF) Fixed-Dose Combination (FDC)
Dose and Formulation:	FDC tablet containing LDV/SOF 90 mg/400 mg
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404USA
Study No.:	GS-US-337-0121 (SIRIUS)
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	115268 2013-002296-17
Study Start Date:	26 September 2013 (First Subject Screened)
Study End Date:	12 November 2014 (Last Subject Observed)
Principal or Coordinating Investigator:	Name: Marc Bourlière, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Phil Pang, MD, PhD Telephone: PPD Fax: PPD
Report Date:	04 March 2015

STUDY SYNOPSIS
Study GS-US-337-0121
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks with Ribavirin or for 24 Weeks Without Ribavirin in Treatment-Experienced Cirrhotic Subjects with Chronic Genotype 1 HCV Infection

Investigators: This was a multicenter study.

Study Centers: There were 20 sites in France.

Publications:

Bourlière M, Sulkowski MS, Omata M, Zeuzem S, Feld JJ, Lawitz E, et al. An Integrated Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with Ledipasvir/Sofosbuvir with or without Ribavirin. Hepatology (2014), 60: 4 (suppl) 239A.

Bourlière M, Bronowick J-P, de Ledinghen V, Hézode C, Zoulim F, Mauthrin P, et al. Ledipasvir/Sofosbuvir Fixed Dose Combination is Safe and Efficacious in Cirrhotic Patients Who Have Previously Failed Protease-Inhibitor Based Triple Therapy. Hepatology (2014), 60: 6 (suppl) 1270A.

Study Period:

26 September 2013 (First Subject Screened)
12 November 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 (LDV)/sofosbuvir (SOF) fixed-dose combination (FDC) for 24 weeks and LDV/SOF + ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (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 discontinuation of therapy (SVR4 and SVR24)

- To compare the safety profile during the first 12 weeks of treatment of the 24-week LDV/SOF treatment group with the 12-week placebo control treatment period
- To compare, in the deferred start group, the safety profile during the first 12 weeks of the study (placebo period) with the second 12 weeks (LDV/SOF+RBV period) of the study
- 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 evaluate the effect of treatment on markers for liver cirrhosis including LOXL-2, Fibrotest®/aspartate aminotransferase (AST):platelet ratio index (APRI), and transient elastography
- 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
- To assess the effect of treatment on health-related quality of life

Methodology: This Phase 2, randomized, double-blind, placebo-controlled, multicenter study assessed the antiviral efficacy and safety of LDV/SOF for 12 weeks with RBV or for 24 weeks without RBV in treatment-experienced cirrhotic subjects with chronic genotype 1 HCV infection.

Approximately 155 subjects were randomized (1:1) to 1 of the following 2 treatment groups:

- Group 1 - LDV/SOF + placebo RBV 24 weeks (referred to as the LDV/SOF 24 week group): LDV/SOF FDC (90 mg/400 mg) tablet once daily + matched RBV placebo tablet (divided twice daily [BID]) for 24 weeks
- Group 2 - placebo 12 weeks followed by LDV/SOF+RBV 12 weeks (referred to as the LDV/SOF+RBV 12 week group): Matched LDV/SOF placebo tablet once daily + matched RBV placebo tablet (divided BID) for 12 weeks followed by 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 genotype (1a or 1b; mixed or other genotype 1 results were stratified as genotype 1a) and prior response to HCV treatment therapy (never achieved HCV RNA less than the lower limit of quantitation [< LLOQ] or achieved HCV RNA < LLOQ). Study treatment assignment and on-treatment HCV RNA results were double-blinded.

All subjects were eligible to participate in a pharmacogenomics substudy if consent was obtained. Subjects who did not achieve SVR were eligible for enrollment in the Sequence Registry Study (GS-US-248-0123). Subjects who achieved SVR24 were eligible for enrollment in the SVR Registry Study (GS-US-248-0122) to evaluate durability of SVR for up to 3 years after treatment.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 150 subjects (75 in each treatment group)

Analyzed:

- All randomized subjects: 155 subjects
- Full Analysis Set (FAS): 154 subjects
- Safety Analysis Set: 155 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males and nonpregnant/nonlactating females ≥ 18 years of age with chronic genotype 1 HCV infection, screening HCV RNA levels ≥ 10^4 IU/mL, documentation of prior virologic failure after treatment with a protease inhibitor (PI) + pegylated interferon (Peg-IFN) + RBV regimen following prior virologic failure after treatment(s) with Peg-IFN+RBV regimen, and documentation of compensated cirrhosis.

Duration of Treatment: Treatment duration was 12 weeks (LDV/SOF+RBV 12 week group) or 24 weeks (LDV/SOF 24 week group).

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

- LDV/SOF was administered orally at a dose of 90 mg/400 mg (1 LDV/SOF FDC tablet once daily). Subjects in the LDV/SOF 24 week group took 1 tablet daily with or without food. Subjects in the LDV/SOF+RBV 12 week group took 1 tablet daily with or without food starting at their Week 12 visit and for the remaining 12 weeks.
- RBV was administered orally at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided BID). Subjects in the LDV/SOF+RBV 12 week group took RBV with food starting at their Week 12 visit and for the remaining 12 weeks.

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

The RBV lot number of drug administered in this study was A97944X.

Reference Therapy, Dose, Mode of Administration, and Lot No.:

- Placebo tablets to match LDV/SOF FDC tablets were administered orally once daily. Subjects in the LDV/SOF+RBV 12 week group took 1 tablet daily with or without food for the first 12 weeks of treatment.
- Placebo tablets to match RBV tablets were administered orally (divided BID). Subjects in the LDV/SOF 24 week group took 5 or 6 tablets with food for 24 weeks. Subjects in the LDV/SOF+RBV 12 week group took 5 or 6 tablets with food for the first 12 weeks of treatment.

The LDV/SOF placebo lot number of drug administered in this study was DK1207B1.

The RBV placebo lot number of drug administered in this study was A88159Z.

Criteria for Evaluation:

Efficacy: Blood samples to determine HCV RNA levels were collected from subjects at screening, Day 1 (predose), and at every subsequent on-treatment and posttreatment visit. The COBAS® Taqman® HCV Test v2.0 assay for use with the High Pure System was used to quantify HCV RNA in this study. The LLOQ of the assay was 25 IU/mL.

Pharmacokinetics: A single pharmacokinetic (PK) blood sample was collected at each on-treatment visit for all subjects.

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

Quality of Life: Health-related quality of life was assessed with the Short Form Health Survey (SF-36), Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, and the Work Productivity and Activity Impairment: Hepatitis C (WPAI: Hep C) questionnaire.

Statistical Methods:

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the FAS. The primary efficacy endpoint analysis was performed after all randomized subjects had completed the posttreatment Week 12 visit or prematurely discontinued from the study. In the primary efficacy analysis, the SVR12 rate in each of the 2 treatment groups was estimated with 2-sided 95% exact confidence interval (CI) using the binomial distribution (Clopper-Pearson method). Secondary efficacy endpoints included SVR4, SVR24, the proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through Week 12, and the proportion of subjects with virologic failure.

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

Pharmacokinetics: Pharmacokinetic analyses were not conducted for this study.

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 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. By visit safety laboratory and vital sign data were summarized according to the following groups: 1) LDV/SOF for 24 weeks, 2) LDV/SOF+RBV for 12 weeks, and 3) placebo for 12 weeks. Adverse events and other safety data not summarized by visit were summarized according to the following groups: 1) LDV/SOF for 24 weeks, 2) placebo for 12 weeks followed by LDV/SOF+RBV for 12 weeks, 3) LDV/SOF for 12 weeks (first 12 weeks of LDV/SOF for 24 weeks), 4) LDV/SOF+RBV for 12 weeks (second 12 weeks of placebo for 12 weeks followed by LDV/SOF+RBV for 12 weeks), and 5) placebo for 12 weeks (first 12 weeks of placebo for 12 weeks followed by LDV/SOF+RBV for 12 weeks).

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.1.

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 4, 12, 16, and 24, early termination (if applicable), and posttreatment Weeks 4, 12, and 24 (if applicable). Questionnaire data were summarized according to the following groups: 1) LDV/SOF for 24 weeks, 2) LDV/SOF+RBV for 12 weeks, and 3) placebo LDV/SOF + placebo RBV for 12 weeks. 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 group differences between LDV/SOF for 24 weeks and placebo by time point. A Wilcoxon signed rank test explored group differences between placebo and LDV/SOF+RBV for 12 weeks by time point.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Of the 155 randomized subjects, 155 (100.0%) received at least 1 dose of study drug and were included in the Safety Analysis Set. A total of 154 subjects (99.4%) received active study treatment and were included in the FAS. One subject randomized to the LDV/SOF+RBV 12 week group discontinued placebo treatment on Day 32 due to AEs (bacterial arthritis and hepatic cirrhosis) prior to receiving LDV/SOF+RBV and was therefore excluded from the FAS. This was the only subject who did not complete study treatment or receive active study drug.

One subject was randomized to the LDV/SOF+RBV 12 week group but instead received LDV/SOF + placebo RBV for 24 weeks. This subject was included in the LDV/SOF 24 week group for the safety analysis and included in the LDV/SOF+RBV 12 week group for the efficacy analysis per the prespecified intent-to-treat approach.

All subjects were treatment-experienced and had failed treatment with Peg-IFN+RBV followed by a PI+Peg-IFN+RBV regimen.

The majority of subjects were male (73.5%), white (97.4%), and not Hispanic or Latino (97.4%), with a mean age of 56 years (range: 23 to 77 years). The mean baseline body mass index (BMI) was 27.1 kg/m2 (range: 19.1 to 47.1 kg/m2), and 20.6% of subjects had a BMI ≥ 30 kg/m2.

All subjects in the Safety Analysis Set had genotype 1a (63.2%), genotype 1b (35.5%), or genotype 1 with no confirmed subtype (1.3%) HCV infection. All subjects met the protocol defined definition of cirrhosis, with the exception of 1 subject randomized without their cirrhosis status having been determined in a protocol approved manner. This subject was randomized to the LDV/SOF+RBV 12 week group.

Most subjects (93.5%) had non-CC (CT or TT) IL28B alleles. The overall mean baseline HCV RNA was 6.5 $\log_{10}$ IU/mL (range: 3.9 to 7.7 $\log_{10}$ IU/mL).

Efficacy Results: A total of 149 of 154 subjects achieved SVR12 across both treatment groups; 97.4% of subjects in the LDV/SOF 24 week group and 96.1% of subjects in the LDV/SOF+RBV 12 week group achieved SVR12. The difference in SVR12 between the 2 treatment groups was not statistically significant (p = 0.63). All 5 subjects who did not achieve SVR12 relapsed. All subjects in the FAS completed study treatment and no subject in either treatment group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse).

Overall, SVR4 results were the same as SVR12 results with the exception of 1 subject in the LDV/SOF+RBV 12 week group who achieved SVR4, but relapsed at posttreatment Week 12. All subjects who achieved SVR12 who had posttreatment Week 24 assessments also achieved SVR24, resulting in 100% concordance between SVR12 and SVR24.

The high SVR12 rates observed in both treatment groups preclude meaningful interpretation of subgroup analyses.

Potent and rapid suppression of HCV RNA was observed in both treatment groups. By Week 2, > 50% of subjects in each treatment group had HCV RNA < LLOQ, which increased to > 97% of subjects at Week 4.

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly in both treatment groups. After 1 week of treatment, mean (SD) changes from baseline across both groups ranged from −4.27 (0.547) to −4.10 (0.558) $\log_{10}$ IU/mL, demonstrating that similar decreases in HCV RNA were observed in both treatment groups, irrespective of inclusion of RBV in the treatment regimen.

Virologic Resistance Results: Overall, a total of 30 of 154 subjects (19.5%) had pretreatment nonstructural protein 5A (NS5A) resistance-associated polymorphisms (RAPs); 8 of 97 subjects (8.2%) with genotype 1a HCV infection had pretreatment NS5A RAPS, 20 of 55 subjects (36.4%) with genotype 1b HCV infection had pretreatment NS5A RAPs, and 2 of 2 subjects (100.0%) with genotype 1e HCV infection had pretreatment NS5A RAPs. These 30 subjects included 15 of 77 subjects (19.5%) in the LDV/SOF+RBV 12 week group and 15 of 77 subjects (19.5%) in the LDV/SOF 24 week group. Among these 30 subjects with NS5A RAPs, all 15 subjects (100.0%) in the LDV/SOF+RBV 12 week group achieved SVR12 while 13 of 15 subjects (86.7%) in the LDV/SOF 24 week group achieved SVR12.

Six subjects (4%) had pretreatment NS5B RAPs; 5 of 6 subjects achieved SVR12 including 4 of 5 subjects with genotype 1b HCV infection with L159F and 1 subject with genotype 1b HCV infection with V321I.

Fifty-two of 151 subjects (34.4%) were observed to have NS3 resistance-associated variants (RAVs) at baseline. All 52 subjects achieved SVR12.

The 5 subjects who did not achieve SVR12 experienced virologic relapse. Both relapse subjects treated with LDV/SOF for 24 weeks had pretreatment NS5A RAPs that were maintained or enriched posttreatment. No pretreatment RAPs were observed in the 3 relapse subjects treated with LDV/SOF+RBV; however, all 3 subjects had 1 or more NS5A RAVs or RAPs emerge posttreament. Relapse was associated with single class NS5A resistance. No SOF RAV S282T or treatment emergent variants (TEVs) emerged in any subjects who relapsed in this study.

Pharmacokinetics Results: Pharmacokinetic analyses were not conducted for this study.

Safety Results:

Safety data for subjects who received LDV/SOF + placebo RBV for 24 weeks for the overall treatment period are referred to as LDV/SOF 24 week data. Safety data for the first 12 weeks of this 24-week treatment period are referred to as LDV/SOF 12 week data. Safety data for subjects who received placebo for 12 weeks followed by LDV/SOF+RBV for 12 weeks for the overall treatment period are referred to as LDV/SOF+RBV overall data. Safety data for the first 12 weeks for this group are referred to as placebo data. Safety data for the second 12 weeks for this group are referred to as LDV/SOF+RBV data. The LDV/SOF 24 week data and LDV/SOF+RBV overall data include the 30 day posttreatment follow-up period.

LDV/SOF for 24 weeks and LDV/SOF+RBV for 12 weeks were both well tolerated with no subjects discontinuing active treatment due to AEs. Comparing these 2 regimens overall, a higher frequency of AEs and treatment-related AEs were observed with LDV/SOF+RBV for 12 weeks compared with LDV/SOF for 24 weeks. This difference is attributable to a higher incidence in RBV-associated AEs such as pruritus and dyspnea in the LDV/SOF+RBV group. A comparison of the three 12-week treatment periods (the first 12 weeks of LDV/SOF + placebo RBV, placebo for 12 weeks, and LDV/SOF+RBV for 12 weeks) is provided below.

When comparing the three 12-week treatment periods, similar percentages of subjects with any AE were observed during treatment with LDV/SOF (84.6%, 66 subjects), placebo (81.6%, 63 subjects), and LDV/SOF+RBV (86.8%, 66 subjects). The AEs reported more commonly (> 10%) than placebo were headache and fatigue for LDV/SOF 12 week; there were no events that occurred more commonly (> 10%) for LDV/SOF+RBV compared to placebo.

Only 1 subject, who was receiving placebo, permanently discontinued study treatment. Discontinuation was due to AEs of bacterial arthritis and hepatic cirrhosis (reported as Grade 2 gonarthritis [left knee] staphylococcus aureus and Grade 4 decompensated cirrhosis). These AEs were serious, and the hepatic cirrhosis was considered life-threatening. The events were considered unrelated to study drug. The subject subsequently received an emergency liver transplant.

Most AEs were Grade 1 or 2 in severity. Grade 3 and 4 AEs were rare. When comparing the three 12-week treatment periods, 2 subjects (2.6%) receiving LDV/SOF, 1 subject (1.3%) receiving placebo, and 5 subjects (6.6%) receiving LDV/SOF+RBV had Grade 3 or 4 AEs. Overall, asthenia, headache, anemia, and back pain were the only Grade 3 AEs reported in > 1 subject. There were no Grade 4 AEs other than hepatic cirrhosis as described above.

Overall, serious adverse events (SAEs) were rare. No trends in SAE type or onset time were observed, as no SAE was reported in > 1 subject. All SAEs were considered unrelated to study drug with the exception of anemia reported in 1 subject during treatment with LDV/SOF+RBV. Other than the 2 SAEs (bacterial arthritis and hepatic cirrhosis) described above, no SAEs led to treatment discontinuation.

No deaths or pregnancies were reported in the study.

The majority of laboratory abnormalities were Grade 1 or 2 in severity. When comparing the three 12-week treatment periods, there was a higher percentage of subjects with Grade 3 and 4 laboratory abnormalities during treatment with placebo (Grade 3, 19.5%, 15 subjects; Grade 4, 3.9%, 3 subjects) compared with LDV/SOF (Grade 3, 12.8%, 10 subjects; Grade 4, 1.3%,

1 subject) and LDV/SOF+RBV (Grade 3, 10.5%, 8 subjects; Grade 4, 0.0%, no subjects). This higher incidence of Grade 3 and 4 laboratory abnormalities during placebo treatment was due in large part to abnormalities of alanine aminotransferase and AST, which are expected for the natural history of untreated HCV infection.

During the entirety of treatment, inclusive of all subjects, other notable Grade 3 or 4 chemistry laboratory abnormalities included 7 cases of elevated lipase, none of which were associated with an AE of pancreatitis, and 11 cases of hyperglycemia, all of which occurred in subjects with a history of diabetes or abnormal glucose/hemoglobin $A1_c$ at baseline.

With respect to Grade 3 hematology laboratory abnormalities, the most common abnormality was decreased hemoglobin, which was observed only during treatment with placebo (1 subject) or LDV/SOF+RBV (3 subjects). No subjects in the RBV-free (LDV/SOF) group had Grade 3 decreased hemoglobin at any time. No Grade 4 hematology laboratory abnormalities were reported with the exception of a Grade 4 decrease in lymphocytes that was reported in the subject who experienced SAEs of bacterial arthritis and hepatic cirrhosis described above.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study. No clinically significant abnormal 12-lead ECGs were captured.

Quality of Life Results: Overall, the mean scores for all scales (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C quality of life questionnaires) improved from end of treatment to posttreatment Week 24 for both the LDV/SOF 24 week and LDV/SOF+RBV 12 week groups. 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 conclusions for Study GS-US-337-0121 are as follows:

- Treatment with LDV/SOF+RBV for 12 weeks or LDV/SOF for 24 weeks resulted in similarly high SVR12 rates in treatment-experienced cirrhotic subjects with genotype 1 HCV infection who had previously failed sequential treatment with Peg-IFN+RBV and PI+Peg-IFN+RBV.
- Treatment with LDV/SOF±RBV was generally well tolerated in this study, with no deaths, few SAEs, few Grade 3 AEs, and few Grade 3 or 4 laboratory abnormalities.
- The side effect profile of LDV/SOF+RBV treatment was similar to the expected profile of RBV.