FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir in Adults with Chronic HCV Infection
Name of Test Drug:	Ledipasvir (LDV)/Sofosbuvir (SOF) 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-337-1463
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	Not Applicable 2015-000690-13
ClinicalTrials.gov Identifier:	NCT02472886
Study Start Date:	17 June 2015 (First Subject Screened)
Study End Date:	30 June 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Vasily Isakov, MD, PhD, Dr. Med Sci Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Anu Osinusi, MD Telephone: PPD Fax: PPD
Report Date:	13 October 2016
Previous Report Date(s):	10 June 2016 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-337-1463
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404,
USA

Title of Study: A Phase 3b, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir in Adults with Chronic HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 19 sites in Russia and 2 sites in Estonia.

Publications: Zhdanov K., Morozov V., Orlova-Morozova E.A., Salupere R., Kozhevnikova G., et al. Preliminary Results of an Evaluation of Ledipasvir/Sofosbuvir in Treatment-Naive Patients with Chronic HCV or HCV/HIV Co-Infection and Retreatment of Sofosbuvir-treated Patients. 8th International Conference of the White Nights of Hepatology. Saint Petersburg, Russia. June 2-3, 2016. Oral presentation.

Study Period:

17 June 2015 (First Subject Screened)
30 March 2016 (Last Subject Observation for the Primary Endpoint)
30 June 2016 (Last Subject Observation)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To determine the antiviral efficacy of ledipasvir/sofosbuvir (LDV/SOF) ± ribavirin (RBV) in subjects with chronic hepatitis C virus (HCV) infection as measured by the proportion of subjects in each treatment group with sustained viral response 12 weeks after discontinuation of therapy (SVR12)
- To assess the safety and tolerability of LDV/SOF ± RBV in subjects with chronic HCV infection as measured by review of the accumulated safety data

The secondary objectives of this study were as follows:

- To determine the proportion of subjects in each treatment group who attain SVR at 4 and 24 weeks after discontinuation of therapy (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 SOF and/or LDV, as relevant, during treatment and after treatment discontinuation

- To assess the proportion of HCV/human immunodeficiency virus (HIV)-coinfected subjects that maintain HIV-1 RNA <50 copies (cp) /mL while on HCV treatment and at posttreatment Week 4
- To assess the change from baseline in cluster determinant 4 (CD4) T-cell count at the end of treatment and at posttreatment Week 4

Exploratory objectives of this study were as follows:

- To identify or validate genetic markers that may predict the natural history of disease, virologic response to therapy and/or tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics), in subjects who provide their separate and specific consent
- To assess the effect of treatment on quality of life

Methodology: This Phase 3, multicenter, open-label, nonrandomized, and parallel cohort study evaluated the safety and efficacy of LDV/SOF in 3 treatment groups of adults with chronic HCV infection. Subjects were enrolled in 1 of 3 groups:

- **Treatment-naive (TN), HCV-monoinfected group (LDV/SOF 8 Week [Group 1]):** Approximately 60 TN subjects with genotype 1 HCV infection without cirrhosis received LDV/SOF fixed dose combination (FDC) (90/400 mg once daily) for 8 weeks
- **TN, HCV/HIV-coinfected group (LDV/SOF 8 Week [Group 2]):** Approximately 60 TN subjects with genotype 1 HCV infection without cirrhosis and coinfected with HIV-1 received LDV/SOF FDC (90/400 mg once daily) for 8 weeks
- **SOF-Treated, HCV-monoinfected group (LDV/SOF+RBV 12 Week [Group 3]):** Treatment-experienced subjects with genotype 1 or 3 HCV infection who failed to achieve SVR12 in Study GS-US-334-0119 received LDV/SOF FDC (90/400 mg once daily) + weight based RBV (1000 or 1200 mg/day divided twice daily) for 12 weeks

Approximately 20% of the TN, HCV/HIV-coinfected subjects may have been antiretroviral (ARV)-naive while approximately 80% were on a stable ARV regimen for at least 8 weeks prior to screening.

All subjects were required to complete the posttreatment Week 4 visit regardless of treatment duration. Subjects with HCV RNA < LLOQ (lower limit of quantitation) were also to complete the posttreatment Weeks 12 and 24 visits unless confirmed viral relapse occurred. Investigators were unblinded to individual subject HCV RNA results at their respective center throughout the study.

This final synoptic clinical study report (CSR) summarizes the results of the final analysis of data collected throughout the course of the study, after all subjects had completed the posttreatment Week 24 visit or had prematurely discontinued from the study. Analysis of data collected for the primary efficacy endpoint (SVR12) was also reported in the interim CSR (10 June 2016).

Number of Subjects (Planned and Analyzed):

Planned:

approximately 60 TN, HCV-monoinfected subjects
approximately 60 TN, HCV/HIV-coinfected subjects
up to 35 SOF-treated, HCV-monoinfected subjects

Analyzed:

A total of 153 subjects were enrolled and analyzed in the Full and Safety Analysis Sets
- 67 TN, HCV-monoinfected subjects
- 59 TN, HCV/HIV-coinfected subjects
- 27 SOF-treated, HCV-monoinfected subjects

Diagnosis and Main Criteria for Inclusion:

HCV-monoinfected and HCV/HIV-coinfected subjects: Eligible subjects were males or nonpregnant/nonlactating females ≥ 18 years of age, with chronic genotype 1 HCV infection (monoinfected or coinfected with HIV), who had screening HCV RNA levels ≥ 10^4 IU/mL, were HCV TN, and had documentation of the absence of cirrhosis. HCV/HIV-coinfected subjects who were ARV-naive had CD4 T-cell counts > 500 cells/ mm^3. HCV/HIV-coinfected subjects who were ARV-experienced were required to have completed at least 6 months of any prior HIV ARV therapy, maintained HIV RNA < 50 cp/mL, been on a stable protocol-approved ARV regimen for at least 8 weeks, or for at least 6 months for abacavir-containing regimens, prior to screening, and had a CD4 T-cell count > 200 cells/mm^3 at screening.

SOF-treated, HCV-monoinfected subjects: Eligible subjects had HCV RNA > LLOQ with chronic genotype 1 or 3 HCV infection, documentation of the presence or absence of cirrhosis, and had failed to achieve SVR12 following treatment with SOF+RBV in Study GS-US-334-0119.

Duration of Treatment: Treatment duration was 8 weeks for HCV-monoinfected and HCV/HIV-coinfected subjects, and 12 weeks for SOF-treated, HCV-monoinfected subjects.

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

- **LDV/SOF** was administered orally to all subjects at a dose of 90/400 mg (1 FDC tablet once daily)
- **RBV** was administered orally to SOF-treated, HCV-monoinfected subjects at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided twice daily)

The lot numbers of the study drugs administered in this study were as follows:

- **LDV/SOF**: DK1313B3 and DK1312B3
- **RBV**: AB1933Z

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

Criteria for Evaluation:

Efficacy: This final synoptic CSR provides analyses of HCV RNA levels at posttreatment Week 24. Efficacy analyses at all other scheduled assessment time points were described in the interim CSR (10 June 2016) and are updated in this final CSR. The Roche COBAS® Ampliprep/COBAS® Taqman HCV Test, v2.0 (HCV RNA PCR) assay was used to determine HCV RNA results in this study. The LLOQ of the assay was 15 IU/mL.

Pharmacokinetics: No pharmacokinetic assessments were performed for this report or for the interim CSR (10 June 2016).

Safety: The interim CSR (10 June 2016) provides analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital sign measurements, and physical examinations. This final synoptic CSR summarizes any new treatment-emergent AEs or changes to previously reported AEs between the data cuts for the interim CSR and the final CSR. Additionally, all serious adverse events (SAEs) collected after the data cutoff for the interim CSR to the end of the study (posttreatment Week 24) are summarized. Serious adverse events occurring > 30 days after the last dose of study drug were considered nontreatment emergent.

Other: Health-related quality of life analyses were described in the interim CSR (10 June 2016).

Statistical Methods:

All tables, figures, and listings produced for this study are provided in Section 15.1 and Appendix 16.2. Documentation of statistical methods is provided in Appendix 16.1.9 of this report and described in detail in Section 7.7 of the interim CSR (10 June 2016).

Efficacy:

The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the Full Analysis Set (FAS). The 2-sided 95% exact confidence interval (CI) based on Clopper-Pearson method was provided for the SVR12 rate in each of the 3 treatment groups.

The 2-sided 95% Clopper-Pearson exact CIs for SVR12 were provided for the SVR12 rate within each treatment group by key demographic and baseline characteristic and treatment adherence subgroups. A forest plot graphically presents estimates and 95% CIs in SVR12 rates for each of the subgroups by treatment group.

Secondary efficacy endpoints include the proportion of subjects with SVR4, SVR24, virologic outcomes (on-treatment virologic failure and relapse), HCV RNA < LLOQ (ie, < 15 IU/mL) by visit, and absolute HCV RNA and change from baseline through Week 12, and emergence of viral resistance to SOF during treatment and after treatment discontinuation. In addition, an analysis to assess the concordance of SVR12 with SVR24 was performed.

If an HCV RNA value was missing and was preceded and followed by HCV RNA values that were "< LLOQ target not detected (TND)," then the missing HCV RNA value was imputed to be "< LLOQ TND." Therefore, missing posttreatment Week 4 and 12 HCV RNA values were imputed to achieve SVR4 and SVR12 if preceding and posttreatment Week 24 HCV RNA values were "< LLOQ TND". SVR24 rates were calculated using the same method as described for SVR12. If a subject achieved SVR12 and had no further HCV RNA measurements, the subject

was counted as a success for SVR24 due to the high correlation between the 2 endpoints {Chen et al 2013}.

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

Pharmacokinetics: No pharmacokinetic assessments were performed for this report or for the interim CSR (10 June 2016).

Safety: All enrolled subjects who received at least 1 dose of any 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. For TN, HCV/HIV-coinfected subjects, HIV RNA, CD4, and renal functions were also assessed. 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 19.

Other: The health-related quality of life questionnaire, SF-36, was completed at baseline/Day 1, and end of treatment (ie, Week 8 for HCV-monoinfected and HCV/HIV-coinfected subjects, Week 12 for SOF-treated, HCV-monoinfected subjects), or the early termination visit, if applicable, posttreatment Week 4, and posttreatment Week 12 (if applicable). A Wilcoxon signed rank test was used to explore within treatment group changes in status from baseline to each of the time points, and from end of treatment to posttreatment time points.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 153 subjects were enrolled in the study: 67 TN subjects with genotype 1 HCV infection and 59 TN subjects with genotype 1 HCV infection who were coinfected with HIV-1 infection who were to receive LDV/SOF for 8 weeks, and 27 subjects who had failed to achieve SVR12 in Study GS-US-334-0119 who were to receive LDV/SOF+RBV for 12 weeks (Section 15.1, Table 15.8.1.3; Appendix 16.2, Listings 16.2.1.1 and 16.2.1.2). Notably, 1 subject (Subject PPD who missed the posttreatment Week 4 and Week 12 visits had a posttreatment Week 24 visit; therefore, the posttreatment Week 4 and Week 12 HCV RNA values were imputed based on the posttreatment Week 24 HCV RNA value (Section 15.1, Table 15.8.1.3; Appendix 16.2, Listing 16.2.6.1). Full details on subject disposition are reported in Section 8 of the interim CSR (10 June 2016), and subject disposition at posttreatment Week 24 is summarized in Section 15.1, Table 15.8.1.3).

There were no differences in demographic or baseline disease characteristics or concomitant medications between the interim analyses and the final analyses (Section 15.1, Tables 15.8.3.1 and 15.11.8.1; Appendix 16.2, Listings 16.2.4.1-16.2.4.2.2 and 16.2.4.4.1-16.2.4.4.2).

Analyses related to disposition, demographics, medical history, concomitant medications, exposure, and prior treatment response for subjects who had failed to achieve SVR12 in Study GS-US-334-0119 who received LDV/SOF+RBV for 12 weeks are presented in Section 15.1, Tables 15.8.1.1 to 15.8.4 and 15.11.8.1; Figure 15.8; Appendix 16.2, Listings 16.2.1.1 to 16.2.5.2,and 16.2.8.1.3.2. In addition, an updated Important Protocol Deviations Log for the

study is provided in Appendix 16.2.2.

Efficacy Results: Analysis of the primary efficacy endpoint is reported in Section 9 of the interim CSR (10 June 2016). Results for SVR24, a secondary efficacy endpoint, are summarized in this CSR. The proportion of subjects with SVR4, SVR12, and SVR24 is presented in the table below.

Differences were observed in the SVR4 and SVR12 results between the interim analysis and the final analysis. For Group 1 at the interim analysis, 1 subject (Subject PPD did not achieve SVR4 or SVR12 (due to missed posttreatment Week 4 and 12 visits); for the final analysis, this subject had a posttreatment Week 24 visit and SVR24 was achieved (no HCV RNA detected). Therefore the posttreatment Week 4 and Week 12 HCV RNA values were imputed to be "< LLOQ TND" based on the posttreatment Week 24 HCV RNA value and the subject was considered to have achieved SVR4 and SVR12 (Section 15.1, Table 15.9.2.2; Appendix 16.2, Listing 16.2.6.1). The revised SVR4 and SVR12 rates for TN HCV-monoinfected subjects were 100% (67 of 67 subjects) for both time points (Section 15.1, Table 15.9.2.2).

The SVR12 and SVR24 rates were the same for all groups (Section 15.1, Table 15.9.2.2; Appendix 16.2, Listing 16.2.6.2). At the final analysis, there was 100% concordance between SVR12 and SVR24 for subjects who had an observed HCV RNA measurement within both posttreatment Week 12 and 24 visit windows (Section 15.1, Tables 15.9.1, 15.9.2.2, and 15.9.2.3; Appendix 16.2, Listing 16.2.6.2).

	Group 1 TN, HCV-monoinfected subjects	**Group 2 TN, HCV/HIV-coinfected subjects**	**Group 3 SOF-treated, HCV-monoinfected subjects**
	LDV/SOF 8 Weeks (N=67)	**LDV/SOF 8 Weeks (N=59)**	**LDV/SOF+RBV 12 Weeks (N=27)**
Number of subjects who were < LLOQ at their last observed on-treatment HCV RNA value	67	58	27
SVR4	67/67 (100.0%)	57/59 (96.6%)	26/27 (96.3%)
95% CI	94.6% to 100.0%	88.3% to 99.6%	81.0% to 99.9%
SVR12	67/67 (100.0%)	57/59 (96.6%)	26/27 (96.3%)
95% CI	94.6% to 100.0%	88.3% to 99.6%	81.0% to 99.9%
SVR24	67/67 (100.0%)	57/59 (96.6%)	26/27 (96.3%)
95% CI	94.6% to 100.0%	88.3% to 99.6%	81.0% to 99.9%

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation 15 IU/mL.
SVRx is 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 are 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 is based on the Clopper-Pearson method.
Group 1 - Treatment-naïve, HCV-monoinfected subjects; Group 2 - Treatment-naïve, HCV/HIV-coinfected subjects;
Group 3 - Sofosbuvir-treated, HCV-monoinfected subjects.
Subject PPD in Group 1 missed FU12 and returned at FU24. SVR12 was imputed as < LLOQ TND.
Source: Section 15.1, Tables 15.9.1 and 15.9.2.2; Appendix 16.2, Listing 16.2.6.1

No subject in any treatment group had on-treatment virologic failure (ie, breakthrough, rebound,

or nonresponse) (Section 15.1, Table 15.9.2.1). No subjects relapsed between posttreatment Weeks 12 and 24 (Section 15.1, Table 15.9.2.2; Appendix 16.2, Listing 16.2.6.2).

All efficacy analyses are provided in Section 15.1, Tables 15.9.2.1 to 15.9.4.1, and Figures 15.9.2.3 to 15.9.2.5.4, and Appendix 16.2, Listings 16.2.6.1 to 16.2.6.4.

Virologic Resistance: Full details on the virologic resistance analysis are reported in Section 9.3.2 of the interim CSR (10 June 2016). No additional resistance analyses were performed since no subjects relapsed after the data cutoff for the interim CSR (10 June 2016).

Pharmacokinetic/Pharmacodynamic Results: No pharmacokinetic or pharmacodynamics assessments were performed for this report or for the interim CSR (10 June 2016).

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. Evaluations of safety data through 30 days after the last dose of study drugs were summarized in Section 11 of the interim CSR (10 June 2016).

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. These changes were primarily associated with AE resolution dates or minor clarifications to AE terms and a newly reported Grade 1 AE (lymphadenopathy for Subject PPD (Appendix 16.2, Listing 16.2.7.1 and Ad Hoc Listing 8302.1). These changes did not impact the overall interpretation or conclusions of the safety profile of LDV/SOF with RBV in this study. Ad Hoc Listing 8302.1 provides a detailed listing of the newly reported AE and AEs that had changes in reported or preferred term, onset date, or action(s) taken between the data cuts taken at the posttreatment Week 12 and posttreatment Week 24 time points.

No treatment-emergent SAEs were reported, no AEs leading to discontinuation of LDV/SOF from the first dose of study drug through the end of the study (ie, the SVR24 visit) were reported, and no subjects died during the study (Appendix 16.2, Listing 16.2.7.1, 16.2.7.3, 16.2.7.5, and Ad Hoc Listing 8302.1).

One new, nontreatment-emergent SAE was reported for this CSR; Subject PPD (SOF-treated, HCV-monoinfected subject in Group 3) had a Grade 2, serious nasal fracture due to a motor vehicle accident on posttreatment Day 73, which was considered not related to study drug by the investigator (Section 15.2; Appendix 16.2, Listings 16.2.4.2.1 and 16.2.7.4 and Ad Hoc Listing 8302.1).

Two pregnancies were reported in this study (Section 15.2; Appendix 16.2, Listing 16.2.8.3). An ongoing pregnancy (reported in the interim CSR, 10 June 2016) that occurred more than 28 days after the end of treatment resolved with the birth of a healthy baby. One additional ongoing pregnancy that occurred more than 28 days after the end of treatment was reported.

Narratives for SAEs and pregnancies are provided in Section 15.2. All AE results are provided in Section 15.1, Tables 15.11.2.1.1 to 15.11.5.6, and Appendix 16.2, Listings 16.2.7.1 to 16.2.7.6, 16.2.8.1.3.3, and 16.2.8.3.

Clinical Laboratory Results

Urinalysis was collected through the posttreatment Week 24 visit and blood samples for clinical laboratory analyses were collected through the posttreatment Week 12 visit. No notable changes in the clinical laboratory results were observed.

All laboratory results are provided in Section 15.1, Tables 15.11.6.1.1 to 15.11.6.4, Figures 15.11.6.1 to 15.11.6.12, and Appendix 16.2, Listings 16.2.8.1.1 to 16.2.8.17.

Vital Sign Measurements and Electrocardiograms

Vital signs (systolic blood pressure, diastolic blood pressure, temperature, respiration, and pulse) and weight were collected through the posttreatment Week 24 visit. No notable changes to vital sign measurements were observed (Appendix 16.2, Listings 16.2.8.2.1 and 16.2.8.2.2).

All vital sign and ECG results are provided in Section 15.1, Tables 15.11.7.1 to 15.11.7.3, and Appendix 16.2, Listings 16.2.8.2.1 to 16.2.8.2.3.2.

Other Results: Analysis of health-related quality of life is reported in Section 12 of the interim CSR (10 June 2016).

CONCLUSIONS: The conclusions from this final analysis of Study GS-US-337-1463 are as follows:

- In TN, genotype 1 HCV-monoinfected subjects, LDV/SOF administered once daily for 8 weeks resulted in an SVR12 rate of 100.0% (67 of 67 subjects).
- In TN, genotype 1 HCV/HIV-coinfected subjects, LDV/SOF administered once daily for 8 weeks resulted in a high SVR12 rate (96.6% [57 of 59 subjects]).
- In HCV-monoinfected subjects who had failed to achieve SVR12 following treatment with SOF+RBV, retreatment with LDV/SOF+RBV for 12 weeks resulted in a high SVR12 rate (96.3% [26 of 27 subjects]).
- Relapse rates were low in all 3 subject populations. No genotype 1 TN, HCV-monoinfected subjects who received LDV/SOF for 8 weeks relapsed; 2 TN, genotype 1 HCV/HIV-coinfected subjects who received LDV/SOF for 8 weeks and 1 SOF-treated, HCV-monoinfected subject with genotype 3 HCV who received LDV/SOF+RBV for 12 weeks relapsed by posttreatment Week 4.
- For all groups, the SVR12 and SVR24 rates were the same. No subjects relapsed between posttreatment Week 12 and 24.
- The presence of nonstructural protein (NS) 5A and NS5B nucleoside inhibitor (NI) resistance-associated variants (RAVs) did not impact the treatment outcome in all 3 groups. Viral relapse was associated with no or minimal emergence of resistance.
- Treatment with LDV/SOF for 8 weeks or LDV/SOF+RBV for 12 weeks was well tolerated in this study, with no deaths, no permanent discontinuations of study drug due to AEs, no treatment-emergent SAEs, only one Grade 3 AE, no Grade 4 AEs, and a few Grade 3 or 4 laboratory abnormalities.

- There was no clinically meaningful effect of LDV/SOF treatment on CD4 count or HIV RNA levels. No clinically significant differences were observed between TN, HCV/HIV-coinfected subjects who were ART-naive and ART-experienced.