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-337-0124 (SOLAR-2)
Phase of Development:	Phase 2
IND No.:	115268
EudraCT No.:	2013-002802-30
ClinicalTrials.gov Identifier:	NCT02010255
Study Start Date:	14 January 2014 (First Subject Screened)
Study End Date:	27 August 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Michael Manns, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Theo Brandt-Sarif, MD Telephone: PPD Fax: PPD
Report Date:	22 December 2015
Previous Report Date(s):	22 July 2015 (Interim Clinical Study Report)

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-337-0124
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 at 2 sites in Australia, 4 sites in France, 4 sites in Germany, 2 sites in Italy, 2 sites in Switzerland, 2 sites in Austria, 2 sites in Belgium, 6 sites in Canada, 2 sites in The Netherlands, 4 sites in Spain, 3 sites in the United Kingdom, and 1 site in New Zealand.

Publications:

Manns M, Forns X, Samuel D, Denning J, Arterburn S, Brandt-Sarif T, Dvory-Sobol H, Pang PS, McHutchison JG, Gane E, Mutimer D. Ledipasvir/Sofosbuvir with Ribavirin is Safe and Efficacious in Decompensated and Post-Liver Transplantation Patients with HCV Infection: Preliminary Results of the Prospective SOLAR-2 Trial [Presentation]. Presented at the European Association for the Study of the Liver (EASL) 50th International Liver Congress 2015, April 22-26, 2015, Vienna, Austria.

Samuel D, Manns M, Forns X, Flamm SL, Reddy KR, Denning J, Arterburn S, Brandt-Sarif T, Pang PS, McHutchison JG, Afdhal N, Charlton M, Gane E, Mutimer D, Everson GT. Ledipasvir/Sofosbuvir with Ribavirin is Safe in >600 Decompensated and Post-Liver Transplantation Patients with HCV Infection: An Integrated Safety Analysis of the SOLAR-1 and SOLAR-2 Trials [Poster P0774]. Presented at the European Association for the Study of the Liver (EASL) 50th International Liver Congress 2015, April 22-26, 2015, Vienna, Austria.

Forns X, Mutimer D, Manns M, Reddy KR, Everson GT, Flamm SL, Denning J, Arterburn S, Brandt-Sarif T, Pang PS, McHutchison JG, Afdhal N, Charlton M, Samuel D, Gane E. Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of Fibrosing Cholestatic Hepatitis C after Liver Transplantation [Poster P0779]. Presented at the European Association for the Study of the Liver (EASL) 50th International Liver Congress 2015, April 22-26, 2015, Vienna, Austria.

Study Period:

14 January 2014 (First Subject Screened)
12 May 2015 (Last Subject Observation for the Primary Endpoint)
27 August 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) 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 as measured by sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12 defined as HCV RNA < lower limit of quantification [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 can prevent posttransplant recurrence as determined by a sustained posttransplant virological response (pTVR: HCV RNA < LLOQ) at 12 weeks posttransplantion (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 be 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 provide 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 the severity of hepatic impairment:

- **Group 1**: approximately 50 subjects with cirrhosis and moderate hepatic impairment (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 posttransplantion subjects with or without cirrhosis were enrolled into 1 of 5 groups based on the 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 Class A [CPT A]; severity of cirrhosis score 5 to 6 [compensated])
- **Group 5**: approximately 50 posttransplantation subjects with cirrhosis and moderate hepatic impairment (CPT B; severity of cirrhosis score 7 to 9 [decompensated])
- **Group 6**: approximately 50 posttransplantation subjects with cirrhosis and severe hepatic impairment (CPT C; severity of cirrhosis score 10 to 12 [decompensated])
- **Group 7**: approximately 50 posttransplantation subjects with fibrosing cholestatic hepatitis (FCH)

Within each of the 7 treatment 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 (after stopping all study drugs) 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 interim CSR (22 July 2015).

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

- Randomized Analysis Set: 334 subjects
- Full Analysis Set: 330 subjects
- Safety Analysis Set: 333 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, kidney, or corneal 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.

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

- **LDV/SOF** was administered 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 the dose 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**: DK1303B1, DK1312B3
- **RBV**: AA2773Z, 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/posttransplantation Week 24. Efficacy analyses at all other scheduled assessment time points were described in the interim CSR (22 July 2015). 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: The interim CSR (22 July 2015) describes details on the collection of blood samples for the PK analyses.

Safety: The interim CSR (22 July 2015) provides analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital sign measurements, electrocardiogram (ECG), and physical examinations. In addition, changes in CPT and MELD scores were assessed using the Full Analysis Set. 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.

Statistical Methods:

All tables, figures, and listings produced for this study are provided in Appendix 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 (22 July 2015).

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ [< 15 IU/mL] 12 weeks after discontinuation of all study drugs). The proportion of subjects with SVR12 by group and treatment duration was determined along with the exact 2-sided 90% 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 the 2 endpoints {24697}. In addition, an analysis to assess the concordance of SVR12 with SVR24 was performed.

Pharmacokinetics: A population PK model was developed to characterize the PK of LDV and SOF (and its major metabolite, GS-331007) and LDV in plasma. Results for all PK analyses 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. Three subjects who did not meet disease criteria were analyzed with Group 1 (the group closest to matching their disease stage). Safety assessments including monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, and physical examinations. In addition, changes in CPT and MELD scores were assessed using the Full Analysis Set. Safety data were analyzed by group and treatment duration and included all data collected on or after the first dose of study drug through the date of last dose of study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Affairs (MedDRA), Version 17.1.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 333 randomized subjects received treatment in this study and were included in the Safety Analysis Set; 330 subjects met the entry criteria for 1 of the 7 disease groups and were included in the Full Analysis Set (3 subjects were neither decompensated nor post-liver transplantation) (Section 15.1, Table 3, and Appendix 16.2, Listings 1 and 2.2). Full details on subject disposition are reported in Section 8 of the interim CSR (22 July 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 5.1-5.9, 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 9.1-10.6, and Appendix 16.2, Listings 8.1 and 9).

Analyses related to disposition, demographics, medical history, 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 interim CSR (22 July 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, 6 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 (by imputation based on SVR12 and no subsequent HCV RNA measurements) (Section 15.1, Tables 14.1-14.4 and Appendix 16.2, Listing 25).

The SVR12 and SVR24 rates were the same for all groups, with the exception of 3 subjects (2 pretransplantation subjects [1 CPT B cirrhosis in Group 1 and 1 CPT C cirrhosis in Group 2] who received LDV/SOF for 12 weeks and 1 posttransplantation subject with CPT C cirrhosis who received LDV/SOF for 24 weeks in Group 5). These subjects (Subject PPD in Group 1 [12 Weeks], Subject PPD in Group 2 [12 Weeks], and Subject PPD in Group 5 [24 Weeks]) received a liver transplant after posttreatment Week 12 and were 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	22/26 (84.6%)	68.2% to 94.6%	21/25 (84.0%)	67.0% to 94.3%
		24 Weeks	24/25 (96.0%)	82.4% to 99.8%	24/25 (96.0%)	82.4% to 99.8%
	CPT C Cirrhosis (Group 2)	12 Weeks	17/21 (81.0%)	61.6% to 93.2%	16/20 (80.0%)	59.9% to 92.9%
		24 Weeks	19/25 (76.0%)	58.0% to 89.0%	19/25 (76.0%)	58.0% to 89.0%
Posttransplantation	Stage F0-F3 Fibrosis (Group 3)	12 Weeks	49/52 (94.2%)	85.8% to 98.4%	49/52 (94.2%)	85.8% to 98.4%
		24 Weeks	49/49 (100.0%)	94.1% to 100.0%	49/49 (100.0%)	94.1% to 100.0%
	CPT A Cirrhosis (Group 4)	12 Weeks	33/34 (97.1%)	86.8% to 99.8%	33/34 (97.1%)	86.8% to 99.8%
		24 Weeks	32/33 (97.0%)	86.4% to 99.8%	32/33 (97.0%)	86.4% to 99.8%
	CPT B Cirrhosis (Group 5)	12 Weeks	21/22 (95.5%)	80.2% to 99.8%	21/22 (95.5%)	80.2% to 99.8%
		24 Weeks	23/23 (100.0%)	87.8% to 100.0%	22/22 (100.0%)	87.3% to 100.0%
	CPT C Cirrhosis (Group 6)	12 Weeks	1/3 (33.3%)	1.7% to 86.5%	1/3 (33.3%)	1.7% to 86.5%
		24 Weeks	4/5 (80.0%)	34.3% to 99.0%	4/5 (80.0%)	34.3% to 99.0%
	FCH (Group 7)	12 Weeks	3/3 (100.0%)	36.8% to 100.0%	3/3 (100.0%)	36.8% to 100.0%
		24 Weeks	2/2 (100.0%)	22.4% to 100.0%	2/2 (100.0%)	22.4% to 100.0%

CPT = Child-Pugh-Turcotte; FCH = fibrosing cholestatic hepatitis
HCV RNA was analyzed using the Roche COBAS Ampliprep/COBAS Taqman HCV Test, v2.0 with lower limit of quantitation 15 IU/mL.
SVRx is sustained virologic response (HCV RNA < LLOQ) x weeks after stopping study treatment.
Subject is a success if their latest observed HCV RNA value in the visit window is <LLOQ, or if they have a missing value for the visit window bracketed by observed HCV RNA values that are termed successes (i.e., '< LLOQ TND' or '< LLOQ detected'). TND = target not detected.
Subjects PPD PPD (Group 1, CPT B/24 Wk); PPD PPD PPD PPD (Group 2, CPT C/12 Wk); and PPD (Group 2, CPT C/24 Wk) transplanted on study (w/ HCV RNA <LLOQ at transplant) prior to lower bound of FU-12 visit window and are excluded from analysis; Subjects PPD (Group 1, CPT B/12 Wk), PPD (Group 2, CPT C/12 Wk), and PPD (Group 5, CPT B/24 Wk) were excluded after SVR12 because these subjects received a transplant after the posttreatment Week 12 and prior to posttreatment Week 24 visit (Appendix 16.2, Listing 27).
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 10 subjects who underwent liver transplantation while on study and had HCV RNA < LLOQ at the last measurement prior to liver transplantation, all 10 achieved pTVR12. All subjects except for 1 who achieved pTVR12 also achieved pTVR24. The 1 subject (Subject PPD who did not achieve pTVR24 discontinued the study due to an AE and died after the posttransplantation Week 12 visit (Appendix16.2, Listings 15.1 and 27).

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

Across all groups, a total of 24 subjects included in the SVR analyses did not achieve SVR12 or SVR24 (Section 15.1, Tables 12.1-13.4). Of the 15 subjects with decompensated (CPT B or CPT C) cirrhosis (Groups 1 and 2) who did not achieve SVR12 or SVR24, 8 subjects relapsed (5 subjects with CPT B cirrhosis and 3 subjects with CPT C cirrhosis) and 7 subjects were categorized as having an "other" outcome. All relapses occurred by posttreatment Week 8 (Appendix 16.2, Listing 26.1). Of the 7 subjects who had an "other" outcome, 6 died during the

study (Appendix 16.2, Listings 3, 15.1, and 25). The other subject (Subject PPD who had CPT C cirrhosis withdrew consent after Week 12 (no HCV RNA detected at last on-treatment observation on Day 86) (Appendix 16.2, Listings 3 and 25).

Of the 3 posttransplantation subjects with stage F0-F3 fibrosis (Group 3) who did not achieve SVR12 or SVR24, 1 subject relapsed by posttreatment Week 4 (Appendix 16.2, Listing 26.1) and 2 subjects died during the study and were categorized as having an "other" outcome (Appendix 16.1, Listings 3, 15.1, and 25).

Of the 6 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, 1 subject (with CPT C cirrhosis who received LDV/SOF 12 Weeks) relapsed by posttreatment Week 8 (Appendix 16.2, Listing 26.1). Five subjects (2, 1, and 2 subjects with CPT A, CPT B, and CPT C cirrhosis, respectively) died and were categorized as having an "other" outcome (Appendix 16.2, Listings 3, 15.1, and 25).

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 interim CSR (22 July 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, 55.1-56.4, and 58.1-58.8, and Figures 2.1-2.4, and Appendix 16.2, Listings 25-29.

Virologic Resistance: Full details on the virologic resistance analysis are reported in Section 9.5 of the interim CSR (22 July 2015). No additional resistance analyses were performed since no subjects relapsed after the data cutoff for the interim CSR (22 July 2015).

Pharmacokinetic Results:

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 interim CSR (22 July 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 7522). An SAE was clarified for Subject PPD a posttransplantion subject with decompensated (CPT C) cirrhosis, who had a Grade 3 SAE (renal failure acute that was not considered related to study drug) updated to indicate that LDV/SOF had been interrupted. No additional treatment-emergent Grade 3 or 4 AEs were reported

(Appendix 16.2, Listing 11). 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 7522 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.

Two subjects had additional nontreatment-emergent SAEs; 1 pretransplantation subject with decompensated (CPT C) cirrhosis (Group 2, Subject PPD and 1 posttransplantation subject with decompensated (CPT B) cirrhosis (Group 5, Subject PPD Subject PPD had an SAE of cardiac arrest on posttreatment Day 291, which was fatal and considered not related to study drug by the investigator. This subject also experienced SAEs of transplant rejection, klebsiella pneumonia, sepsis, and cellulitis; none of these SAEs were treatment emergent and none were considered related to study drug. Subject PPD had an SAE of gastrointestinal hemorrhage on posttreatment Day 200, which was life threatening and considered not related to study drug by the investigator (Appendix 16.2, Listings 10, 13, 15.1, and Ad Hoc Listing 7522).

Another pretransplantation subject (Subject PPD with decompensated (CPT C) cirrhosis (Group 2) experienced a Grade 2 femoral hernia on Day 160 that was ongoing at the time of data cutoff for the interim CSR. During the follow-up, the subject was hospitalized for the AE, which was reclassified to an inguinal hernia as well as an SAE for the final analysis. The inguinal hernia resolved on posttreatment Day 155 (5 days after hospital admission) and was not considered by the investigator to be related to study drug (Appendix 16.2, Listings 10, 15.1, and Ad Hoc Listing 7522).

No subject pregnancies were reported in this study (Appendix 16.2, Listing 14).

Except for the fatal cardiac arrest for Subject PPD no additional deaths were reported (Appendix 16.2, Listing 15.1).

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. No notable changes in the clinical laboratory results were observed.

All laboratory results are provided in Section 15.1, Tables 35.1-45.4, 46.1-47.9, 51.1-51.4, 53.1-53.4, 57.1-57.2, Figures 3.1-10.4, and Appendix 16.2, Listings 16-24, 28-29, and 32-33.

Vital Sign Measurements and Electrocardiograms

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

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

CONCLUSIONS: The 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 Week 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 was associated with detection of NS5A resistance-associated variant (RAVs) at the time of failure 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 treatment discontinuation and the majority of AEs and laboratory abnormalities being attributable to treatment with RBV and/or the subject's disease state.