FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naive and Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection
Name of Test Drug:	Ledipasvir (LDV)/sofosbuvir (SOF) fixed-dose combination (FDC)
Dose and Formulation:	LDV/SOF 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-337-0131
Phase of Development:	Phase 3b
IND No.:	Not applicable
EudraCT No.:	Not applicable
ClinicalTrials.gov Identifier:	NCT02021656
Study Start Date:	10 December 2013 (First Subject Screened)
Study End Date:	08 July 2017 (Last Subject Last Observation for the Primary Endpoint) 29 September 2017 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Lai Wei, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Brian McNabb, MD Telephone: PPD Fax: PPD
Report Date:	08 February 2018
Previous Report Date(s):	11 September 2017 (Third Interim Clinical Study Report [CSR]) 26 February 2015 (Second Interim Synoptic CSR) 10 October 2014 (Interim CSR)

STUDY SYNOPSIS

Study GS-US-337-0131
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naive and Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection

Investigators: This was a multicenter study.

Study Centers: 45 study sites (18 in Mainland China, 15 in Korea, and 12 in Taiwan).

Publications:

Wei L, Xie Q, Hou JL, et al. Safety and Efficacy of Ledipasvir/Sofosbuvir in a Genotype 1 HCV Infected Chinese Population: Results from a Phase 3 Clinical Trial., [Abstract 1191]. 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.

Lim YS, Ahn SH, Lee KS, Paik SW, Lee YJ, Jeong SH, et al. A phase IIIb study of ledipasvir/sofosbuvir fixed-dose combination tablet in treatment-naive and treatment-experienced Korean patients chronically infected with genotype 1 hepatitis C virus. Hepatol Int 2016 Nov;10(6):947-955. Epub 2016 May 20.

Chuang WL, Chien RN, Peng CY, Chang TT, Lo GH, Sheen IS, et al. Ledipasvir/sofosbuvir fixed-dose combination tablet in Taiwanese patients with chronic genotype 1 hepatitis C virus. J Gastroenterol Hepatol 2016;31 (7):1323-9.

Study Period:

10 December 2013 (First Subject Screened)
08 July 2017 (Last Subject Last Observation for the Primary Endpoint)
29 September 2017 (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 treatment with ledipasvir (LDV)/sofosbuvir (SOF) fixed-dose combination (FDC) as measured by the proportion of subjects with sustained virologic response [SVR] 12 weeks after discontinuation of study drug (SVR12, defined as hepatitis C virus [HCV] RNA < lower limit of quantitation [LLOQ] 12 weeks posttreatment)
- 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 and 24 weeks after discontinuation of study drug (SVR4 and SVR24)
- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation
- To evaluate the emergence of viral resistance to LDV and SOF during treatment and after treatment discontinuation

The exploratory objectives of this study were:

- To identify or validate genetic markers that may be predictive of virologic response to treatment and/or tolerability of treatment through genetic discovery research (eg, pharmacogenomics), in subjects who provide their separate and specific consent
- To assess the effect of treatment with LDV/SOF FDC on health-related quality of life (QoL)

Methodology: This Phase 3, international, multicenter, open-label study assessed the efficacy and safety of LDV/SOF in HCV treatment-naive and treatment-experienced subjects with chronic genotype 1 HCV infection enrolled in Mainland China (referred to as China throughout this clinical study report [CSR]), Korea, and Taiwan.

Approximately 200 subjects in China, 80 subjects in Korea, and 80 subjects in Taiwan were to be enrolled in the study. All subjects were to receive 12 weeks of once-daily treatment with LDV/SOF(90/400 mg), and all were to complete the posttreatment Week 4 and Week 12 follow-up visits. Subjects who had HCV RNA < LLOQ at the posttreatment Week 12 visit were also to complete the posttreatment Week 24 visit unless a confirmed viral relapse occurred.

The First Interim CSR (10 October 2014) presented all data collected through the posttreatment Week 12 visit for subjects enrolled in Korea and Taiwan. The Second Interim CSR (26 February 2015) reported all data collected through posttreatment Week 24 for subjects enrolled in Korea and Taiwan. The Third Interim CSR (11 September 2017) presented all data collected through posttreatment week 12 for subjects enrolled in China and overall (China, Korea, and Taiwan). This Final CSR presents the final results through posttreatment Week 24 for China and overall (China, Korea, and Taiwan). These analyses were conducted when all subjects had completed the posttreatment Week 24 visit or had prematurely discontinued from the study. All data collected by the data finalization date (14 November 2017) were included in these analyses.

Number of Subjects (Planned and Analyzed):

Planned:

- Approximately 360 subjects (200 in China)

Analyzed:

- Enrolled Analysis Set (384 subjects [206 in China]):
  - 194 treatment-naive (106 in China) and 190 treatment-experienced (100 in China)

- Full Analysis Set (FAS; 384 subjects [206 in China]):
  - 194 treatment-naive (106 in China) and 190 treatment-experienced (100 in China)
- Safety Analysis Set:
  - 384 subjects (206 in China)
- Pharmacokinetic (PK) Analysis Set:
  - 383 subjects (206 in China)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males and nonpregnant, nonlactating females aged ≥ 20 years who weighed ≥ 40 kg. Subjects were HCV treatment-naive or treatment-experienced with chronic genotype 1 HCV infection, and documentation of the presence or absence of cirrhosis.

Duration of Treatment: 12 weeks of treatment and up to 24 weeks of posttreatment follow-up

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

LDV/SOF FDC 90/400 mg was administered orally once daily without regard to food.

The batch numbers of LDV/SOF administered in this study were DK1302B1 and 15SFC034.

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

Criteria for Evaluation:

Efficacy: This CSR provides analyses of HCV RNA levels at posttreatment Week 24. Efficacy analyses at all other scheduled assessment time points were described in previous CSRs (First Interim, Second Interim, and Third Interim). Blood samples to determine serum HCV RNA levels were collected from subjects at screening; Day 1 (predose); Weeks 1, 2, 4, 6, 8, 10, and 12 during treatment (or early termination); and posttreatment Weeks 4, 12, and 24 (if applicable). For subjects in China, the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA. The LLOQ of the assay is 15 IU/mL. For subjects in Korea and Taiwan, the COBAS® TaqMan® HCV Test v2.0 for use with the High Pure System assay was used to quantify HCV RNA. The LLOQ of the assay is 25 IU/mL.

Pharmacokinetics: The previous CSRs (First Interim, Second Interim, and Third Interim) provide details on the collection of blood samples for the intensive PK substudy and the sparse PK blood sample collection

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 analyses were described in the First Interim and Third Interim CSRs.

Statistical Methods:

All tables, figures, and listings produced for the subjects in China and overall (China, Korea, and Taiwan) are provided in Section 15.1 and Appendix 16.2. Documentation of statistical methods is provided in Appendix 16.1.9 of this report.

Efficacy: Efficacy data were analyzed by prior HCV treatment status (treatment-naive, treatment-experienced, and overall) for subjects in China and overall for China, Korea, and Taiwan using the FAS. This analysis set included all subjects with chronic genotype 1 HCV infection who were enrolled and received at least 1 dose of study drug.

The primary efficacy endpoint was SVR12 (defined as HCV RNA < LLOQ 12 weeks after discontinuation of study drug) for subjects in the FAS. Details of the statistical methods for the primary endpoint are provided in the First and Third Interim CSRs.

Secondary efficacy endpoints included the proportions of subjects with SVR4, SVR24, and each virologic outcome (SVR12, on-treatment virologic failure, relapse, and "Other"), HCV RNA < LLOQ while on treatment by visit; HCV RNA (log_{10} IU/mL) and change from baseline by visit through Week 12 (end of treatment); and viral resistance to LDV and SOF at baseline and emergent at the time of virologic failure.

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 number and percentage of subjects. Results for all secondary efficacy endpoints for Korea and Taiwan were presented in the Second Interim CSR, and results for all secondary efficacy endpoints except SVR24 for China and overall for China, Korea, and Taiwan were presented in the Third Interim CSR.

The SVR24 rate was calculated along with 2-sided 95% exact CI using the binomial distribution based on Clopper-Pearson method {Clopper et al 1934}. If a subject achieved SVR12 and had no further HCV RNA measurement, the subject was counted as a success for SVR24 due to the high correlation between these 2 endpoints {Chen et al 2013}. In addition, an analysis to assess the concordance of SVR12 with SVR24 was performed.

Pharmacokinetics: The previous CSRs (First Interim, Second Interim, and Third Interim) provide details on the statistical methods for the PK substudy

Safety: All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety data were summarized for subjects in China and overall (China, Korea, and Taiwan) and included all data collected on or after the date of 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 20.0.

Quality of Life: Details on the QoL analyses are presented in the First Interim and Third Interim CSRs.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 384 subjects (206 in China) were enrolled and received treatment in this study and were included in the FAS and Safety Analysis Set. Of these, 381 subjects (99.2%) completed study treatment and the posttreatment Week 12 visit. Full details on subject disposition, demographics, and baseline disease characteristics for Korea and Taiwan through posttreatment Week 24 and for China through posttreatment Week 12 were reported in Section 8.3 of the Third Interim CSR. Subject disposition overall for China, Korea, and Taiwan at posttreatment Week 24 is summarized in Section 15.1, Table 2. Two subjects enrolled in China prematurely discontinued the study between the posttreatment Week 12 and Week 24 visits (1 due to AE and 1 due to withdrawal of consent).

No notable differences in demographic or baseline disease characteristics were observed between the interim analyses and the final analysis. Analyses related to disposition, demographics, study drug adherence, and exposure are presented in Section 15.1, Tables 1 through 7, and Appendix 16.2, Listings 1 through 7.

For this Final CSR, an updated important protocol deviation log is provided in Appendix 16.2.2 (Important Protocol Deviation Log).

Efficacy Results:

Full analysis of the primary efficacy endpoint for China and overall for China, Korea, and Taiwan is reported in Section 9 of the Third Interim CSR. Full analysis of the primary efficacy endpoint and SVR24 for Korea and Taiwan are reported in Section 9 of the First Interim CSR and in the Second Interim CSRs. Results for SVR24 for China and overall for China, Korea, and Taiwan are summarized in this Final CSR.

China

The proportion of subjects with SVR12 and SVR24 is presented in the table below. All subjects enrolled in China achieved SVR12 (Section 15.1, Table 10, Appendix 16.2, Listing 8.2). There was 100.0% concordance between SVR12 and SVR24 for subjects enrolled in China (Section 15.1, Tables 8.1, 9, and 12, and Appendix 16.2, Listing 8.1).

Overall for China, Korea, and Taiwan

Of the 384 subjects in China, Korea, and Taiwan, 381 subjects achieved SVR12 (99.2% [95% CI: 97.7% to 99.8%]), including 100.0% of treatment-naive subjects (95% CI: 98.1% to 100.0%) and 98.4% of treatment-experienced subjects (95% CI: 95.5% to 99.7%; Section 15.1, Table 8.1). There were no changes to the SVR12 and SVR24 results for subjects from Korea and Taiwan as reported in the First Interim and Second Interim CSRs.

Overall, except for 1 subject who was reinfected with HCV of a different genotype after achieving SVR12 (enrolled in Korea and described in the Second Interim CSR), all subjects who achieved SVR12 achieved SVR24.

All efficacy analyses are provided in Section 15.1, Tables 8.1 through 13, Figures 2 through 4.4, and Appendix 16.2, Listings 8.1 and 8.2.

	Treatment-Naive LDV/SOF 12 Weeks		Treatment-Experienced LDV/SOF 12 Weeks		Total	
	China (N=106)	Overall (N=194)	China (N=100)	Overall (N=190)	China (N=206)	Overall (N=384)
SVR12	106/106 (100.0%)	194/194 (100.0%)	100/100 (100.0%)	187/190 (98.4%)	206/206 (100.0%)	381/384 (99.2%)
95% CI	96.6% to 100.0%	98.1% to 100.0%	96.4% to 100.0%	95.5% to 99.7%	98.2% to 100.0%	97.7% to 99.8%
SVR24	106/106 (100.0%)	194/194 (100.0%)	100/100 (100.0%)	186/190 (97.9%)	206/206 (100.0%)	380/384 (99.0%)
95% CI	96.6% to 100.0%	98.1% to 100.0%	96.4% to 100.0%	94.7% to 99.4%	98.2% to 100.0%	97.4% to 99.7%

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Test v2.0 with limit of quantitation 15 IU/mL in China.
HCV RNA was analyzed using Roche TaqMan V 2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL in Korea and Taiwan.
SVRxx was sustained virologic response (HCV RNA < LLOQ) xx weeks after stopping study treatment.
A missing SVR12 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 SVR12 value was imputed as a failure. TND = target not detected.
A missing SVR24 value was imputed as a success if preceded by SVR12 success due to the high correlation between these two endpoints.
The exact 95% CI for the proportion was based on the Clopper-Pearson method.
Source: Section 15.1, Table 12

Virologic Resistance Results:

There are no Week 24 resistance analyses reported for China, as no subjects in China relapsed between the posttreatment Week 12 through Week 24. Full details on the Week 12 resistance analyses for China are reported in Section 9.3.2 of the Third Interim CSR.

The sole virologic failure between posttreatment Week 12 and Week 24 for the overall (China, Korea, and Taiwan) study population was the subject enrolled in Korea who was reinfected with a different genotype of HCV, as described above. Full details of the case are presented in the Second Interim CSR. Beyond this reinfected patient, no subjects relapsed between the posttreatment Week 12 through Week 24, so no resistance analyses were performed at Week 24 for Korea and Taiwan. Full details on the Week 12 resistance analyses for Korea and Taiwan are presented in the First Interim CSR.

Pharmacokinetics Results:

Full details of the PK results for China and overall for China, Korea, and Taiwan are reported in Section 10 of the Third Interim CSR.

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. Evaluation of safety through 30 days after the last dose of study drugs through SVR24 for subjects from Korea and Taiwan were summarized in Section 11 of the First Interim and Second Interim CSRs and safety data for subjects from China and overall (China, Korea and Taiwan) through posttreatment Week 12 was summarized in Section 11 of the Third Interim CSR.

China

Adverse Events and Serious Adverse Events

A small number of updates were made to previously reported AE data due to the ongoing nature of the study and data reconciliation. Adhoc Listing 3 provides a detailed listing of any AEs that had changes or were newly reported between the Third Interim CSR and this Final CSR. The single newly reported AE of depression was Grade 1 in severity. AEs that had changes included change of study drug-related paroxysmal palpitation to non-study drug-related paroxysmal palpitation in 1 subject and change of preferred AE term from keratitis to conjunctivitis in 1 subject; all changes were reported for subjects in China (Appendix 16.2, Listing 10 and Adhoc Listing 3).

No new subject pregnancies, SAEs, Grade 3 or 4 AEs, or AEs that led to study drug discontinuation were reported for this Final CSR (Section 15.1, Table 15 and Appendix 16.2, Listings 14 and 15).

All AE results are provided in Section 15.1 Tables 15 through 30, and Appendix 16.2, Listings 10 through 15.

Clinical Laboratory Results

Blood samples for clinical laboratory analyses were not collected at the posttreatment Week 24 visit; therefore, there were no changes to the clinical safety laboratory results previously reported in the Third Interim CSR for subjects enrolled in China.

All laboratory results are provided in Section 15.1, Tables 31.1 through 33, Figures 5.1 through 5.10, and Appendix 16.2, Listings 17 through 21.2.

Electrocardiograms and Vital Signs

Electrocardiograms were not collected at the posttreatment Week 24.

Vital sign measurements (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) and weight were collected at the posttreatment Week 24 visit. No notable changes relative to posttreatment Week 12 (Third Interim CSR) were observed for subjects enrolled in China.

All vital sign measurements and ECG results are provided in Section 15.1, Tables 34 through 35.3, and Appendix 16.2, Listings 22 through 23.2 and Ad Hoc Listing 2.

Overall for China, Korea, and Taiwan

Adverse Events and Serious Adverse Events

Overall, no subject pregnancies were reported and no subjects died (Section 15.1, Table 15 and Appendix 16.2, Listings 14 and 15).

Aside from changes to AE data described above for subjects enrolled in China, no other changes in AEs were identified between the Third Interim CSR and this Final CSR. All AE results are provided in Section 15.1 Tables 15 through 30, and Appendix 16.2, Listings 10 through 15.

Narratives for all SAEs from the first dose of study drug through the end of the study (ie, the SVR24 visit) and for all early discontinuations from study treatment due to an AE are provided in Section 15.2.

Clinical Laboratory Results

Blood samples for clinical laboratory analyses were not collected at the posttreatment Week 24 visit; therefore, there were no changes to the clinical safety laboratory results previously reported in the Third Interim CSR for subjects overall (China, Korea, and Taiwan).

All laboratory results are provided in Section 15.1, Tables 31.1 through 33, Figures 5.1 through 5.10, and Appendix 16.2, Listings 17 through 21.2.

Electrocardiograms and Vital Signs

Electrocardiograms were not collected at the posttreatment Week 24.

Vital sign measurements (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) and weight were collected at the posttreatment Week 24 visit. There are no additional data or changes to data previously reported in the Third Interim CSR for subjects overall (China, Korea, and Taiwan).

All vital sign measurements and ECG results are provided in Section 15.1, Tables 34 through 35.3, and Appendix 16.2, Listings 22 through 23.2 and Ad Hoc Listing 2.

Quality of Life Results:

Quality of life surveys (SF-36) were not collected during the posttreatment Week 24 visit. There are no additional data or changes to data that were previously reported in the Third Interim CSR. Full details on the quality of life survey (SF-36) for China and overall for China, Korea, and Taiwan are reported in Section 12 of the Third Interim CSR.

Quality of life analyses are provided in Section 15.1, Table 36, Figure 6, and Appendix 16.2, Listing 9.

CONCLUSIONS: The conclusions from interim and final analyses for subjects in China and overall for China, Korea, and Taiwan are as follows:

<u>China</u>

- Treatment with LDV/SOF for 12 weeks in HCV treatment-naive and treatment-experienced subjects, including those with and without cirrhosis, resulted in an SVR12 rate of 100.0%.
  - The SVR12 rate for treatment-naive subjects met the prespecified criterion for superiority compared with the historic SVR rate.
- SVR24 was 100.0% concordant with SVR12 across all treatment groups.
- The presence of NS5A and NS5B NI RAVs at baseline had no impact on treatment outcome.
- There were no clinically relevant differences in SOF, GS-331007, or LDV exposures in the China PK population compared with the LDV/SOF US NDA population.
- Treatment with LDV/SOF for 12 weeks was generally well tolerated. There was a low incidence of SAEs, no study drug discontinuations due to AEs, and no clinically meaningful laboratory abnormalities.

Overall for China, Korea, and Taiwan

- Treatment with LDV/SOF for 12 weeks in HCV treatment-naive and treatment-experienced subjects, including those with and without cirrhosis, resulted in a high SVR12 rate of 99.2%.
- SVR24 was 100.0% concordant with SVR12 across all treatment groups, with the exception of 1 subject who achieved SVR12 and was newly infected with HCV of another genotype prior to their posttreatment Week 24 visit.
- The presence of NS5A and NS5B NI RAVs at baseline had no impact on treatment outcome.
- There were no clinically relevant differences in SOF, GS-331007, or LDV exposures in the overall China, Korea, and Taiwan PK population compared with the LDV/SOF US NDA population.
- Treatment with LDV/SOF for 12 weeks was generally well tolerated. There was a low incidence of SAEs and discontinuations due to AEs and no clinically meaningful laboratory abnormalities.