FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	Open-Label Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) for 6 Weeks in Subjects with Acute Genotype 1 or 4 Hepatitis C Virus (HCV) and Chronic Human Immunodeficiency Virus (HIV)-1 Co-Infection
Name of Test Drug:	Ledipasvir/sofosbuvir fixed-dose combination (FDC)
Dose and Formulation:	Ledipasvir/sofosbuvir FDC (90/400 mg) tablet
Indication:	Acute HCV infection in patients with chronic HIV infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-337-1612
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	NA 2014-004812-12
ClinicalTrials.gov Identifier:	NCT02457611
Study Start Date:	11 June 2015 (First Subject Screened)
Study End Date:	08 January 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Jürgen Rockstroh, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Robert H. Hyland, DPhil Telephone: PPD Fax: PPD
Report Date:	10 May 2016

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-337-1612
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: Open-Label Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) for 6 Weeks in Subjects with Acute Genotype 1 or 4 Hepatitis C Virus (HCV) and Chronic Human Immunodeficiency Virus (HIV)-1 Co-Infection

Investigators: Multicenter study

Study Centers: Subjects were enrolled in 3 sites in Germany and 2 sites in the United Kingdom.

Publications: There are no publications at the time of this report.

Study Period:

11 June 2015 (First Subject Screened)
08 January 2016 (Last Subject Observation)
08 January 2016 (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 LDV/SOF FDC as measured by the proportion of subjects who attained sustained virologic response (SVR) at 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of LDV/SOF FDC 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 weeks after discontinuation of study treatment (SVR4)
- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation
- To evaluate the emergence of HCV viral resistance to LDV and SOF during treatment and after treatment discontinuation
- To evaluate the change in HIV RNA from Day 1 to end of treatment

- To assess, among subjects receiving antiretroviral therapy (ART) for HIV-1, the proportion of subjects that maintained HIV-1 RNA < 50 copies/mL while on HCV treatment and at posttreatment Week 4
- To assess the change from Day 1 in CD4 T-cell count at the end of treatment and at posttreatment Week 4

The exploratory objectives of this study were:

- 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 evaluate any change in liver fibrosis from Day 1 to posttreatment Week 12

Methodology: This Phase 2, open-label, multicenter study evaluated the safety and efficacy of LDV/SOF FDC (90/400 mg) in subjects with acute genotype 1 or 4 HCV and chronic HIV-1 coinfection.

Following screening, subjects were enrolled and treated with LDV/SOF once daily for 6 weeks.

Number of Subjects (Planned and Analyzed):
Planned: 25 subjects
Analyzed:

- Full Analysis Set: 26 subjects
- Safety Analysis Set: 26 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males and nonpregnant/nonlactating females, aged 18 years or older, with acute genotype 1 or 4 HCV infection and chronic HIV-1 coinfection, and with a body mass index (BMI) ≥ 18 kg/m^2.

Subjects must not have had prior exposure to any interferon, ribavirin, or other approved or experimental HCV-specific direct-acting antiviral agent within the previous 6 months.

Subjects must have had confirmed HIV-1 infection and were either receiving an HIV antiretroviral (ARV) regimen consisting of at least 3 agents with HIV RNA < 200 copies/mL, or were not receiving ART with no immediate plans to start ART during the 6-week study duration. HIV ARV agents/regimens were those allowed per the Harvoni® Summary of Product Characteristics {Gilead Sciences Inc 2015}. Subjects on ART were required to have a CD4 T-cell count > 200/µl at screening and subjects not on ART were required to have a CD4 T-cell count > 500/µl at screening.

Duration of Treatment: Treatment duration was 6 weeks with a 12-week posttreatment follow-up period.

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

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

The batch number of LDV/SOF administered in this study was DK1312B3.

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), at Weeks 2, 4, and 6 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 determine HCV RNA results in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: A single pharmacokinetics (PK) blood sample was collected from all subjects at each on-treatment visit. The PK of SOF (and its metabolites, GS-566500 and GS-331007), LDV, and tenofovir may have been assessed if applicable.

Safety: Safety assessments included physical examinations through the end of treatment, monitoring of adverse events (AEs) and concomitant medications through the posttreatment Week 4 visit, and clinical laboratory analyses, vital sign measurements, and HIV-1 RNA and CD4 T-cell counts through the posttreatment Week 12 visit.

Statistical Methods:

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of study drug) in the Full Analysis Set. The primary efficacy endpoint analysis was conducted when all subjects completed the posttreatment Week 12 visit or prematurely discontinued from the study. The point estimate of the SVR12 rate was calculated and the 2-sided 95% exact CI was constructed using the Clopper-Pearson method. Secondary efficacy endpoints included SVR4, the percentage of subjects with HCV RNA below LLOQ by study visit, HCV RNA and change from baseline, and the percentage of subjects with virologic failure.

Subgroup analyses were performed to assess the relationship between SVR12 and baseline demographic and disease characteristics. Point estimates and 2-sided 95% exact CIs of the SVR12 rates were calculated for each subgroup.

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, HIV-1 RNA and CD4 T-cell counts, vital signs, and physical examinations. Summaries of safety data included all data collected on or after the first dose of 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 18.1.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 26 subjects were enrolled and received at least 1 dose of study drug (Table 15.8.1.3.1). All subjects completed study treatment. Of the 26 subjects, 3 subjects (11.5%) were lost to follow-up after completing the posttreatment Week 4 visit. All patients received at least the planned 6 weeks of LDV/SOF. One subject (Subject PPD received 8 weeks of treatment (Listing 16.2.1.1).

All of the subjects were male, and the majority were white (92.3%) and non-Hispanic/Latino (84.6%), with a mean age of 41 years (range: 25-58 years) (Table 15.8.3.1). The mean (SD) baseline BMI for subjects was 23.9 (3.32) kg/m^2, and 7.7% of subjects had a BMI $\geq$ 30 kg/m^2 (Table 15.8.3.2).

Nineteen of 26 subjects (73.1%) had genotype 1a and 7 subjects (26.9%) had genotype 4 HCV infection. The majority of subjects (53.8%, 14 subjects) had a non-CC (CT or TT) IL28B genotype. The mean (SD) baseline HCV RNA value for subjects was 5.4 (1.60) log_{10} IU/mL, and most subjects had baseline HCV RNA < 800,000 IU/mL (53.8%, 14 subjects). The mean (SD) baseline alanine aminotransferase (ALT) value for subjects was 249 (298.9) U/L and most subjects had baseline ALT > 1.5 × upper limit of normal (80.8%, 21 subjects) (Table 15.8.3.2).

The mean (SD) estimated glomerular filtration rate was 112.1 (19.51) mL/min. The overall median (first quartile, third quartile [Q1, Q3]) baseline CD4 count was 643 (494, 774) cells/µL, and 73.1% of subjects had CD4 counts > 500 cells/µL. Twenty-five of 26 subjects were receiving an ARV regimen at enrollment; the most common regimens were: efavirenz + emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF) (26.9%), raltegravir + FTC + TDF (19.2%), dolutegravir + FTC + TDF (11.5%), and atazanavir (ATV) + ritonavir (RTV) + FTC + TDF (11.5%). Overall, 8 of the subjects were receiving an RTV-boosted regimen. One subject (3.8%) was not on an ARV regimen at enrollment (Table 15.8.3.2 and Listing 16.2.4.3.3).

Efficacy Results:

The proportion of subjects with SVR4 and SVR12 is presented in the table below. Twenty of 26 subjects (76.9%) treated with LDV/SOF FDC (90/400 mg) achieved the primary endpoint of SVR12.

	LDV/SOF (N = 26)
SVR4	22/26 (84.6%)
95% CI	65.1% to 95.6%
SVR12	20/26 (76.9%)
95% CI	56.4% to 91.0%

HCV RNA was analyzed using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 with a lower limit of quantitation of 15 IU/mL.
SVRx was sustained virologic response (HCV RNA < LLOQ) x weeks after stopping study treatment.
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.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Table 15.9.2.3

Six subjects did not achieve SVR12. Four subjects experienced virologic failure prior to the posttreatment Week 4 visit (Listing 16.2.6.2) and 2 subjects were lost to follow-up after posttreatment Week 4 and were imputed to have HCV RNA values ≥ LLOQ (Listing 16.2.6.3). These two subjects had HCV RNA values < LLOQ at posttreatment Week 4. One subject experiencing virologic failure had genotype 1a HCV infection at screening and was shown to be reinfected with genotype 4d HCV infection at posttreatment. No relapse occurred among the 21 subjects with a baseline HCV RNA ≤ 6.9 $\log_{10}$ IU/mL (Listing 16.2.6.1).

These SVR rates were achieved across both HCV genotypes and subtypes enrolled, with SVR12 rates of 71.4% for subjects with genotype 4 HCV infection to 78.9% for subjects with genotype 1a HCV infection.

Virologic Resistance Analysis:

Virology listings are provided in Appendix 16.2, Virology Listings 1 through 5.

The full-length nonstructural protein (NS)5A and NS5B coding regions were successfully deep sequenced at pretreatment (baseline) for 25 of 26 and 24 of 26 subjects, respectively, and for the 4 subjects who had virologic failure. Baseline and posttreatment analyses were conducted with a 1% cutoff.

Of the 26 subjects who received study drug, 2 subjects were lost to follow-up after posttreatment Week 4 and were imputed to have HCV RNA values ≥ LLOQ. These two subjects were excluded from the virology analysis. In addition, one subject (Subject PPD who had genotype 1a HCV infection at screening, was found to be reinfected with genotype 4d HCV infection by BLAST analysis and NS5B short fragment sequencing assay at posttreatment.

Among the 23 remaining subjects, seven subjects had genotype 4 HCV infection but no subtype definition at screening and were found to be infected with genotype 4d by BLAST analysis using the NS5A and NS5B sequences (Appendix 16.2, Virology Listing 5).

Overall, 8 of 23 subjects (34.8%) (2/17 with genotype 1 HCV infection and 6/6 with genotype 4 HCV infection) had NS5A resistance-associated variants (RAVs) at baseline and 6 of the 8 subjects (75.0%) achieved SVR12, compared with 13 of 15 subjects (86.7%) without NS5A RAVs who achieved SVR12. None of the subjects had NS5B RAVs at baseline.

A total of 3 subjects (2 subjects with genotype1a HCV infection and 1 subject with genotype 4d HCV infection) experienced virologic relapse. No NS5A or NS5B nucleotide inhibitor (NI) RAVs emerged in any of the 3 subjects at relapse.

			NS5A RAVs		NS5B NI RAVs	
Subject ID	Genotype	Treatment	Baseline	Posttreatment	Baseline	Posttreatment
PPD	4d	LDV/SOF FDC 6 weeks	L30R (>99%)	L30R (>99%)	None	None
PPD	1a	LDV/SOF FDC 6 weeks	M28A (3.7%) Q30R (98.6%)	Q30R (>99%)	None	None
PPD	1a	LDV/SOF FDC 6 weeks	None	None	None	None

Source: Virology Listings 3 and 4

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

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.

Adverse Events and Serious Adverse Events

Twenty-two subjects (84.6%) reported at least 1 AE. Of these, 2 subjects (7.7%) experienced an AE of Grade 3 or above, and 15 subjects (57.7%) experienced an AE that was considered to be related to study drug by the investigator. One subject experienced serious adverse events (SAEs) that were considered to be unrelated to study drug by the investigator. There were no AEs leading to discontinuation of study drug and no deaths occurred during the study (Table 15.11.2.1.1).

The most frequently reported AEs included fatigue and nasopharyngitis (26.9% each; 7 subjects) and headache (23.1%; 6 subjects) (Table 15.11.2.1.3). Of the 2 subjects that experienced Grade 3 or above AEs, 1 subject (Subject PPD reported a Grade 3 decreased neutrophil count, and Subject PPD reported Grade 4 loss of consciousness and Grade 4 pneumonia aspiration (Listing 16.2.7.2). These 2 Grade 4 AEs were also reported as SAEs and were considered unrelated to study drug by the investigator. This subject also had SAEs of pyrexia and thrombophlebitis which were of Grade 2 and Grade 1 severity, respectively. All SAEs had an onset date between posttreatment Days 3 and 7 and were resolved by posttreatment Day 9. No other SAEs were reported (Listing 16.2.7.4).

Clinical Laboratory Results

Twenty of 26 subjects (76.9%) experienced at least 1 laboratory abnormality, the majority of which were Grade 1 or 2 in severity (Table 15.11.6.2). Four subjects (15.4%) experienced Grade 3 or 4 laboratory abnormalities.

- One subject reported a Grade 3 elevated ALT (Subject PPD at posttreatment Week 4 associated with virologic failure (Listing 16.2.6.2).
- One subject experienced transient Grade 3 elevated lipase (Subject PPD at Week 6 with normal lipase levels at all other on-treatment study time points. This subject had also experienced a Grade 3 urinary occult blood at posttreatment Week 4 with Grade 2 urinary occult blood at all other time points during the study and posttreatment period.
- Two subjects reported hyperbilirubinemia, both of whom received ARV therapy with ATV+RTV+FTC+TDF. Asymptomatic elevations in bilirubin related to inhibition of uridine diphosphate glucuronosyltransferase is a known side effect of ATV administration ({Bristol-Myers Squibb Company 2015}. Subject PPD experienced a Grade 3 elevated bilirubin at Week 4 and had elevated levels at baseline and at various time points throughout the study and posttreatment period. Subject PPD experienced Grade 4 hyperbilirubinemia at Weeks 4 and 6 and had levels ranging from Grade 2 to Grade 4 at baseline and throughout the study and posttreatment period (Listing 16.2.8.1.3). This subject reported an AE of jaundice on Day 29 that was ongoing through the posttreatment period. The AE was of Grade 1 severity and was considered to be related to the study drug by the investigator (Listing 16.2.7.1).

Effect of LDV/SOF on HIV

Twenty-one of 26 subjects (80.8%) had HIV RNA < 50 copies/mL at baseline. This level of suppression remained approximately constant during the study and posttreatment period with a range of 25 to 22 subjects (96.2% to 84.6%) with HIV RNA < 50 copies/mL from Week 2 through posttreatment Week 4 (Table 15.11.9.1.3). No subjects had confirmed HIV rebound during the study (Table 15.11.9.1.1).

The overall median (Q1, Q3) CD4 count at baseline was 643 (494, 774) cells/μL (Table 15.11.6.1.13). Median changes from baseline in CD4 count during the study up to posttreatment Week 4 ranged from 1 to 24 cells/μL. No clinically meaningful changes in CD4 count from baseline were observed.

Vital Signs Measurements and Electrocardiograms

There were no notable changes in vital sign measurements (systolic blood pressure, diastolic blood pressure, and pulse) (Tables 15.11.7.1 through 15.11.7.3) or 12-lead electrocardiograms (Listing 16.2.8.2.3).

CONCLUSIONS:

- Twenty of 26 subjects (76.9%) with acute HCV infection and HIV-1 coinfection treated with LDV/SOF FDC (90/400 mg) for 6 weeks achieved SVR12 (95% CI: 56.4% to 91.0%).
- The baseline NS5A RAVs did not appear to affect the treatment outcome. Viral relapse was not associated with the selection of resistance.
- Treatment with LDV/SOF for 6 weeks was well tolerated with a safety profile similar to that observed in subjects with HCV monoinfection. No subjects prematurely discontinued study drug.
- There was no effect of LDV/SOF treatment on CD4 count or HIV RNA levels.