FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant
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-337-0123 (SOLAR-1)
Phase of Development:	Phase 2
IND No.:	115268
EudraCT No.:	2012-003387-43
ClinicalTrials.gov Identifier:	NCT01938430
Study Start Date:	06 September 2013 (First Subject Screened)
Study End Date:	25 March 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Michael Charlton, MBBS, FRCP Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Theo Brandt-Sarif, MD Telephone: PPD Fax: PPD
Report Date:	16 December 2015
Previous Report Date(s):	21 July 2015 (Second Interim Clinical Study Report Amendment) 20 March 2015 (Second Interim Clinical Study Report) 25 June 2014 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-337-0123:
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant

Investigators: Multicenter

Study Centers: Subjects were enrolled in 29 sites in the United States (US).

Publications:

Flamm SL, Everson GT, Charlton MR, Denning JM, Arterburn S, Brandt-Sarif T, et al. Ledipasvir/Sofosbuvir With Ribavirin for the Treatment of HCV in Patients With Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study [Presentation #239]. The 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting (AASLD); 2014 November 07-11; Boston MA United States.

Reddy KR, Everson GT, Flamm SL, Denning JM, Arterburn S, Brandt-Sarif T, et al. Ledipasvir/Sofosbuvir With Ribavirin for the Treatment of HCV in Patients With Post-Transplant Recurrence: Preliminary Results of a Prospective, Multicenter Study [Presentation #8]. The 65th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting (AASLD); 2014 November 07-11; Boston MA United States.

Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology. 2015;149(3):649-659.

Study Period:

06 September 2013 (First Subject Screened)
09 January 2015 (Last Subject Observation for the Primary Endpoint)
25 March 2015 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To explore the antiviral efficacy of combination therapy with ledipasvir/sofosbuvir (LDV/SOF) as a fixed-dose combination (FDC) plus ribavirin (RBV) for 12 or 24 weeks in subjects with advanced liver disease (either pre-liver transplantation or not currently wait-listed) and post-liver transplantation subjects with hepatitis C virus (HCV) infection with or without cirrhosis as measured by sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12 defined as HCV ribonucleic acid (RNA) < lower limit of quantitation [LLOQ] 12 weeks posttreatment)
- To evaluate the safety and tolerability of LDV/SOF FDC + RBV administered for 12 or 24 weeks in each subject population

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attained SVR at 2, 4, 8, and 24 weeks after discontinuation of therapy (SVR2, SVR4, SVR8, and SVR24)
- To determine if the administration of LDV/SOF FDC to HCV-infected subjects undergoing liver transplantation could prevent posttransplantation recurrence as determined by a sustained post-transplant virologic response (pTVR: HCV RNA < LLOQ) at 12 weeks posttransplant (in those subjects who underwent liver transplantation while on study)
- To determine therapeutic efficacy as measured by the change of Child-Pugh-Turcotte (CPT) score and Model for End-Stage Liver Disease (MELD) score during treatment and follow-up
- To evaluate the emergence of viral resistance to LDV/SOF FDC during and after treatment discontinuation
- To evaluate the kinetics of circulating HCV RNA during and after treatment
- To characterize steady-state pharmacokinetics (PK) of study drugs

The exploratory objective of this study was as follows:

- To identify or validate genetic markers that may have been predictive of the natural history of disease, virologic response to therapy, and/or the tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics) in subjects who provided a separate and specific consent

Methodology: This Phase 2, open-label, multicenter study evaluated the efficacy and safety of LDV/SOF+RBV treatment in subjects with genotype 1 or 4 HCV infection who had advanced liver disease and/or who had undergone liver transplantation.

Following screening, subjects were enrolled into 1 of 2 cohorts based on liver transplantation status (Cohorts A and B).

In Cohort A, approximately 100 subjects with cirrhosis who had not undergone transplantation were enrolled into 1 of 2 groups based on severity of hepatic impairment:

- **Group 1:** approximately 50 subjects with cirrhosis and moderate hepatic impairment (CPT Class B [CPT B]; severity of cirrhosis score of 7 to 9 [decompensated])

- **Group 2:** approximately 50 subjects with cirrhosis and severe hepatic impairment (CPT C; severity of cirrhosis score of 10 to 12 [decompensated])

In Cohort B, approximately 300 posttransplantation subjects with or without cirrhosis were enrolled into 1 of 5 groups based on severity of hepatic impairment:

- **Group 3:** approximately 100 posttransplantation subjects without cirrhosis (fibrosis stage F0-F3) and with no evidence of hepatic decompensation
- **Group 4:** approximately 50 posttransplantation subjects with cirrhosis and mild hepatic impairment (CPT A; severity of cirrhosis score of 5 to 6 [compensated])
- **Group 5:** approximately 50 posttransplantation subjects with cirrhosis and moderate hepatic impairment (CPT B; severity of cirrhosis score of 7 to 9 [decompensated])
- **Group 6:** approximately 50 posttransplantation subjects with cirrhosis and severe hepatic impairment (CPT C; severity of cirrhosis score of 10 to 12 [decompensated])
- **Group 7:** approximately 50 posttransplantation subjects with fibrosing cholestatic hepatitis (FCH)

Within each of the 7 groups, subjects were randomized in a 1:1 ratio to receive LDV/SOF+RBV for 12 or 24 weeks.

Subjects who did not achieve SVR or who had HCV recurrence after the posttreatment and/or posttransplantation Week 4 visit were eligible to participate in the Sequence Registry Study (Study GS-US-248-0123). Subjects who achieved SVR or pTVR at the posttreatment and/or posttransplantation Week 24 follow-up visit were eligible for the SVR Registry Study (Study GS-US-248-0122).

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 or posttransplantation 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 second interim CSR (20 March 2015). The results of the PK substudy are described in the interim CSR (25 June 2014).

Number of Subjects (Planned and Analyzed):
Planned: Approximately 400 subjects (100 in Cohort A and 300 in Cohort B)
Analyzed:

- Randomized Analysis Set: 339 subjects
- Full Analysis Set (FAS): 337 subjects
- Safety Analysis Set: 337 subjects

Diagnosis and Main Criteria for Inclusion: Males and nonpregnant, nonlactating female subjects aged ≥ 18 years who had chronic genotype 1 or 4 HCV infection with advanced liver disease or who had undergone liver transplantation, including those with decompensated cirrhosis, were eligible for this study. Subjects were treatment naive or treatment experienced and had documentation of the presence or absence of cirrhosis. Subjects did not have any serious or active medical or psychiatric illnesses at screening, including hepatocellular carcinoma. In addition, no history of prior organ transplantation other than liver (with or without simultaneous kidney) was allowed. Treatment-experienced subjects could not have received any treatment with interferon, RBV, telaprevir, boceprevir, or any other approved or experimental medication with known anti-HCV activity within 1 month prior to screening nor have any prior exposure to an HCV nonstructural protein 5A (NS5A) specific inhibitor.

Duration of Treatment: Treatment duration was either 12 or 24 weeks, with 24 weeks of posttreatment follow-up.

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

- **LDV/SOF** was administered to all subjects orally at a dose of 90/400 mg (1 tablet once daily).
- **RBV** was administered orally at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided daily dose) to subjects in Groups 3, 4, and 7. RBV was initiated at a total daily dose of 600 mg/day and dose level was adjusted according to clinical study protocol-defined criteria to subjects in Groups 1, 2, 5, and 6.

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

- **LDV/SOF**: DK1302B1 and DK1303B1
- **RBV**: A97943Z

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/posttransplantation Week 24. Efficacy analyses at all other scheduled assessment time points were described in the second interim CSR (20 March 2015). The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 assay was used to determine HCV RNA results in this study. The LLOQ of the assay was 15 IU/mL.

Pharmacokinetics: The second interim CSR (20 March 2015) describes details on the collection of blood samples for the PK analyses.

Safety: The second interim CSR (20 March 2015) provides analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital sign measurements, electrocardiograms (ECGs), physical examinations, and safety-related assessments to determine MELD and CPT scores. This final synoptic CSR summarizes any new treatment-emergent AEs or changes to previously reported AEs between the data cuts for the second interim CSR and the final CSR. Additionally, all serious adverse events (SAEs) collected after the data cutoff for the

second 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.

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 second interim CSR (20 March 2015).

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ [< 15 IU/mL] 12 weeks after discontinuation of all study drugs) in the Full Analysis Set excluding subjects who underwent transplantation (HCV RNA < LLOQ at transplantation) prior to posttreatment Week 12 visit. The proportion of subjects with SVR12 by group and treatment duration was determined along with the exact 2-sided 90% confidence interval (CI) calculated using the Clopper-Pearson method. No hypothesis testing was performed. Secondary efficacy endpoints included virologic outcomes, the proportion of subjects with SVR4, SVR24, and the proportion of subjects with posttransplantation virologic response at Week 12 (pTVR12).

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

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 {24697}. 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.

Pharmacokinetics: Steady-state PK over a 24-hour dosing interval was determined in subjects who participated in the PK substudy at the Week 2 or 4 on-treatment visit. The results of the PK substudy were described in the interim CSR (25 June 2014). A population PK model was developed to characterize the PK of LDV and SOF and its major metabolite, GS-331007. Results for population PK analyses based on sparse PK sampling are presented in a separate Population PK Report.

Safety: All randomized 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 sign measurements, physical examinations, and changes in CPT and MELD scores. Safety data were analyzed by group and treatment duration and included all data collected on or after the date of the first dose of any study drug through 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 17.1.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 337 randomized subjects received treatment in this study and were included in the FAS and Safety Analysis Set (Section 15.1, Table 3). Full details on subject disposition are reported in Section 8 of the second interim CSR (20 March 2015), and subject disposition at posttreatment Week 24 is summarized in Section 15.1, Tables 3-4.4).

There were no differences in demographic or baseline disease characteristics between the interim analyses and the final analyses (Section 15.1, Tables 5.1-5.5, and Appendix 16.2, Listing 4). There were a small number of changes to concomitant medications that did not change the interpretation of the study results (Section 15.1, Tables 9.1-9.4, and Appendix 16.2, Listing 8.1).

Analyses related to disposition, demographics, and exposure are presented in Section 15.1, Tables 1.1-10.6 and 52.1-52.4 and Figure 1, and Appendix 16.2, Listings 1-9, 26.2, and 34. 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 second interim CSR (20 March 2015). Results for SVR24, a secondary efficacy endpoint, are summarized in this final CSR.

The proportion of subjects with SVR12 and SVR24 is presented in the table below. Of note, 9 subjects across all groups who achieved SVR12 did not have HCV RNA measurements at the posttreatment Week 24 visit and were imputed to achieve SVR24 (achieving SVR12 and having observed HCV RNA values < LLOQ obtained after the posttreatment Week 24 visit window [6 subjects] or by imputation based on SVR12 and no subsequent HCV RNA measurements [3 subjects]) (Section 15.1, Tables 14.1-14.4 and Appendix 16.2, Listing 25).

With the exception of subjects with CPT C cirrhosis who received treatment for 12 weeks (Group 2), the SVR12 and SVR24 rates were the same for all groups. In Group 2, 1 subject (Subject PPD received a liver transplant after posttreatment Week 12 and was excluded from the SVR24 analysis (Appendix 16.2, Listing 27). At the final analysis, there was 100% positive predictive value 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 11.1-11.4, 13.1-13.4, and 15.1-15.4, and Appendix 16.2, Listing 25).

	Liver Disease Status (Group)	Duration of Treatment	SVR12		SVR24	
			SVR12 (n/N [%])	90% CI	SVR24 (n/N [%])	90% CI
Pretransplantation	CPT B Cirrhosis (Group 1)	12 Weeks	26/30 (86.7%)	72.0% to 95.3%	26/30 (86.7%)	72.0% to 95.3%
		24 Weeks	24/27 (88.9%)	73.7% to 96.9%	24/27 (88.9%)	73.7% to 96.9%
	CPT C Cirrhosis (Group 2)	12 Weeks	19/22 (86.4%)	68.4% to 96.2%	18/21 (85.7%)	67.1% to 96.0%
		24 Weeks	20/23 (87.0%)	69.6% to 96.3%	20/23 (87.0%)	69.6% to 96.3%
Posttransplantation	Stage F0-F3 Fibrosis (Group 3)	12 Weeks	53/55 (96.4%)	89.0% to 99.4%	53/55 (96.4%)	89.0% to 99.4%
		24 Weeks	55/56 (98.2%)	91.8% to 99.9%	55/56 (98.2%)	91.8% to 99.9%
	CPT A Cirrhosis (Group 4)	12 Weeks	25/26 (96.2%)	83.0% to 99.8%	25/26 (96.2%)	83.0% to 99.8%
		24 Weeks	24/25 (96.0%)	82.4% to 99.8%	24/25 (96.0%)	82.4% to 99.8%
	CPT B Cirrhosis (Group 5)	12 Weeks	22/26 (84.6%)	68.2% to 94.6%	22/26 (84.6%)	68.2% to 94.6%
		24 Weeks	23/26 (88.5%)	72.8% to 96.8%	23/26 (88.5%)	72.8% to 96.8%
	CPT C Cirrhosis (Group 6)	12 Weeks	3/5 (60.0%)	18.9% to 92.4%	3/5 (60.0%)	18.9% to 92.4%
		24 Weeks	3/4 (75.0%)	24.9% to 98.7%	3/4 (75.0%)	24.9% to 98.7%
	FCH (Group 7)	12 Weeks	4/4 (100.0%)	47.3% to 100.0%	4/4 (100.0%)	47.3% to 100.0%
		24 Weeks	2/2 (100.0%)	22.4% to 100.0%	2/2 (100.0%)	22.4% to 100.0%

HCV RNA was analyzed using the Roche COBAS Ampliprep/COBAS Taqman HCV Test, v2.0 with LLOQ 15 IU/mL.
SVR12 was sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
Subject was a success if their latest observed HCV RNA value in the visit window was < LLOQ, or if they had a missing value for the visit window bracketed by observed HCV RNA values that are termed successes (ie, '< LLOQ TND' or '< LLOQ detected'). TND = target not detected.
Seven subjects transplanted on-study with HCV RNA < LLOQ at the last measurement prior to transplant were excluded: Subjects PPD and PPD from Group 1 (24 Weeks), Subject PPD from Group 2 (12 Weeks), and Subjects PPD and PPD from Group 2 (24 Weeks) were excluded from all SVR analyses. Subject PPD from Group 2 (24 Weeks) was excluded after SVR2 and Subject PPD from Group 2 (12 Weeks) was excluded after SVR12.
The exact 90% CI for the proportion within group and treatment duration is based on the Clopper-Pearson method.
Source: Section 15.1, Tables 11.1-11.4 and 13.1-13.4

Of the 7 subjects who underwent liver transplantation while on study and had HCV RNA < LLOQ at the last measurement prior to liver transplantation, 6 achieved pTVR12. All subjects who achieved pTVR12 also achieved pTVR24. The 1 subject who did not achieve pTVR died 1 day after the posttransplantation Week 2 visit (Appendix16.2, Listings 15.1 and 27).

No subject in any group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse) (Section 15.1, Tables 12.1-12.4, and Appendix 16.2, Listing 26.1)

Across all groups, a total of 28 subjects included in the SVR analyses did not achieve SVR12 or SVR24 (Section 15.1, Tables 12.1-13.4). Of the 13 subjects with decompensated (CPT B or CPT C) cirrhosis (Groups 1 and 2) who did not achieve SVR12 or SVR24, 7 subjects relapsed (4 subjects with CPT B cirrhosis and 3 subjects with CPT C cirrhosis) and 6 subjects were categorized as having an "other" outcome. The majority of relapses (71.4%, 5 of 7 subjects) occurred by posttreatment Week 8 (Appendix 16.2, Listing 26.1). Of the 6 subjects who had an "other" outcome, 5 died during the study (Appendix 16.2, Listings 3, 15.1, and 25). The other subject (Subject PPD who had CPT C cirrhosis and received LDV/SOF+RBV for 12 weeks, was lost to follow-up after achieving SVR4.

Of the 3 posttransplantation subjects with stage F0-F3 fibrosis (Group 3) who did not achieve SVR12 or SVR24, 2 subjects relapsed by posttreatment Week 4 (Appendix 16.2, Listing 26.1). The third subject (Subject PPD who was categorized as having an "other" outcome was randomized to receive LDV/SOF+RBV for 24 weeks, but withdrew consent and discontinued study drug on Day 8 (Appendix 16.1, Listings 3 and 25).

Of the 12 posttransplantation subjects with compensated (CPT A) or decompensated (CPT B or CPT C) cirrhosis (Groups 4, 5, and 6, respectively) who did not achieve SVR12 or SVR24, 4 subjects relapsed (1 and 3 posttransplantation subjects with CPT B and CPT C cirrhosis, respectively). Two of the subjects, with CPT B and CPT C cirrhosis, respectively, relapsed by posttreatment Week 2, while the remaining 2 subjects with CPT C cirrhosis relapsed by posttreatment Week 8, (Appendix 16.2, Listing 26.1). Eight subjects were categorized as having an "other" outcome. Of these subjects, 7 died during this study (2 and 5 subjects with CPT A and CPT B cirrhosis, respectively) (Appendix 16.2, Listings 3, 15.1, and 25). The other subject (Subject PPD who had CPT B cirrhosis and was randomized to receive LDV/SOF+RBV for 12 weeks, withdrew consent on Day 4 of study treatment.

All posttransplantation subjects with FCH (Group 7) achieved SVR12 and SVR24 (Section 15.1, Tables 12.4 and 13.4).

No subjects relapsed between posttreatment Weeks 12 and 24 (Section 15.1, Tables 14.1-14.4 and Appendix 16.2, Listings 25-26.1).

There were no notable changes to the results of the analyses of changes in MELD and CPT scores as reported in Sections 9.4.1 and 9.4.2, respectively, of the second interim CSR (20 March 2015) (Section 15.1, Tables 46.1-47.9).

All efficacy analyses are provided in Section 15.1, Tables 11.1-19.2, 46.1-47.9, 58.1-58.4, and 55.1-56.4 and Figures 2.1-2.4, and Appendix 16.2, Listings 25-26.1, 26.3-27, and 32.

Virologic Resistance: Full details on the virologic resistance analysis are reported in Section 9.5 of the second interim CSR (20 March 2015). No additional resistance analyses were performed since no subjects relapsed after the data cutoff for the second interim CSR (20 March 2015).

Pharmacokinetic Results:

Full details on the PK substudy analysis are reported in Section 6 of the interim CSR (25 June 2014). Results for all population PK analyses are presented in a separate Population PK Report.

Safety Results:

All AEs and laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as AEs and laboratory abnormalities in this report, unless otherwise specified. Evaluations of safety data through 30 days after the last dose of study drugs were summarized in Section 11 of the second interim CSR (20 March 2015).

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 newly reported Grade 1 or 2 AEs (Appendix 16.2, Listing 10 and Ad Hoc Listing 7521). No additional treatment-emergent Grade 3 or 4 AEs were

reported. 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 7521 provides a detailed listing of any newly reported AEs 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 additional treatment-emergent SAEs were reported. Two additional nontreatment-emergent SAEs were reported for a posttransplantation subject with decompensated (CPT C) cirrhosis (Group 6) (Subject PPD this subject experienced Grade 3 empyema on posttreatment Day 143, which was considered unrelated to study drug by the investigator and resolved on posttreatment Day 162. This subject also experienced Grade 4 adenocarcinoma of the lung on posttreatment Day 163, which was considered unrelated to study drug by the investigator and was ongoing at the completion of the study (Appendix 16.2, Listing 13 and Ad Hoc Listing 7521). No additional deaths were reported (Appendix 16.2, Listing 15.1). No subject pregnancies were reported in this study (Appendix 16.2, Listing 14).

Three subjects experienced AEs that were reported but not included in the database (data on file). Subject PPD experienced amputation of the right second toe which was associated with an SAE that is included in the database (skin ulcer; reported term: ulcer on the right toe); although not in the database, the amputation is described within the SAE narrative for ulcer on the right toe. This subject also experienced cellulitis of the right lower extremity and wound infection, which were associated with an SAE that is included in the database (pain in extremity; reported term: right leg pain lower extremity); although not in the database, the cellulitis and wound infection are described within the SAE narrative for right leg pain lower extremity. Subject PPD experienced Grade 1 dehydration on Day 36 which was considered related to study drug by the investigator and resolved without a change in the LDV/SOF or RBV dose. Subject PPD experienced Grade 2 anemia on Day 56 that was considered related to study drug by the investigator and resolved after a reduction in the RBV dose. These additional AEs did not impact the overall interpretation or conclusions of the safety profile of LDV/SOF with RBV in this study.

Narratives for all SAEs, AEs leading to discontinuation of LDV/SOF, and deaths from the first dose of study drug through the end of the study (ie, the SVR24 visit) are provided in Section 15.2. All AE results are provided in Section15.1, Tables 20.1-34.4 and 59.1-60.4, and Appendix 16.2, Listings 10-15.3.

Clinical Laboratory Results

Blood samples for clinical laboratory analyses were collected through the posttreatment Week 24 visit. Based on discussions with the FDA, between the data cuts for the second interim CSR (20 March 2015) and the final CSR, the third criterion for liver-related laboratory events was changed from total bilirubin > 2 × ULN to direct bilirubin > 3 mg/dL (Section 15.1, Tables 53.1-53.4 and Appendix 16.2, Listing 24). This change did not impact the overall interpretation or conclusions of the clinical laboratory data. No other notable changes to clinical laboratory results were observed.

All laboratory results are provided in Section 15.1, Tables 35.1-45.4, 51.1-51.4, 53.1-53.4, 57.1-57.2 and Figures 3.1-10.4, and Appendix 16.2, Listings 16-24, 28-29, and 33.

Vital Signs Measurements and ECGs

Vital sign measurements (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) were not collected at the posttreatment Week 24 visit. No notable changes were observed (Appendix 16.2, Listing 30).

All vital sign measurements and ECG results are provided in Section 15.1, Tables 48.1-50.4 and 54.1-54.4, and Appendix 16.2, Listings 30-31.

CONCLUSIONS:

The overall conclusions of this study were as follows:

- Treatment with LDV/SOF+RBV for 12 or 24 weeks in subjects with genotype 1 and 4 HCV infection with advanced liver disease and/or who had undergone liver transplantation resulted in high rates of SVR12.
- Both the SVR12 and SVR24 rates were similar between the 12 week and 24 week durations of treatment, across all groups.
- No subjects relapsed between posttreatment Weeks 12 and 24.
- Among subjects with cirrhosis, treatment was often associated with an improvement in CPT and MELD scores.
- Treatment with LDV/SOF+RBV resulted in rapid and sustained viral suppression. No subjects experienced on-treatment virologic failure.
- Relapse rate was not affected by the presence of NS5A resistance-associated polymorphisms (RAPs) or resistance-associated variant (RAVs) in any group; relapse was associated with detection of NS5A RAVs in the majority of subjects who relapsed.
- LDV/SOF was generally well tolerated in these subjects with advanced liver disease, as evidenced by low rates of study discontinuation and the majority of AEs and laboratory abnormalities being attributable to treatment with RBV and/or the subject's disease state.