FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3b Open-Label Study of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 2 Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) Coinfection
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-337-1655
Phase of Development:	Phase 3b
IND No.: **EudraCT No.:**	Not Applicable Not Applicable
ClinicalTrials.gov Identifier:	NCT02613871
Study Start Date:	22 December 2015 (First Subject Screened)
Study End Date:	04 January 2017 (Last Subject Last Observation for the Primary Endpoint) 07 November 2018 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Chun-Jen Liu, MD, PhD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Anuj Gaggar, MD, PhD Telephone: PPD Fax: PPD
Report Date:	14 June 2019

STUDY SYNOPSIS

Study GS-US-337-1655
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3b Open-Label Study of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 2 Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) Coinfection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 14 sites in Taiwan.

Publications:

Liu CJ, Chuang WL, Sheen IS, Wang HY, Chen CY, Tseng KC, et al. Ledipasvir/Sofosbuvir for 12 Weeks Is Safe and Effective in Patients With Chronic Hepatitis C and Hepatitis B Coinfection: a Phase 3 Study in Taiwan [Poster SAT-243]. EASL: The International Liver Congress; 2019 10-14 April; Vienna, Austria.

Liu CJ, Chuang WL, Sheen IS, Wang HY, Chen CY, Tseng KC, et al. Efficacy of Ledipasvir and Sofosbuvir Treatment of HCV Infection in Patients Coinfected With HBV. Gastroenterology 2018; 154(4):989-97.

Liu CJ, Chuang WL, Sheen IS, Wang HY, Chen CY, Tseng KC, et al. Declines in HBsAg Levels Observed During Treatment With Ledispavir/Sofosbuvir in Patients With Chronic Hepatitis B Virus and Hepatitis C Virus Infection [Poster 1083]. The Liver Meeting® 2017 - The 68th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); 2017 20-24 October; Washington, D. C.

Liu CJ, Chuang WL, Sheen IS, Wang HY, Chen CY, Tseng KC, et al. Ledipasvir/Sofosbuvir for 12 Weeks Is Safe and Effective in Patients with Chronic Hepatitis C and Hepatitis B Coinfection: A Phase 3 Study in Taiwan [Presentation]. The International Liver Congress™ 2017: European Association for the Study of the Liver (EASL); 2017 19-23 April; Amsterdam, the Netherlands.

Study Period:

22 December 2015 (First Subject Screened)
04 January 2017 (Last Subject Last Observation for the Primary Endpoint)
07 November 2018 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3b

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) on chronic genotype 1 or 2 HCV infection as measured by the proportion of subjects with sustained viral response (SVR) 12 weeks after discontinuation of therapy (SVR12) in subjects who were coinfected with HBV
- 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 HCV SVR at 4 weeks after discontinuation of therapy (SVR4)
- To evaluate the kinetics of circulating HCV RNA and HBV DNA during treatment and after treatment discontinuation
- To evaluate the emergence of HCV resistance to SOF and LDV during treatment and after treatment discontinuation
- To evaluate HBV disease progression
- To evaluate liver disease progression

The exploratory objective of this study was as follows:

- To assess the effect of treatment with LDV/SOF FDC on health-related quality of life

Methodology: This Phase 3b, open-label, multicenter study evaluated the safety and efficacy of LDV/SOF administered for 12 weeks in subjects with chronic genotype 1or 2 HCV infection who were coinfected with HBV and not receiving HBV treatment.

Approximately 100 subjects were planned to be enrolled and treated with LDV/SOF FDC (90/400 mg) tablet once daily for 12 weeks. Up to 50% of subjects enrolled could have had compensated cirrhosis. Subjects with clinical evidence of hepatic decompensation or hepatocellular carcinoma (HCC) were excluded.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 100 subjects

Analyzed:

- All Enrolled Analysis Set: 111 subjects
- Safety Analysis Set: 111 subjects
- Full Analysis Set (FAS): 111 subjects
- Serologically Evaluable FAS: 101 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males and nonpregnant/non-nursing females, aged 20 years or older, with chronic genotype 1 or 2 HCV infection and HBV coinfection, who were not on HBV treatment, and had documentation of the presence or absence of cirrhosis.

Duration of Treatment: Treatment duration was 12 weeks with a 108-week posttreatment follow-up period.

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

LDV/SOF was administered orally at a dose of 90/400 mg (1 FDC tablet once daily).

The lot number of LDV/SOF administered in this study was DK1309B1.

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

Criteria for Evaluation:

Efficacy: Blood samples to determine serum HCV RNA levels were collected from subjects at screening; Day 1 (predose); Weeks 1, 2, 4, 8, and 12; and posttreatment Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96, and 108. The COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA results in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Blood samples were collected to determine serum levels of HBV DNA at screening, at baseline, and at each study visit during the on-treatment and posttreatment periods. The COBAS® AmpliPrep®/COBAS® TaqMan® HBV Quantitative Test, v2.0 was used to quantify HBV DNA in this study. The LLOQ of the assay was 20 IU/mL.

Virology: Plasma samples were collected from all subjects on Day 1, and at each subsequent visit, for HCV and/or HBV viral sequence analysis. An unscheduled plasma sample was also to be collected to confirm HCV virologic failure, if applicable.

Pharmacokinetics: A single blood sample was collected from all subjects at each on-treatment visit after Day 1, for possible assessment of the pharmacokinetics (PK) of SOF (and its metabolites, GS-566500 and GS-331007) and LDV.

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

Quality of Life: Health-related quality of life was assessed with the 36-item Short Form Survey (SF-36) at Day 1; on-treatment Weeks 2, 4, 8, and 12; and posttreatment Weeks 4 and 12.

Statistical Methods:

Efficacy: The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs in the FAS. Point estimates and 2-sided 95% exact confidence intervals (CIs) based on the Clopper-Pearson method were provided for each HCV genotype and overall.

Secondary efficacy endpoints included the percentage of subjects with HCV RNA < LLOQ at 4 weeks and at other posttreatment visits after discontinuation of treatment (SVR4 and SVRxx); percentage of subjects with HCV RNA < LLOQ while on treatment by study visit; HCV RNA (log_{10} IU/mL) and changes from baseline through the end of treatment; percentage of subjects with virologic failure; characterization of HCV drug resistance substitutions; HBV DNA (IU/mL and log_{10} IU/mL) and changes from baseline while on treatment and during posttreatment follow up; HBsAg (IU/mL and log_{10} IU/mL) and change from baseline while on treatment and during posttreatment follow up; serum lysyl oxidase-like 2 and change from baseline while on treatment and during posttreatment follow up; proportion of subjects who initiated HBV therapy; fibrosis status as assessed by FibroScan® at posttreatment Weeks 12, 60, and 108; and proportion of subjects who developed HCC.

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

Pharmacokinetics: No PK analyses 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 signs, 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 21.1.

Quality of Life: Health-related quality of life was assessed by evaluating subject answers to the SF-36. A Wilcoxon signed rank test was used to explore changes in status from baseline to each postbaseline time point, and from end of treatment to each posttreatment time point.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 111 subjects were enrolled, received at least 1 dose of study drug, and were included in both the Safety Analysis Set and FAS. All subjects completed study treatment.

The majority of the subjects were female (62.2%, 69 subjects), with a mean age of 55 years (range: 32-76). All subjects were Asian. The mean (SD) baseline body mass index (BMI) value was 24.5 (3.92) kg/m^2, with 37.8% (42 subjects) having a BMI $\geq$ 25 kg/m^2.

All subjects in the Safety Analysis Set had genotype 1 or 2 HCV infection, with the majority of subjects (61.3%, 68 subjects) having genotype 1 and the remainder (38.7%, 43 subjects) having genotype 2. Of the 68 subjects with genotype 1, 64 subjects had genotype 1b, 3 subjects had genotype 1a, and 1 subject had genotype 1 with no confirmed subtype. The majority of subjects had IL28B CC alleles (76.6%, 85 subjects). The mean (SD) baseline HCV RNA value was 5.9 (0.73) log_{10} IU/mL, with the majority of subjects (60.4%, 67 subjects) having baseline HCV RNA $\geq$ 800,000 IU/mL. The majority of subjects (83.8%, 93 subjects) did not have cirrhosis at baseline.

Of the 37 subjects (33.3%) who received previous HCV treatment, 10 subjects (27.0%) were nonresponders, 20 subjects (54.1%) had relapse/breakthrough, and 7 subjects (18.9%) had a response of "other" to their most recent HCV treatment.

All but 1 subject was positive for HBsAg at baseline; this subject was HBsAg-positive at screening but was found to be HBsAg-negative at baseline. Among the 92 subjects who were able to be tested for their HBV genotype, the predominant HBV genotype was genotype B (85.9%, 79 subjects), followed by genotype C (13.0%, 12 subjects), and genotype D (1.1%, 1 subject). The mean (SD) baseline HBV DNA value was 2.1 (0.92) $\log_{10}$ IU/mL, with most subjects having HBV DNA ≥ LLOQ at baseline (66.7%, 74 subjects). At baseline, the majority of subjects were HBV treatment naive (95.5%; 106 subjects). Per protocol, no subject was receiving HBV therapy at screening.

The mean (SD) baseline creatinine clearance, calculated by Cockcroft-Gault equation, was 92.8 (23.46) mL/min.

Efficacy Results: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of study drug) in the FAS. The SVR12 rate in this study was 100.0% (95% CI: 96.7% to 100.0%), with no subjects experiencing virologic failure after 12 weeks of treatment with LDV/SOF.

The overall SVR4 rate was also 100.0% (95% CI: 96.7% to 100.0%). Viral response was sustained at 100.0% at all posttreatment follow-up visits through posttreatment Week 108 (SVR108), irrespective of HCV genotype.

SVR12 rates of 100.0% were observed across all subgroups.

Potent and rapid suppression of HCV RNA while on treatment was observed. At Week 1, 33.3% of subjects had HCV RNA < LLOQ. At Week 2, 82.0% of subjects had HCV RNA < LLOQ. The proportion of subjects who had HCV RNA < LLOQ at Weeks 4, 8, and 12 was 100.0%.

An analysis was performed to evaluate the proportion of subjects with HBV reactivation, defined as a change in HBV DNA from baseline < LLOQ to a postbaseline value ≥ LLOQ or an increase in HBV DNA > 1 $\log_{10}$ IU/mL postbaseline from baseline ≥ LLOQ. Eighty-one subjects (73.0%) had HBV reactivation through posttreatment Week 108. Eight subjects (7.2%) initiated HBV therapy during the study based on investigator judgment. None of the subjects who met criteria for HBV reactivation or initiated subsequent HBV therapy had any related clinical signs or symptoms.

FibroScan values decreased following LDV/SOF treatment for 12 weeks. Mean changes from baseline were −1.3, −2.1, and −2.3 kPa at posttreatment Weeks 12, 60, and 108, respectively.

No subject developed HCC during the course of the study.

Virologic Resistance Results: Baseline HCV nonstructural protein (NS)5A resistance-associated variants (RAVs) were detected in 9 of 68 subjects (13.2%) with genotype 1 HCV infection and 35 of 43 subjects (81.4%) with genotype 2 HCV infection; all subjects with NS5A RAVs at baseline achieved SVR12. Additionally, NS5B nucleoside inhibitor (NI) RAVs were detected in 7 of 111 subjects (6.3%); all 7 subjects with NS5B NI RAVs at baseline achieved SVR12.

None of the 111 subjects in this study had virologic failure; no subjects qualified for sequencing analysis postbaseline.

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

Safety Results: Overall, treatment with LDV/SOF for 12 weeks was generally safe and well tolerated. No subject permanently discontinued LDV/SOF due to an AE.

The majority of subjects (60.4%, 67 subjects) had at least 1 AE during the study. The 3 most commonly reported AEs were headache (9.9%, 11 subjects), upper respiratory tract infection (8.1%, 9 subjects), and fatigue (7.2%, 8 subjects). Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One subject experienced a Grade 3 (severe) AE of optic neuritis, which was assessed as not related to study drug. No Grade 4 (life-threatening) AEs were reported. The most commonly reported treatment-related AEs were fatigue (5.4%, 6 subjects), headache (4.5%, 5 subjects), and malaise (3.6%, 4 subjects). No subject experienced a Grade 3 or above treatment-related AE.

Four subjects (3.6%) experienced SAEs during the study. All SAEs were assessed as not related to study drug. One pregnancy was reported, during the posttreatment follow-up period; the subject elected to terminate the pregnancy.

Two subject deaths, both nontreatment emergent, were reported: 1 due to traumatic shock on posttreatment Day 547 (posttreatment Week 78) and 1 due to multiple organ failure on posttreatment Day 595 (posttreatment Week 85). Both deaths were assessed as not related to study drug.

No subject experienced a Grade 3 or 4 hematology laboratory abnormality. Overall, 5 of 111 subjects (4.5%) had a postbaseline hemoglobin value < 10 g/dL, and 1 subject (0.9%) had a postbaseline hemoglobin value < 8.5 g/dL. No subject had a Grade 3 or 4 coagulation laboratory abnormality. No subject had a Grade 3 chemistry laboratory abnormality. A Grade 4 chemistry laboratory abnormality of increased lipase was reported in 1 subject (0.9%); this subject's lipase value returned to normal by the subsequent visit.

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

Quality of Life Results: Mean values for the SF-36 physical component and mental component scores did not significantly change from baseline at any postbaseline visit, or from end of treatment at any posttreatment visit, through posttreatment Week 12. These results should be interpreted with caution as the study was not powered to test these exploratory endpoints.

CONCLUSIONS: The conclusions from this study are as follows:

- Treatment with LDV/SOF for 12 weeks in subjects with HCV/HBV coinfection resulted in an SVR12 rate of 100.0%. This rate is similar to the high SVR12 rates observed in subjects with HCV monoinfection treated with LDV/SOF in other clinical studies.
- The presence of NS5A RAVs and NS5B NI RAVs at baseline did not impact treatment outcome in HCV/HBV-coinfected subjects, as all subjects with RAVs at baseline achieved SVR12.
- HCV virologic suppression was achieved in all subgroups; SVR12 rates of 100.0% were observed in all subjects irrespective of HCV genotype, cirrhosis status at baseline, and prior HCV treatment history.
- While the majority of subjects (73.0%) met the criteria for HBV reactivation, none of the subjects developed any related clinical symptoms.
- LDV/SOF once daily for 12 weeks was safe and well tolerated in HCV-infected subjects who were coinfected with HBV. The AE and laboratory safety profile observed was consistent with that expected for HCV/HBV-coinfected subjects. No new safety signals or toxicities were observed.