FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Randomized, Open-Label Study of Sofosbuvir/Ledipasvir Fixed-Dose Combination with Ribavirin or GS-9669 250 mg or GS-9669 500 mg in Naïve or Treatment-Experienced Cirrhotic Subjects with Chronic Genotype 1 HCV Infection
Name of Test Drug:	Ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC); GS-9669
Dose and Formulation:	LDV/SOF FDC (90 mg/400 mg) tablet; GS-9669 (250 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-337-0133
Phase of Development:	Phase 2
IND No.:	115268
EudraCT No.:	Not applicable
Study Start Date:	29 October 2013 (First Subject Screened)
Study End Date	18 July 2014 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Eric Lawitz, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Phil Pang, MD, PhD Telephone: PPD
Report Date:	20 November 2014

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS
Study GS-US-337-0133
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Randomized, Open-Label Study of Sofosbuvir/Ledipasvir Fixed-Dose Combination with Ribavirin or GS-9669 250 mg or GS-9669 500 mg in Naïve or Treatment-Experienced Cirrhotic Subjects with Chronic Genotype 1 HCV Infection

Investigators: Eric Lawitz, MD

Study Centers: 1 site in the United States

Publications:
Lawitz E, Poordad F, Hyland RH, Wang J, Pang PS, Symonds WT, et al. High Rates of SVR in Patients With Genotype 1 HCV Infection and Cirrhosis After Treatment With Ledipasvir/Sofosbuvir + Ribavirin or Ledipasvir/Sofosbuvir + GS-9669 for 8 Weeks. American Association for the Study of Liver Disease (AASLD): The Liver Meeting; 2014 November 7-11; Boston, MA United States

Study Period:

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

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To evaluate the antiviral efficacy of combination therapy with ledipasvir (LDV)/sofosbuvir (SOF) fixed-dose combination (FDC) + ribavirin (RBV), LDV/SOF + GS-9669 250 mg, or LDV/SOF + GS-9669 500 mg for 8 weeks in treatment-naive or treatment-experienced subjects, as measured by sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of LDV/SOF+RBV, LDV/SOF + GS-9669 250 mg, and LDV/SOF + GS-9669 500 mg administered for 8 weeks

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attained SVR at 2, 4, 8, and 24 weeks after discontinuation of therapy (SVR2, SVR4, SVR8, and SVR24)
- To evaluate the emergence of viral resistance to SOF, LDV, and GS-9669 during and after treatment discontinuation

- To characterize viral dynamics during and after treatment discontinuation
- To characterize steady-state pharmacokinetics (PK) of study drugs

The exploratory objective of this study was 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 the tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics) in subjects who provided a separate and specific consent

Methodology: This Phase 2, randomized, open-label study evaluated the antiviral efficacy of treatment with LDV/SOF FDC in combination with RBV or GS-9669 for 8 weeks in treatment-experienced and treatment-naive subjects with genotype 1 hepatitis C virus (HCV) infection and cirrhosis.

Approximately 90 eligible subjects were randomized 1:1:1 into one of the following treatment groups:

- **LDV/SOF+RBV:** LDV/SOF (90 mg/400 mg) once daily + RBV (1000 or 1200 mg/day) divided into 2 doses for 8 weeks (Group 1)
- **LDV/SOF+GS-9669 250 mg:** LDV/SOF (90 mg/400 mg) once daily + GS-9669 (250 mg) once daily for 8 weeks (Group 2)
- **LDV/SOF+GS-9669 500 mg:** LDV/SOF (90 mg/400 mg) once daily + GS-9669 (500 mg) once daily for 8 weeks (Group 3)

Randomization was stratified by prior treatment experience (treatment naive, treatment experienced < 12 weeks duration, or treatment experienced ≥ 12 weeks duration) and HCV genotype (1a or 1b). Subjects with mixed HCV genotype were stratified as genotype 1a. Approximately 60 subjects had prior treatment with a pegylated interferon alfa (Peg-IFN) + RBV-containing regimen for ≥ 12 weeks.

Number of Subjects (Planned and Analyzed):

Planned: 90 subjects (30 subjects per treatment group)

Analyzed (by analysis set):

- Full Analysis Set: 100 subjects (35 in the LDV/SOF+RBV group; 32 in the LDV/SOF+GS-9669 250-mg group; 33 in the LDV/SOF+GS-9669 500-mg group)
- Safety Analysis Set: 100 subjects (35 in the LDV/SOF+RBV group; 32 in the LDV/SOF+GS-9669 250-mg group; 33 in the LDV/SOF+GS-9669 500-mg group)
- PK Analysis Set: 43 subjects (21 in the LDV/SOF+GS-9669 250-mg group; 22 in the LDV/SOF+GS-9669 500-mg group)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were treatment-experienced and treatment-naive males and nonpregnant, nonlactating females ≥ 18 years old with genotype 1 HCV infection; compensated cirrhosis; screening HCV RNA ≥ 10^4 IU/mL; and body mass index (BMI) ≥ 18 kg/m^2.

Duration of Treatment: 8 weeks

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

- **LDV/SOF** was administered orally once daily at a dose of 90 mg/400 mg (1 × 90 mg/400 mg FDC tablet).
- **GS-9669** was administered orally once daily with food at a dose of 250 mg or 500 mg (1 or 2 × 250-mg tablets).
- **RBV** was administered orally with food at a dose of 1000 or 1200 mg/day divided into 2 doses (5 or 6 × 200-mg tablets).

LDV/SOF lot number: DK1209B1R

GS-9669 lot number: CU1301B1R

RBV lot number: A97943Z

Criteria for Evaluation:

Efficacy: Efficacy was evaluated by measuring HCV RNA levels at baseline/Day 1; on-treatment Weeks 1, 2, 4, and 8; and posttreatment Weeks 2, 4, 8, 12, and 24 using the COBAS® AmpliPrep/COBAS® TaqMan® V2.0 assay. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: Single PK blood samples were collected for all subjects at each on-treatment visit. For subjects who consented to participate in the PK substudy, intensive serial PK samples were obtained over 24 hours postdose at or between the Week 2 or Week 4 on-treatment visits.

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

Statistical Methods:

Efficacy: The primary efficacy endpoint was the proportion of subjects with HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after discontinuation of study treatment (SVR12) for the Full Analysis Set. The proportion of subjects who achieved SVR12 in each treatment group was calculated; exact 2-sided 95% confidence intervals (CIs) were constructed using the Clopper-Pearson method. No statistical hypothesis testing was performed.

Point estimates and 95% exact CIs for SVR12 rates for each randomization stratum (ie, prior treatment experience and genotype) and for select demographic and baseline characteristic subgroups were provided as described above for each treatment group.

Pharmacokinetics: Steady-state PK over a 24-hour dosing interval was determined in subjects who participated in the PK substudy at or between the Week 2 or Week 4 on-treatment visits.

Plasma concentrations of LDV, SOF (and its metabolites GS-566500 and GS-331007), and GS-9669 were determined using validated bioanalytical assays. Pharmacokinetics parameters for these analytes were computed for all subjects with evaluable PK profiles. Descriptive statistics (sample size, mean, standard deviation [SD], coefficient of variation [%CV], median, first quartile, third quartile, minimum, maximum, and geometric mean and its 95% CI) were presented for PK concentration data and PK parameter data.

Safety: All randomized subjects who received at least 1 dose of study drug were included in the safety analysis. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, ECGs, and physical examinations. Safety data were analyzed by treatment group and 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. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 101 subjects with genotype 1 HCV infection were randomized in this study: 35 to the LDV/SOF+RBV group, 32 to the LDV/SOF+GS-9669 250-mg group, and 34 to the LDV/SOF+GS-9669 500-mg group. All subjects were enrolled at 1 study site in the US.

One subject who was randomized to the LDV/SOF+GS-9669 500-mg group did not receive study drug. Of the 100 randomized subjects who received at least 1 dose of study drug and were included in the Safety Analysis Set and the Full Analysis Set, 99 (99.0%) completed study treatment; 1 subject (1.0%) in the LDV/SOF+GS-9669 250-mg group prematurely discontinued study treatment due to an AE.

Baseline disease characteristics were balanced across treatment groups. All subjects had genotype 1 HCV infection (62.0% genotype 1a, 38.0% genotype 1b), and 82.0% had a non-CC IL28B allele (58.0% CT, 24.0% TT). The overall mean (SD) baseline HCV RNA value for subjects was 6.0 (0.56) $\log_{10}$ IU/mL, and a majority of subjects (65.0%) had baseline HCV RNA ≥ 800,000 IU/mL. All of the subjects (100.0%) had cirrhosis. The mean (SD) baseline alanine aminotransferase (ALT) value was 121 (65.9) U/L, and most subjects (73.0%) had baseline ALT values > 1.5 × the upper limit of the normal range. Mean (SD) baseline estimated glomerular filtration rate using the Cockcroft-Gault equation was 118.8 (38.35) mL/min.

Twenty-six subjects (26.0%) were naive to previous HCV treatment. Of the 74 (74.0%) treatment-experienced subjects, 11 (11.0%) had been treated for < 12 weeks, and 63 (63.0%) had been treated for ≥ 12 weeks.

Efficacy Results: The proportion of subjects who achieved SVR12 was similar across treatment groups: 88.6% in the LDV/SOF+RBV group, 90.6% in the LDV/SOF+GS-9669 250-mg group, and 81.8% in the LDV/SOF+GS-9669 500-mg group.

Overall, 13 of 100 subjects did not achieve SVR12. Each of these subjects had virologic relapse after achieving HCV RNA < LOOQ at their last on-treatment visit. With the exception of 1 subject who prematurely discontinued study drug due to AEs at Week 4, each of the subjects who relapsed had completed 8 weeks of study treatment. No subjects had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse).

Rapid suppression of HCV RNA was observed in all treatment groups. By Week 2, approximately half of the subjects in each treatment group (46.9% to 54.3%) had HCV RNA < LLOQ. That proportion had increased to 81.3% to 94.3% at Week 4; and by Week 8, 100% of subjects had HCV < LLOQ.

At Week 8, the mean (SD) change from baseline in HCV RNA was -4.83 (0.496) $\log_{10}$ IU/mL, -4.96 (0.639) $\log_{10}$ IU/mL, and -4.84 (0.570) $\log_{10}$ IU/mL for subjects in the LDV/SOF+RBV, LDV/SOF+GS-9669 250-mg, and LDV/SOF+GS-9669 500 mg-groups, respectively.

Virologic Resistance

Overall, 23 of 100 enrolled subjects (23.0%) were identified as having baseline NS5A resistance-associated variants (RAVs). Of these, 5 subjects (21.7%) had virologic relapse. The specific NS5A RAVs detected at baseline in these 5 subjects were L31M and Q30R. Of 77 subjects without baseline NS5A RAVs, 8 (10.4%) had virologic relapse, including 1 subject who prematurely discontinued study drug due to AEs. NS5B deep sequencing was successfully obtained for 99 subjects (99.0%). The NS5B RAV S282T was not detected in any subject, and none of the subjects had other nucleoside inhibitor (NI) RAVs or SOF treatment-emergent variants (TEVs) at baseline.

The NS5B gene was also analyzed for GS-9669 RAVs at baseline. One subject with M423I (> 99%) at baseline achieved SVR12 following 8 weeks of treatment with LDV/SOF+GS-9669 500 mg.

Overall, 13 subjects had virologic relapse: 4 in the LDV/SOF+RBV group, 3 in the LDV/SOF+GS-9669 250-mg group (including 1 subject who prematurely discontinued study drug due to AEs), and 6 in the LDV/SOF+GS-9669 500-mg group. Ten of these subjects had HCV genotype 1a, and 3 had genotype 1b; 3 were treatment naive, and 10 were treatment experienced. Of the 13 subjects with virologic relapse, 5 (38.5%) had NS5A RAVs (L31M or Q30R) at baseline that persisted or were enriched at relapse, 3 (23.1%) had NS5A variants (2 with Q30R and 1 with H58D) that emerged at relapse, and 5 subjects did not have any detected NS5A variants at baseline or relapse. No S282T or other NI RAVs or TEVs or GS-9669 RAVs were detected in any subject at relapse. The common NS5A RAVs detected at relapse were L31M, Q30R, and H58D.

For subjects with virologic relapse with NS5A RAVs detected at baseline or relapse, phenotypic analysis of the NS5A gene showed reduced susceptibility to LDV. For the remaining subjects with relapse who did not have any NS5A RAVs detected at baseline or postbaseline, there was no change in susceptibility to LDV. No change in susceptibility to SOF or GS-9669 was detected for any subjects who experienced virologic relapse.

Pharmacokinetics Results: The PK results for subjects in the LDV/SOF+GS-9669 treatment groups who participated in the intensive PK substudy showed similar plasma exposures of LDV and the SOF metabolites GS--566500 and GS-331007 in the 2 groups. The overall exposure (AUC_{tau}) for SOF, but not C_{max}, was moderately (approximately 25%) higher in the treatment group that contained a higher dose of GS-9669 (500 mg). In agreement with the results from a previous drug interaction evaluation (Study GS-US-334-0101), GS-9669 exposures were

moderately higher following administration of GS-9669 500 mg + LDV/SOF compared with GS-9669 500 mg + SOF (Study P7977-0523). Overall, the PK of LDV/SOF in this study was within the range of exposures observed in pooled population PK analyses in the Phase 2/3 program.

Safety Results: The majority of subjects in each treatment group had at least 1 AE: 80.0% in the LDV/SOF+RBV group, 68.8% in the LDV/SOF+GS-9669 250-mg group, and 78.8% in the LDV/SOF+GS-9669 500-mg group. The most frequently reported AEs were headache, diarrhea, and nausea. None of the AEs occurred at > 10% increased frequency in any 1 treatment group compared with the other 2 treatment groups, with the exception of nausea and headache, which were reported for a greater proportion of subjects in the LDV/SOF+GS-9669 500-mg group (21.2% each) compared with the LDV/SOF+RBV (8.6% and 14.3%, respectively) and LDV/SOF+GS-9669 250-mg (6.3% each) groups. Nearly all AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. No Grade 4 AEs were reported. Grade 3 AEs were reported for 2 subjects (6.3%) in the LDV/SOF+GS-9669 250-mg group and included 1 event each of acute myocardial infarction, cardiomyopathy (both of which were serious), and arrhythmia. None of these events were considered related to study drug.

The frequency of study drug-related AEs was similar across treatment groups, with 54.3% in the LDV/SOF+RBV group, 34.4% in the LDV/SOF+GS-9669 250-mg group, and 45.5% in the LDV/SOF+GS-9669 500-mg group. The most frequently reported treatment-related AEs were headache, diarrhea, and nausea.

Serious adverse events (SAEs) were reported for 2 subjects (6.3%) in the LDV/SOF+GS-9669 250-mg group and included 1 event each of Grade 3 acute myocardial infarction and Grade 3 cardiomyopathy. Neither of the SAEs was considered related to study drug.

One subject (3.1%) in the LDV/SOF+GS-9669 250-mg group prematurely discontinued study drug due to Grade 3 AEs of cardiomyopathy and arrhythmia, and 1 subject (2.9%) in the LDV/SOF+RBV group had an AE of anemia that led to modification of RBV dose. There were no AEs leading to interruption of LDV/SOF, and no pregnancy or death was reported.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. No Grade 3 or 4 hematology laboratory abnormalities were reported. The most common Grade 3 or 4 chemistry laboratory abnormality was hyperglycemia, which was reported for 2.9%, 9.4%, and 6.1% in the LDV/SOF+RBV, LDV/SOF+GS-9669 250 mg, and LDV/SOF+GS-9669 500-mg groups, respectively. Each of the subjects with Grade 3 hyperglycemia had graded elevations in glucose at screening and/or baseline.

Two subjects (5.7%). in the LDV/SOF+RBV group had Grade 3 elevations in total bilirubin. Both of these subjects had Grade 1 elevations in total bilirubin at screening and/or baseline and Grade 2 or 3 elevations in total bilirubin for the duration of treatment, which resolved by posttreatment Week 4.

One subject (3.1%) in the LDV/SOF+GS-9669 250-mg group and 1 subject (3.0%) in the LDV/SOF+GS-9669 500-mg group had Grade 3 lipase elevations, and 1 subject (3.0%) in the LDV/SOF+GS-9669 500-mg group had a Grade 4 lipase elevation. Each of the subjects with Grade 3 or 4 lipase elevations had graded elevations in lipase from screening through posttreatment Week 4, and none of the lipase elevations were associated with pancreatitis.

None of the Grade 3 or 4 chemistry laboratory abnormalities were reported as AEs.

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature) were reported during the study.

Clinically significant ECG results were reported for 2 subjects in the LDV/SOF+GS-9669 250-mg group: 1 subject had sinus bradycardia with occasional supraventricular premature complexes at the Week 8 ECG that was not associated with any concurrent AEs; 1 subject had sinus rhythm with occasional ventricular premature complexes, abnormal left axis deviation, and left bundle branch block at the Week 1 ECG and prematurely discontinued study/study treatment due to AEs of cardiomyopathy and arrhythmia, which were determined to be preexisting conditions.

CONCLUSIONS:

- In treatment-naive and treatment-experienced subjects with genotype 1 HCV infection with cirrhosis, 8 weeks of treatment with LDV/SOF in combination with RBV or GS-9669 250 mg or 500 mg resulted in SVR12 rates 81.8% to 90.6%.
- No S282T or other NI RAVs, SOF TEVs, or GS-9669 RAVs were detected in any subject at the time of virologic relapse. Of subjects with virologic relapse, NS5A RAVs were detected in 38% at baseline and 62% at the time of virologic failure, and the presence of NS5A RAVs did not preclude subjects from achieving SVR12.
- LDV/SOF PK parameters in subjects receiving LDV/SOF + GS-9669 250 mg or 500 mg were within the range of exposures observed in Phase 2/3 population PK analyses. GS-9669 exposures were moderately higher following administration of GS-9669 500 mg + LDV/SOF compared with GS-9669 500 mg + SOF (Study P7977-0523).
- Treatment with LDV/SOF in combination with RBV or GS-9669 250 mg or 500 mg was generally well tolerated, with no deaths and few discontinuations due to AEs, SAEs, Grade 3 or 4 AEs, or laboratory abnormalities.