FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and 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:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-337-0115 (ION-4)
Phase of Development:	Phase 3
IND No.:	115268
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02073656
Study Start Date:	24 February 2014 (First Subject Screened)
Study End Date:	01 December 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Mark Sulkowski, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	21 March 2016
Previous Report Date(s):	12 March 2015

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-337-0115
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Co-infection

Investigators: Multicenter study.

Study Centers: Subjects were enrolled across 60 sites: 53 in the United States (US) (including 2 in Puerto Rico), 5 in Canada, and 2 in New Zealand.

Publications:

Cooper C, Naggie S, Saag M, Yang JC, Stamm LM, Dvory-Sobol H, et al. Retreatment of Patients Who Failed 12 Weeks of Ledipasvir/Sofosbuvir-Based Regimens with Ledipasvir/Sofosbuvir with Ribavirin for 24 Weeks [Poster Presentation]. 23nd Conference on Retroviruses and Opportunistic Infections (CROI); 2016 February 22-25; Boston, MA.

Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med. 2015 Aug 20; 373(8):705-13.

Naggie S, Cooper C, Saag M, Stamm LM, Yang JC, Pang PS, et al. Ledipasvir/Sofosbuvir for 12 Weeks in Patients Coinfected With HCV and HIV-1 [Oral Presentation]. 22nd Conference on Retroviruses and Opportunistic Infections (CROI); 2015 February 23-26; Seattle, WA.

Study Period:

24 February 2014 (First Subject Screened)
01 December 2015 (Last Subject Observation)
25 November 2014 (Last Subject Observation for the Primary Endpoint)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To determine the HCV antiviral efficacy of combination treatment with ledipasvir (LDV)/ sofosbuvir (SOF) fixed-dose combination (FDC) as measured by the proportion of subjects with sustained viral response 12 weeks after discontinuation of study treatment (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 and 24 weeks after discontinuation of study treatment (SVR4 and SVR24)
- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation
- To evaluate the emergence of HCV viral resistance to SOF and LDV during treatment and after treatment discontinuation
- To assess 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 baseline in CD4 T-cell count at the end of treatment and at posttreatment Week 4
- To characterize steady state pharmacokinetics (PK) of SOF, LDV, and metabolites
- To evaluate the HCV antiviral efficacy of combination treatment with LDV/SOF FDC + ribavirin (RBV) for 24 weeks in subjects who entered the Retreatment Substudy, as determined by the proportion of subjects with SVR4, SVR12, and SVR24
- To evaluate the safety and tolerability of LDV/SOF FDC+RBV for 24 weeks in subjects who entered the Retreatment Substudy, as assessed by review of the accumulated safety data

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 assess the effect of treatment on health-related quality of life

Methodology: This Phase 3, open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of LDV/SOF administered for 12 weeks in HCV treatment-naive and treatment-experienced (including treatment intolerant) subjects with chronic genotype 1 or 4 HCV infection who were coinfected with HIV-1.

Approximately 300 subjects were to be enrolled and treated with LDV/SOF FDC (90/400 mg) tablet once daily for 12 weeks.

Subject subgroups included:

- Approximately 50% of the subjects who were HCV treatment-experienced (including treatment-intolerant)
- Approximately 20% of the subjects who had evidence of cirrhosis at screening

All subjects were to complete the posttreatment Week 4, 12, and 24 visits regardless of their treatment duration. Eligible subjects who experienced posttreatment virologic failure at or before posttreatment Week 24 may have enrolled in the Retreatment Substudy. Subjects in the Retreatment Substudy were retreated with LDV/SOF FDC (90/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided twice a day [BID]) for 24 weeks.

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, including data collected in the Primary Study and data collected in the Retreatment Substudy. Analysis of data collected for the primary efficacy endpoint (SVR12) of the Primary Study was also reported in the interim CSR (12 March 2015). The results of the PK substudy are described in the interim CSR.

After completing the current study, eligible subjects could enroll into 1 of 2 follow-on studies: the SVR Registry Study (GS-US-248-0122) or the Sequence Registry Study (GS-US-248-0123).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 300 subjects
Analyzed:

- All enrolled subjects: 335 subjects
- Full Analysis Set (FAS): 335 subjects
- Safety Analysis Set: 335 subjects
- Retreatment Substudy FAS: 9 subjects
- Retreatment Substudy Safety Analysis Set: 9 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were HCV treatment-naive or treatment-experienced (including treatment intolerant) males and nonpregnant/nonlactating females, aged 18 years or older, with chronic genotype 1 or 4 HCV infection and HIV-1 coinfection, had documentation of the presence or absence of cirrhosis, and had a body mass index (BMI) $\geq$ 18 kg/m^2.

Subjects were required to have been HIV-1 suppressed on an antiretroviral (ARV) regimen for at least 6 months prior to screening; must have been on a stable, protocol-approved ARV regimen for $\geq$ 8 weeks prior to screening; and must have been expected to maintain the same ARV regimen for the duration of the study. Subjects were required to have a CD4 T-cell count $>$ 100 cells/mm^3 at screening and not have had an opportunistic infection within 6 months prior to screening.

In addition, subjects in the Retreatment Substudy had confirmed HCV RNA $\geq$ lower limit of quantitation (LLOQ) within 60 days of Retreatment Day 1. Details on the eligibility criteria for subjects in the Retreatment Substudy are described in the protocol (Appendix 16.1.1, Appendix 6).

Duration of Treatment: Treatment duration for the Primary Study was 12 weeks with a 24-week posttreatment follow-up period. Treatment duration for the Retreatment Substudy was 24 weeks with a 24-week posttreatment follow-up period.

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

In the Primary Study, LDV/SOF was administered orally at a dose of 90/400 mg (1 FDC tablet once daily). The lot number for study drug administered in the Primary Study was DK1304B1 for LDV/SOF.

In the Retreatment Substudy, LDV/SOF was administered orally at a dose of 90/400 mg (1 FDC tablet once daily) and RBV was administered orally at a total dose of 1000 or 1200 mg/day (divided BID). The lot numbers for study drug administered in the Retreatment Substudy were DK1304B1 for LDV/SOF and AA2773Z for RBV.

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

Criteria for Evaluation:

Efficacy: For the Primary Study, 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 (12 March 2015).

For the Retreatment Substudy, blood samples to determine serum HCV RNA levels were collected from subjects on Retreatment Day 1 predose, at Retreatment Weeks 2, 4, 8, 12, 16, 20, and 24 during treatment (or upon early termination), and posttreatment Weeks 4, 12, and 24.

The COBAS® TaqMan® HCV Test, v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study. The LLOQ of the assay was 25 IU/mL.

Pharmacokinetics: The interim CSR (12 March 2015) describes details on the collection of blood samples for the PK analyses.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital sign measurements, and physical examinations. For the Primary Study, the interim CSR (12 March 2015) provided analyses of these safety assessments and this final synoptic CSR summarizes any new treatment-emergent AEs or changes to previously reported treatment-emergent 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. For the Retreatment Substudy, analyses of these safety assessments are reported in this final synoptic CSR.

Quality of Life: For the Primary Study, the health-related quality of life surveys (Short Form-36 [SF-36], Chronic Liver Disease Questionnaire [CLDQ-HCV], Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F], Work Productivity and Activity Impairment Questionnaire: Hepatitis C, v2.0 [WPAI: Hepatitis C]) were completed at Day 1 (baseline), Weeks 4, 8, 12, posttreatment Week 4, and early termination (if applicable) visits.

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 (12 March 2015).

Efficacy: In the Primary Study, the primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the FAS. The primary efficacy endpoint analysis was conducted when all subjects in the Primary Study 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 confidence interval (CI) was constructed using the Clopper-Pearson method. Secondary efficacy endpoints included SVR4 and SVR24.

Subgroup analyses were performed to assess the relationship between SVR12 and baseline demographic and disease characteristics, as well as by ARV regimen at enrollment. Point estimates and 95% exact CIs of the SVR12 rates were calculated for each subgroup by ARV regimen at enrollment.

SVR24 rates were calculated using the same method as described for SVR12. 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, Florian et al. 2013). In addition, an analysis to assess the concordance of SVR12 with SVR24 was performed for subjects with an observed HCV RNA within both the posttreatment Week 12 and posttreatment Week 24 visit windows.

In the Retreatment Substudy, the primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the FAS. The final analysis was conducted when all subjects in the Retreatment Substudy completed the posttreatment Week 24 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 and SVR24. SVR24 rates were calculated using the same method as described for SVR12.

Pharmacokinetics: From the Primary Study, the population PK model-derived PK parameters for SOF, GS-331007, LDV, and tenofovir (TFV) were summarized by HIV ARV regimen at enrollment, by treatment outcome (relapse by posttreatment Week 12 and SVR12 success), and by race (black vs non-black). Geometric mean ratio (GMR) and its 90% CI were provided to compare the PK exposure by treatment outcome and race. Pharmacokinetic parameters were also compared in subjects with HCV/HIV coinfection in this study and subjects with HCV monoinfection in the US new drug application (NDA) LDV/SOF Phase 2/3 population.

In addition, the PK parameters for raltegravir [RAL], efavirenz [EFV], rilpivirine (RPV), emtricitabine [FTC], and GS-566500 were computed for all subjects with evaluable PK profiles who participated in the intensive substudy. Descriptive statistics (sample size, mean, standard deviation [SD], coefficient of variation [%CV], median, first quartile [Q1], third quartile [Q3], minimum, maximum, and geometric mean and its 95% CI, mean and SD on natural log scale) were presented for PK concentration data and PK parameter data.

Results for all PK analyses are presented in the interim CSR.

Safety: All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set for the Primary Study and for the Retreatment Substudy. 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 18.1.

Quality of Life: For the Primary Study, the data from the health-related quality of life surveys (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) were summarized by visit. A Wilcoxon signed rank test explored within group changes in status from baseline to each of the time points, and from end of treatment to posttreatment Week 4.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

Primary Study

A total of 335 subjects were enrolled and received at least 1 dose of study drug (Section 15.1, Table 2). Of the 335 enrolled and treated subjects, 4 subjects (1.2%) prematurely discontinued study treatment: 2 subjects (0.6%) due to lack of efficacy, 1 subject (0.3%) due to death, and 1 subject (0.3%) due to a protocol violation. In the interim CSR, 5 additional subjects (Subjects PPD PPD PPD PPD and PPD were incorrectly coded as having prematurely discontinued study treatment; however, these subjects received 81 days of treatment (the protocol-specified treatment duration was 84 ± 3 days) and are classified as completed study treatment in this final analysis (Appendix 16.2, Listing 3).

The majority of the subjects were male (82.4%, 276 subjects), white (60.6%, 203 subjects) or black (34.3%, 115 subjects), of non-Hispanic or non-Latino ethnicity (82.4%, 276 subjects), with a mean age of 52 years (range: 26-72) (Section 15.1, Table 4). The mean (SD) baseline BMI value for subjects was 27.3 (5.21) kg/m^2, and 22.7% of subjects had a BMI ≥ 30 kg/m^2.

All subjects in the Safety Analysis Set had genotype 1a (74.6%, 250 subjects), 1b (23.0%, 77 subjects), or 4 (2.4%, 8 subjects) HCV infection, and the majority of subjects had a non-CC (CT or TT) IL28B genotype (75.8%, 254 subjects). Twenty percent of subjects (67 subjects) had cirrhosis. The mean (SD) baseline HCV RNA value for subjects was 6.7 (0.64) $\log_{10}$ IU/mL, and most subjects had baseline HCV RNA ≥ 800,000 IU/mL (89.3%, 299 subjects).

There were 185 HCV treatment-experienced subjects (55.2%); the most recent HCV treatment regimen was pegylated interferon (Peg-IFN) + RBV for 113 subjects (61.1%), direct-acting antiviral (DAA) + Peg-IFN+RBV for 53 subjects (28.6%), DAA+RBV for 14 subjects (7.6%, 13 of whom failed SOF+RBV; Appendix 16.2, Listing 7.3), and other for 5 subjects (2.7%).

The mean (SD) estimated GFR was 101.6 (30.78) mL/min. The overall median (Q1, Q3) baseline CD4 count was 628 (469, 823) cells/μL, and 237 subjects (70.7%) had CD4 counts > 500 cells/μL. Per protocol, all subjects were on a stable ARV regimen at enrollment: 47.8% (160 subjects) were on EFV+FTC+ tenofovir disoproxil fumarate (TDF), 43.6% (146 subjects) were on RAL+FTC+TDF, and 8.7% (29 subjects) were on RPV+FTC+TDF.

Retreatment Substudy

A total of 9 subjects were enrolled and received at least 1 dose of study drug in the Retreatment Substudy (Section 15.1, Table 2R). One of the 10 subjects who had virologic relapse in the Primary Study was not enrolled in the Retreatment Substudy. Subject PPD was a PPD 61-year-old male subject with cirrhosis who was diagnosed with hepatocellular carcinoma during the Primary Study. He had a complicated postoperative course following tumor resection in the posttreatment period of the Primary Study and was not deemed eligible for the Retreatment Substudy (Appendix 16.2, Listings 4.1, 8.2, and 10). All 9 subjects (100.0%) who enrolled in the Retreatment Substudy completed retreatment.

PPD The majority of subjects were male (77.8%, 7 subjects), with a mean age of 57 years (range: 35-65) (Section 15.1, Table 4R). The mean (SD) baseline BMI value for subjects was 29.2 (6.44) kg/m^2, and 33.3% of subjects had a BMI $\geq$ 30 kg/m^2.

All subjects had genotype 1a (77.8%, 7 subjects) or 1b (22.2%, 2 subjects) HCV infection, and all of the subjects had a non-CC (CT or TT) IL28B genotype (CT: 33.3%, 3 subjects; TT: 66.7%, 6 subjects). Twenty-two percent of subjects (2 subjects) had cirrhosis. The mean (SD) baseline HCV RNA value for subjects at baseline of the Retreatment Substudy was 6.4 (0.80) log_{10} IU/mL, and most subjects had baseline HCV RNA $\geq$ 800,000 IU/mL (88.9%, 8 subjects). The mean time from virologic failure in the Primary Study to baseline of the Retreatment Substudy was 43 days (range: 34−70).

Prior to enrolling into the Primary Study, 5 subjects in the Retreatment Substudy were HCV treatment-experienced (55.6%) and 4 were treatment-naive. The most recent HCV treatment regimen was IFN (3 subjects: Peg-IFN, 1 subject: consensus IFN) + RBV for 4 subjects (80.0%) and DAA (NS5A inhibitor BMS-790052) + Peg-IFN+RBV for 1 subject (20.0%) (Appendix 16.2, Listing 7.3R).

The mean (SD) estimated GFR was 101.8 (21.04) mL/min. The overall median (Q1, Q3) baseline CD4 count was 785 (404, 971) cells/µL, and 55.6% of subjects had CD4 counts > 500 cells/µL. Per protocol, all subjects were on a stable ARV regimen at enrollment into the Retreatment Substudy: 77.8% (7 subjects) were on EFV+FTC+TDF, 22.2% (2 subjects) were on RAL+FTC+TDF, and 0 subjects were on RPV+FTC+TDF.

Efficacy Results:

For the Primary Study, analysis of the primary efficacy endpoint is reported in Section 9 of the interim CSR; results for SVR24, a secondary efficacy endpoint, are summarized in this final CSR. For the Retreatment Substudy, analysis of the proportion of subjects with SVR4, SVR12, and SVR24 are presented in this final CSR.

Primary Study

The proportion of subjects with SVR12 and SVR24 is presented in the table below. The SVR12 and SVR24 rates were the same, with a 100% concordance between SVR12 and SVR24 (Section 15.1, Table 9.1). Subject PPD missed the posttreatment Week 12 visit and was considered a treatment failure in the interim SVR12 analysis. This subject had a posttreatment Week 24 visit and had HCV RNA < LLOQ. In the final analysis, the missing HCV RNA value at

the posttreatment Week 12 was imputed as a success (Appendix 16.2, Listing 8.1). Therefore, the proportion of subject who achieved SVR12 at the final SVR24 analysis increased from 321 subjects (95.8%) to 322 subjects (96.1%).

	LDV/SOF (N = 335)
SVR12	322/335 (96.1%)
95% CI	93.5% to 97.9%
SVR24	322/335 (96.1%)
95% CI	93.5% to 97.9%

HCV RNA analyzed using Roche TaqMan v2.0 assay for use with High Pure system with limit of quantitation 25 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 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.
Section 15.1, Table 9

Overall, 13 subjects (3.9%) did not achieve SVR12 (Section 15.1, Table 8). Of these, 12 subjects (3.6%) had virologic failure: 10 subjects relapsed (3.0%) and 2 subjects (0.6%) had on-treatment virologic failure (both in the setting of non-compliance, per the investigator). The 2 subjects who experienced on-treatment virologic failure are discussed in detail in the interim CSR. The subject with "other" virologic outcome (0.3%) died (sepsis) (Subject PPD Appendix 16.2, Listings 8.3 and 14). A narrative for this subject is provided in Section 15.2.

No subjects relapsed between posttreatment Weeks 12 and 24 (Appendix 16.2, Listing 8.1).

The change in the overall SVR12 led to changes in the SVR12 by subgroup and these changes are summarized in Section 15.2, Table 11.

All efficacy analyses for the Primary Study are provided in Section 15.1, Tables 8 through 15, Figures 2 through 4.4, and Appendix 16.2, Listings 8.1 through 8.5.

Retreatment Substudy

For the Retreatment Substudy, the overall SVR12 rate was 88.9% (95% CI: 51.8% to 99.7%) (8 of 9 subjects) (Section 15.1, Table 9R). The 1 subject with virologic failure (Subject PPD was a 55-year-old, PPD male subject with chronic genotype 1a HCV infection, without cirrhosis, IL28B CT allele, and was HCV treatment-experienced (consensus IFN+RBV) at the start of the Primary Study who was taking EFV+FTC+TDF (Appendix 16.2, Listings 4.1R, 7.3R, and 8.2R). This subject achieved HCV RNA < LLOQ while on retreatment, however, this subject had confirmed HCV RNA ≥ LLOQ at the post-retreatment Week 4 visit.

The SVR4 results were the same as the SVR12 results (Section 15.1, Tables 9R and 10R). The SVR12 and SVR24 rates were the same, with a 100% concordance between SVR12 and SVR24 (Section 15.1, Table 9.1R). No subjects relapsed between post-retreatment Week 4 and Week 24.

	LDV/SOF+RBV 24 Weeks (N = 9)
SVR4	8/9 (88.9%)
95% CI	51.8% to 99.7%
SVR12	8/9 (88.9%)
95% CI	51.8% to 99.7%
SVR24	8/9 (88.9%)
95% CI	51.8% to 99.7%

HCV RNA analyzed using Roche TaqMan v2.0 assay for use with High Pure system with limit of quantitation 25 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 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.
Section 15.1, Table 9R

HCV RNA levels (log_{10} IU/mL) declined rapidly during retreatment (Section 15.1, Table 14R). At Retreatment Week 2, the overall mean (SD) log_{10} IU/mL change from baseline was −5.01 (0.775) log_{10} IU/mL (Section 15.1, Table 14R). The decreases in HCV RNA were maintained from Retreatment Week 2 through Retreatment Week 8, with mean HCV RNA values of 1.38 log_{10} IU/mL and mean change from baseline −5.04 (0.802) log_{10} IU/mL.

All efficacy analyses for the Retreatment Substudy are provided in Section 15.1, Tables 8R through 15R, Figures 2R through 4.4R, and Appendix 16.2, Listings 8.1R through 8.6R.

Virologic Resistance Results:

All virology listings for the Primary Study and the Retreatment Substudy are provided in Appendix 16.2, Virology Listings 1 through 5.

Primary Study

For the Primary Study, full details on the resistance analysis are reported in Section 9.3.1 of the interim CSR. No additional resistance analyses were performed since no subjects relapsed during the posttreatment Week 12 through Week 24.

Retreatment Substudy

Among the 9 subjects who received retreatment with LDV/SOF+RBV for 24 weeks, SVR12 was achieved in 2 subjects without resistance-associated variants (RAVs) and 6 of 7 subjects with RAVs at the time of virologic failure in the Primary Study. Of the 7 subjects with RAVs, 2 had both NS5A and NS5B nucleoside inhibitor (NI) variants (L159F or E237G) prior to retreatment and both achieved SVR12; 4 of 5 subjects with single-class NS5A RAVs prior to treatment achieved SVR12.

The subject who relapsed did not have NS5A or NS5B RAVs at baseline of the Primary Study. At the time of relapse in the Primary Study, the subject was observed to have L31M (> 99%). Following retreatment with LDV/SOF+RBV, the subject had the NS5A RAVs L31M (97.5%) and L31V (2.1%), and the NS5B SOF treatment-emergent variant L159F (10.8%).

		NS5A RAVs			NS5B RAVs			Treatment Response in the Retreatment Substudy
Subject Number	GT	Baseline Primary Study	Virologic Failure Primary Study	Virologic Failure Retreatment Substudy	Baseline Primary Study	Virologic Failure Primary Study	Virologic Failure Retreatment Substudy	
PPD	1a	None	None	—	None	None	—	SVR12
PPD	1a	None	None	—	None	None	—	SVR12
PPD	1a	L31M (> 99%) H58D (92.1%)	L31M (> 99%) H58D (> 99%)	—	None	E237G (28.5%)	—	SVR12
PPD	1a	Y93F (1.2%) Y93N (9.9%)	Y93N (> 99%)	—	None	None	—	SVR12
PPD	1a	L31M (98.8%) Y93N (24.8%)	L31M (> 99%) Y93N (> 99%)	—	None	None	—	SVR12
PPD	1a	None	Y93N (> 99%)	—	None	L159F (9.9%)	—	SVR12
PPD	1b	None	L31V (> 99%)	—	None	None	—	SVR12
PPD	1b	Y93H (> 99%)	L31I (11.12%) Y93H (> 99%)	—	None	None	—	SVR12
PPD	1a	None	L31M (> 99%)	L31M (97.5%) L31V (2.1%)	None	None	L159F (10.8%)	Relapse

GT = genotype; RAV = resistance-associated variant
Source: Appendix 16.2, Virology Listings 3 and 4

Pharmacokinetic Results: For the Primary Study, full details on the PK analyses are reported in Section 10 of the interim CSR. No PK analysis was performed for the Retreatment Substudy.

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. For the Primary Study, evaluations of safety through 30 days after the last dose of study drugs were summarized in Section 11 of the interim CSR.

Primary Study

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 clarification to AE terms, newly reported nontreatment-emergent AEs and Grade 1 AEs, and reclassification of relatedness to either study drug by the investigator (Appendix 16.2, Listing 10 and Adhoc Listing 7830.1). These changes did not impact the overall interpretation or conclusion of the safety profile of LDV/SOF in this study.
Adhoc Listing 7830.1 provides a detailed listing of AEs that had changes in reported or preferred term and onset or resolution date between the data cuts taken at the posttreatment Week 12 and posttreatment Week 24 time points.

There were no additional treatment-emergent SAEs. Three additional nontreatment-emergent SAEs in 1 subject were reported and were not considered related to study drug (Appendix 16.2, Listing 12 and Adhoc Listing 7830.1). Subject PPD (taking RAL+FTC+TDF) was a 64-year-old male subject with a history of hemophilia A who had an SAE of anemia on posttreatment Day 76 (resolved on posttreatment Day 167), an unresolved SAE of worsening factor VIII deficiency on posttreatment Day 163, and an SAE of gastrointestinal hemorrhage on posttreatment Day 163 (resolved on the same day) (Appendix 16.2, Listing 5). Narratives for all SAEs from the first dose of study drug through the end of the study (ie, the SVR24 visit) are provided in Section 15.2.

One subject died during the study (Appendix 16.2, Listing 14). Subject PPD (taking RAL+FTC+TDF) died on posttreatment Day 16, after discontinuing treatment early on Day 41 due to a Grade 4 AE of sepsis, which was reported as serious and not related to study treatment (Appendix 16.2, Listing 10). Full details can be found in Section 11.3 of the interim CSR and a narrative is provided in Section 15.2. There were no additional deaths reported.

No subject pregnancies were reported in this study (Appendix 16.2, Listing 13).

All AE results for the Primary Study are provided in Section 15.1, Tables 16 through 30, Appendix 16.2, Listings 10 through 14, and 23.5.

Clinical Laboratory Results

For the Primary Study, laboratory abnormalities related to clinical safety are discussed in detail in the interim CSR.

All laboratory results for the Primary Study are provided in Section 15.1, Tables 31.1 through 35, and 37.1 through 37.4, Figures 5.1 through 6.2, and Appendix 16.2, Listings 15 through 23.4.

Analysis of Renal Safety

For the Primary Study, laboratory abnormalities related to renal safety are discussed in detail in the interim CSR.

Effect of LDV/SOF on HIV

For the Primary Study, the effect of LDV/SOF on HIV is discussed in detail in the interim CSR.

Vital Signs Measurements

For the Primary Study, vital sign measurements (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) are discussed in detail in the interim CSR. Additional vital sign measurements were collected at the posttreatment Weeks 12 and 24 visits. No notable changes were observed (Appendix 16.2, Listing 24.1).

Retreatment Substudy

Adverse Events and Serious Adverse Events

Overall, retreatment with LDV/SOF+RBV was generally safe and well tolerated. Four subjects (44.4%, 4 of 9 subjects) had an AE that led to modification or interruption of RBV and no subjects had an AE that led to interruption of LDV/SOF (Section 15.1, Table 16R). However, no subjects permanently discontinued LDV/SOF or RBV due to an AE.

All of the subjects experienced at least 1 AE. The most commonly reported AEs were fatigue (66.7%), cough (44.4%), and anemia (33.3%) (Section 15.1, Table 27R). Most AEs were Grade 1 or 2 in severity (Section 15.1, Table 16R). Only 1 subject had a Grade 3 AE (cough), which was reported as related to study drug resulting in RBV interruption (Section 15.1, Table 19R; Appendix 16.2, Listing 10R). No Grade 4 AEs were reported.

There were no treatment-emergent SAEs, deaths, or pregnancies reported during the Retreatment Substudy (Section 15.1, Tables 24R; Appendix 16.2, Listings 13R and 14R). One subject had a nontreatment-emergent SAE of pneumonia on post-retreatment Day 63 (resolved on post-retreatment Day 165) that was not considered related to study drug (Appendix 16.2, Listing 12R).

All AE results for the Retreatment Substudy are provided in Section 15.1, Tables 16R through 30R, and Appendix 16.2, Listings 10R through 14R, and 23.5R.

Clinical Laboratory Results

All subjects in the Retreatment Substudy had at least 1 laboratory abnormality reported; the majority of laboratory abnormalities were Grade 1 or 2 in severity (Section 15.1, Table 33R). The 1 Grade 3 laboratory abnormality (hyperuricemia) was unconfirmed in a subject with graded laboratory abnormalities of uric acid at baseline of the Primary Study through Retreatment Week 16, which then resolved while on treatment (Appendix 16.2, Listing 16R).

A summary of hemoglobin values showed that 3 subjects (33.3%) had postbaseline hemoglobin values < 10 g/dL (Section 15.2, Table 31.6R). No subjects had postbaseline hemoglobin values < 8.5 g/dL.

All laboratory results for the Retreatment Substudy are provided in Section 15.1, Tables 31.1R through 35R, and 37.1R through 37.4R, Figures 5.1R through 5.10R, and Appendix 16.2, Listings 15R through 23.4R.

Analysis of Renal Safety

With respect to renal safety, no AEs or SAEs were reported in the Renal and Urinary Disorders system organ class (SOC) (Section 15.1, Table 17R). There were no clinically significant changes from baseline in serum creatinine or creatinine clearance, electrolytes or proteinuria observed (Appendix 16.2, Listings 20.1, 20.3R, 23.1R-23.4R).

Effect of LDV/SOF+RBV on HIV

All subjects (100.0%) in the Retreatment Substudy had HIV RNA < 50 copies/mL at baseline for the Retreatment Substudy and remained suppressed during the study and at post-retreatment Week 4 (Section 15.2, Table 37.3R). No subjects had confirmed HIV rebound during the Retreatment Substudy (Section 15.2, Table 37.1R).

Median (Q1, Q3) values for CD4 count and CD4% by study visit are presented graphically in Section 15.1, Figures 15.1 and 15.2, respectively. The overall median (Q1, Q3) CD4 count at baseline was 785 (404, 971) cells/μL (Section 15.2, Table 31.13R). Median changes from baseline in CD4 count during retreatment ranged from −77 to 36 cells/μL. No clinically meaningful changes in CD4 count from baseline were observed.

Vital Signs Measurements

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) were reported during the study (Appendix 16.2, Listing 24.1R).

Quality of Life Results:

Overall, improvements from baseline were observed in all results during the treatment period and at posttreatment Week 4 from the SF-36, CLDQ-HCV, and FACIT-F quality of life questionnaires performed during the Primary Study in subjects on LDV/SOF. There was no difference observed from the WPAI: Hep C quality of life questionnaire. All quality of life results are provided in Section 15.1, Tables 41.1 through 41.4, Figures 7.1 through 7.4, and Appendix 16.2, Listings 9.1 through 9.4.

CONCLUSIONS:

- In the Primary Study, treatment with LDV/SOF for 12 weeks in treatment-naive or treatment-experienced subjects with HCV/HIV coinfection, including those with and without cirrhosis, resulted in a high SVR12 rate (96.1%). This rate is similar to the SVR12 rate observed in subjects with HCV monoinfection treated with LDV/SOF in other clinical studies.
- Black race was the only factor associated with relapse after 12 weeks of therapy using logistic regression analysis. This difference in efficacy, by race, was not observed in other studies of LDV/SOF, and is not supported by any PK findings.
- High SVR rates were observed irrespective of the presence of NS5A RAVs. Virologic failure was associated with detection of NS5A RAVs in the majority of subjects.
- There were no clinically relevant differences in LDV/SOF PK across ARV regimens, by treatment outcome, by race, or by historic comparison with subjects with HCV monoinfection.

- The EFV, RAL, RPV, and FTC PK were consistent with historical data in HIV monoinfection studies. The TFV exposure parameters were moderately higher than observed historically following administration of NNRTI or INSTI-based regimens with FTC+TDF, in agreement with the findings from Phase 1 evaluations in healthy volunteers.
- In the Retreatment Substudy, 8 of 9 subjects (88.9%) who failed LDV/SOF for 12 weeks achieved SVR12 with LDV/SOF+RBV for 24 weeks.
- Six of 7 subjects (85.7%) who had NS5A RAVs at the time of relapse in the Primary Study achieved SVR12 following retreatment with LDV/SOF+RBV for 24 weeks.
- Concordance between SVR12 and SVR24 was 100% in both the Primary Study and the Retreatment Substudy.
- Treatment with LDV/SOF for 12 weeks and retreatment with LDV/SOF+RBV for 24 weeks was well tolerated and similar across all ARV regimens, 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, CD4%, or HIV RNA levels.
- All subjects remained HIV RNA suppressed during treatment with LDV/SOF and retreatment with LDV/SOF+RBV.