FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Randomized, Open-Label Study of Ledipasvir/Sofosbuvir Fixed-Dose Combination and Vedroprevir with or without Ribavirin in Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection and Cirrhosis
Name of Test Drug:	Ledipasvir/Sofosbuvir (LDV/SOF) fixed-dose combination (FDC); Vedroprevir (VDV; GS-9451)
Dose and Formulation:	LDV/SOF FDC (90 mg/400 mg) tablet; VDV 80 mg tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-337-1512 (TRILOGY-2)
Phase of Development:	Phase 2
IND No.:	115268
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02226549
Study Start Date:	24 July 2014 (First Subject Screened)
Study End Date:	06 February 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Eric J. Lawitz, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Phil Pang, MD, PhD Telephone: PPD Fax: PPD
Report Date:	27 May 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-337-1512
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Randomized, Open-Label Study of Ledipasvir/Sofosbuvir Fixed-Dose Combination and Vedroprevir with or without Ribavirin in Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection and Cirrhosis
Investigators: Eric J. Lawitz, MD
Study Centers: One site in the United States (PPD)
Publications: No publications at the time of this clinical study report.
Study Period: 24 July 2014 (First Subject Screened) 06 February 2015 (Last Subject Observation) 06 February 2015 (Last Subject Observation for the Primary Endpoint)
Phase of Development: Phase 2
Objectives: The primary objectives of this study were as follows: • To evaluate the antiviral efficacy of combination therapy with ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) + vedroprevir (VDV) ± ribavirin (RBV) for 8 weeks in treatment-experienced subjects as measured by sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12) • To evaluate the safety and tolerability of LDV/SOF+VDV±RBV administered for 8 weeks The secondary objectives of this study were as follows: • To determine the proportion of subjects who attain SVR at 4 weeks after discontinuation of therapy (SVR4) • To evaluate the emergence of viral resistance to LDV, SOF, and VDV during treatment and after treatment discontinuation • To characterize viral dynamics during and after treatment discontinuation 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 provided their separate and specific consent

Methodology: This Phase 2, randomized, open-label study evaluated LDV/SOF+VDV with or without RBV in treatment-experienced subjects with chronic genotype 1 hepatitis C virus (HCV) infection and cirrhosis.

A total of approximately 50 cirrhotic subjects were to be enrolled in this study with approximately 25 subjects randomized to each treatment group. All subjects had received prior treatment with a pegylated interferon (Peg-IFN)- and RBV-containing regimen that did not include a protease inhibitor for ≥ 4 weeks of duration.

Subjects were randomized (1:1) to 1 of the following 2 treatment groups:

- **LDV/SOF+VDV 8 Week group (Group 1):** LDV/SOF FDC (90/400 mg) once daily + VDV 80 mg once daily for 8 weeks
- **LDV/SOF+VDV+RBV 8 Week group (Group 2):** LDV/SOF FDC (90/400 mg) once daily + VDV 80 mg once daily + RBV (1000 or 1200 mg/day divided twice daily [BID]) for 8 weeks

Randomization was stratified by genotype (1a or 1b); subjects with mixed genotype were stratified as genotype 1a.

All subjects completed a screening assessment within 28 days prior to baseline/Day 1. The screening window may have been extended to 42 days for subjects requiring liver biopsy or in extenuating circumstances. Study visits occurred at screening, baseline/Day 1, and on-treatment Weeks 1, 2, 4, and 8. All subjects, including those who prematurely discontinued study drug, completed posttreatment follow-up visits at posttreatment Weeks 2, 4, 8, and 12.

All subjects were eligible to participate in a pharmacogenomics substudy 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. Subjects provided additional, specific consent prior to participation in this substudy.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 50 subjects (25 in each group)
Analyzed:

- Full Analysis Set (FAS): 46 subjects
- Safety Analysis Set: 46 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females with chronic genotype 1 HCV infection, who were ≥ 18 years of age; had screening HCV RNA levels ≥ 10^4 IU/mL; were treatment-experienced; had documentation of the presence of cirrhosis; and had a body mass index (BMI) ≥ 18 kg/m^2.

Duration of Treatment: 8 weeks of treatment followed by a 12-week posttreatment period

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

- **LDV/SOF** was administered orally at a dose of 90/400 mg/day (1 FDC tablet once daily)
- **VDV** was administered orally at a dose of 80 mg/day (1 tablet once daily)
- **RBV** was administered orally to subjects in the LDV/SOF+VDV+RBV group at a total daily dose of 1000 or 1200 mg/day (based on weight; 5 or 6 × 200-mg tablets divided BID).

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

- **LDV/SOF:** DK1209B1R
- **VDV:** BN1201B1
- **RBV:** AB1933Z

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

Criteria for Evaluation:

Efficacy: Blood samples to determine HCV RNA levels were collected from subjects at screening, baseline/Day 1 (predose), Weeks 1, 2, 4, and 8 during treatment (or upon early termination), and posttreatment Weeks 2, 4, 8, and 12. The COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: A single pharmacokinetic (PK) blood sample was collected from all subjects at baseline/Day 1 and at each treatment visit (Weeks 1, 2, 4, and 8). Samples for PK analysis were also drawn at the early termination visit, as applicable. No PK analyses were performed for this report.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital signs measurements, and physical examinations.

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.

The All Randomized Subjects analysis set included subjects who were randomized into the study. The FAS included subjects who were randomized into the study and received at least 1 dose of study drug. The Safety Analysis Set included subjects who received at least 1 dose of study drug.

Subject Disposition: Subject disposition was summarized by randomized treatment group and overall, and included the number of subjects screened, not randomized, randomized, randomized but never treated, in the FAS and Safety Analysis Set, and the number and percentage of subjects who completed study treatment, discontinued study treatment (and the reasons for doing so), completed the study, and did not complete the study (and the reasons for doing so).

Subject Demographics and Baseline Characteristics: Subject demographics and baseline disease characteristics were summarized by treatment group and overall for subjects in the Safety

Analysis Set using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum) for continuous data and by number and percentage of subjects for categorical data.

Efficacy: The primary efficacy endpoint was the proportion of subjects with HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after discontinuation of study treatment (SVR12) for the FAS. The proportion of subjects who achieved SVR12 in each treatment group was calculated; exact 2-sided 95% CIs were constructed using the Clopper-Pearson method {20839}. No statistical hypothesis testing was performed.

The secondary efficacy endpoint was the proportion of subjects who achieved SVR4. Other efficacy endpoints included the proportion of subjects who achieved SVR2 and SVR8, the proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through the end of treatment (ie, Week 8), and the proportion of subjects with virologic failure.

For the proportion of subjects with on-treatment virologic failure or relapse, a summary table of the number and percentage of subjects with SVR12, overall virologic failure (with subgroups for on-treatment virologic failure and relapse), and other (those who did not achieve SVR12 and did not meet virologic failure criteria), was provided. The denominator for relapse was the number of subjects who had HCV RNA < LLOQ at their last observed on-treatment HCV RNA measurement; otherwise, the denominator was the number of subjects in the FAS. In addition, a summary table of the number and percentage of subjects with HCV RNA < LLOQ and ≥ LLOQ at each posttreatment follow-up visit (observed and imputed, with reasons for imputed) was provided; 95% Clopper-Pearson exact CIs were presented for the overall proportion of subjects with HCV RNA< LLOQ.

Exploratory efficacy endpoints included the proportion of subjects with alanine aminotransferase (ALT) normalization (defined as ALT > the upper limit of the normal range [ULN] at baseline and ALT ≤ ULN at each visit) summarized by study visit, and subgroup analyses of SVR12 by demographic and baseline characteristics, by early viral response, and by study drug dose modification.

All continuous endpoints were summarized using descriptive statistics. All categorical endpoints were summarized by the number and percentage of subjects who met the endpoint definition.

Pharmacokinetics: No PK analyses were performed for this report.

Safety: Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, and physical examinations for subjects in the Safety Analysis Set. Safety data were analyzed by treatment group and included all data collected on or after the first dose of study drug through the date of the last dose of study drug plus 30 days. All AEs and laboratory abnormalities discussed in this clinical study report were treatment emergent and are referred to as AEs for the purposes of this report. Adverse events and laboratory abnormalities were graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 16.1.1, Appendix 3). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.1.

Adverse events were summarized (by system organ class and/or preferred term) by treatment group for the number and percentage of subjects who had (1) any AE, (2) Grade 3 or 4 AEs,

(3) Grade 2, 3, or 4 AEs, (4) non-serious AEs occurring in at least 5% of subjects in any treatment group, (5) treatment-related AEs, (6) any Grade 3 or 4 treatment-related AE, (7) Grade 2, 3, or 4 treatment-related AEs, (8) serious adverse events (SAEs), (9) treatment-related SAEs, (10) AEs leading to permanent discontinuation from any study drug, (11) AEs leading to permanent discontinuation from LDV/SOF, (12) AEs leading to permanent discontinuation from VDV, (13) AEs leading to interruption or dose modification of any of the study drugs, (14) AEs leading to interruption of LDV/SOF, and (15) AEs leading to interruption of VDV. Data listings for all AEs, SAEs, deaths, AEs leading to permanent discontinuation from any study drug, AEs leading to permanent discontinuation from LDV/SOF or VDV, and Grade 3 or 4 AEs are provided.

Laboratory results were assigned toxicity grades of Grade 0, Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (potentially life-threatening). Laboratory abnormalities were defined as values that increased at least 1 toxicity grade from baseline at any postbaseline time point to the date of the last dose of any study drug plus 30 days (ie, treatment emergent). The number and percentage of subjects by treatment group who had any graded laboratory abnormality or any Grade 3 or 4 laboratory abnormality were summarized. Laboratory data were summarized using descriptive statistics by treatment group with corresponding changes from baseline for ALT, asparate aminotransferase (AST), total bilirubin, alkaline phosphatase, white blood cell (WBC) counts, neutrophils, lymphocytes, hemoglobin, platelets, reticulocytes, and international normalized ratio (INR). The number of subjects with hemoglobin values < 10 g/dL and < 8.5 g/dL at any postbaseline visit was also summarized by treatment group. Data listings of hematology and chemistry laboratory values and Grade 3 or 4 laboratory abnormalities are provided.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 46 of 47 randomized subjects received treatment in this study (1 subject lost to follow-up prior to the Day 1 visit) and were included in the FAS and Safety Analysis Set: 22 subjects in the LDV/SOF+VDV group and 24 subjects in the LDV/SOF+VDV+RBV group (Section 15.1, Table 3). A total of 45 subjects (97.8%) completed study treatment. One subject prematurely discontinued study treatment (lost to follow-up) after 4 weeks of treatment (Appendix 16.2, Listing 5).

The mean age of subjects was 57 years (range: 35 to 70 years). The majority of subjects were male (65.2%), white (95.7%), and not of Hispanic or Latino ethnicity (60.9%). The mean BMI was 30.8 kg/m^2 (range: 21.5 to 51.9). The majority of subjects had genotype 1a HCV infection (69.6%) and had non-CC IL28B alleles (87.0%). The overall mean (SD) baseline HCV RNA value was 6.0 (0.52) log_{10} IU/mL, and most subjects had baseline HCV RNA ≥ 800,000 IU/mL (60.9%). Overall, demographics were generally similar between the 2 treatment groups; however, a numerically higher percentage of subjects in the LDV/SOF+VDV+RBV group were male (75.0% versus 54.5%) and of Hispanic or Latino ethnicity (45.8% versus 27.3%). In addition, a numerically higher percentage of subjects in the LDV/SOF+VDV group had the IL28B CC allele (18.2% versus 4.2%), baseline HCV RNA ≥ 800,000 IU/mL (68.2% versus 54.2%) and baseline ALT > 1.5 × ULN (68.2% versus 54.2%) (Section 15.1, Table 5).

All subjects in this study had cirrhosis and were treatment-experienced, having most recently received Peg-IFN+RBV as their HCV treatment regimen. The response to prior HCV treatment was relapse or breakthrough for 10 of 46 subjects (21.7%), and nonresponse for 23 of 46 subjects (50.0%); no prior treatment outcome could be determined for 13 of 46 subjects (28.3%) (Section 15.1, Table 5).

Analyses related to disposition, demographics, and exposure are presented in Section 15.1, Tables 1 to 8 and Figure 1, and Appendix 16.2, Listings 1 to 12. In addition, an Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

Efficacy Results:

Table 1 presents the proportion of subjects with SVR12 by treatment group. A total of 21 of 22 subjects (95.5%) in the LDV/SOF+VDV group and 21 of 24 subjects (87.5%) in the LDV/SOF+VDV+RBV group achieved SVR12.

A total of 4 of 46 subjects (8.7%) did not achieve SVR12: 1 subject in the LDV/SOF+VDV group and 3 subjects in the LDV/SOF+VDV+RBV group. In the LDV/SOF+VDV group, the 1 subject relapsed at the posttreatment Week 4 visit. In the LDV/SOF+VDV+RBV group, 2 subjects relapsed at the posttreatment Week 8 visit, and 1 subject was lost to follow-up after Week 4 and could therefore not be assessed for SVR12 (categorized as "other") (Appendix 16.2, Listings 14 and 15). No subjects in either group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse).

Table 1. GS-US-337-1512: Proportion of Subjects with SVR12 and Virologic Outcomes (Full Analysis Set)

	LDV/SOF+VDV 8 Weeks (N = 22)	LDV/SOF+VDV+RBV 8 Weeks (N = 24)
SVR12	21/22 (95.5%)	21/24 (87.5%)
95% CI	77.2% to 99.9%	67.6% to 97.3%
Overall Virologic Failure	1/22 (4.5%)	2/24 (8.3%)
Relapse	1/22 (4.5%)	2/24 (8.3%)
Completed Study Treatment	1/22 (4.5%)	2/23 (8.7%)
Discontinued Study Treatment	0/0	0/1
On-Treatment Virologic Failure	0/22	0/24
Other	0/22	1/24 (4.2%)

HCV RNA analyzed using the Roche COBAS Ampliprep/COBAS TaqMan V2.0 assay with a limit of quantitation of 15 IU/mL.
SVR12 is sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
A missing SVR12 value was imputed as a success if it was bracketed by values that were termed successes (ie, "<LLOQ TND" or "<LLOQ detected"); otherwise, the missing SVR12 value was imputed as a failure. TND = Target not detected.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Relapse = confirmed HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at the last on-treatment visit.
On-Treatment Virologic Failure = breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment), rebound (confirmed > 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment), or nonresponse (HCV RNA persistently ≥ LLOQ through 8 weeks of treatment)
Other = subject did not achieve SVR12 and did not meet virologic failure criteria
Source: Section 15.1, Tables 9 and 13

In the LDV/SOF+VDV group, SVR4 results were the same as the SVR12 results. In the LDV/SOF+VDV+RBV group, 2 subjects who achieved SVR4 did not achieve SVR12 (relapsed at posttreatment Week 8). One subject in the LDV/SOF+VDV group (Subject PPD who had HCV RNA < LLOQ at Week 8, had quantifiable HCV RNA at posttreatment Week 2. Viral sequencing of this sample was not obtained due to assay failure, and the subject subsequently achieved SVR4, SVR8, and SVR12 (Section 15.1, Tables 14 and 16, and Appendix 16.2, Listing 13 and Virology Listings 4 to 6).

At on-treatment Week 4, 19 of 22 subjects (86.4%) in the LDV/SOF+VDV group and 22 of 24 subjects (91.7%) in the LDV/SOF+VDV+RBV group had HCV RNA < LLOQ. At Week 8, 100.0% of subjects had HCV RNA < LLOQ (Section 15.1, Table 15 and Figure 3).

All efficacy analyses are provided in Section 15.1, Tables 9 to 18, Figures 2 to 7, and Appendix 16.2, Listings 13 to 15.

Virologic Resistance Analysis:

The full-length NS5A, NS5B, and NS3/4A coding regions were successfully deep sequenced at pretreatment (baseline) for 46, 45 and 46 subjects, respectively, and for the 3 subjects who relapsed posttreatment. Baseline and posttreatment analyses were conducted with a 1% cutoff.

Of the 46 randomized subjects who received study drug, 1 subject who was lost to follow-up after Week 4 was excluded from this analysis. Subject PPD had no subtype definition at screening and was found to be infected with genotype 1a by BLAST analyses using the NS5A, NS5B, and NS3/4A sequences (Appendix 16.2, Virology Listing 7). The other subjects' HCV subtypes were consistent with those determined at screening.

Overall, 3 of 45 subjects (6.7%) had NS5A resistance-associated variants (RAVs) at baseline and 1 of the 3 subjects achieved SVR12, compared with 41 of 42 subjects without NS5A RAVs achieving SVR12. Two subjects with NS5B nucleotide RAVs L159F (> 99%) and S282G (2.23%), respectively, achieved SVR12.

Twenty-three of 45 subjects (51.1%) had NS3 Q80K/R/L/A variants at baseline; of these, 21 subjects (91.3%) achieved SVR12. The 2 subjects who did not achieve SVR12 had NS5A RAVs at baseline together with Q80K/L variants. Another subject had V170T (1.5%) at baseline and achieved SVR12.

A total of 3 subjects experienced virologic relapse.

Table 2 presents the results of the baseline and posttreatment NS5A, NS5B, and NS3 RAVs analyses with a 1% cutoff for the 3 subjects who relapsed. Two subjects who relapsed had the NS5A L31M RAV at baseline that has been shown to confer > 100-fold reduced susceptibility to LDV in vitro; this NS5A RAV was enriched at posttreatment in both subjects. The NS5A RAV Q30R was observed in 1 subject together with L31M at baseline, but Q30R was not detected at the posttreatment time point. The third subject that relapsed selected Q30R (1.13%) at posttreatment. No NS5B or NS3 RAVs were selected in any of these 3 subjects.

Table 2. GS-US-337-1512: Sequence Analysis for Subjects with Virologic Failure

Subject ID	GT	Treatment	NS5A RAVs		NS5B NI RAVs		NS3 RAVs	
			Baseline	Post-treatment	Baseline	Post-treatment	Baseline	Post-treatment
PPD	1a	LDV/SOF +VDV	Q30R (19.6%) L31M (57.24%)	L31M (> 99%)	None	None	Q80L (87.07%)	Q80L (> 99%)
PPD	1a	LDV/SOF +VDV+RBV	L31M (3.74%)	L31M (> 99%)	None	None	Q80K (> 99%)	Q80K (> 99%)
PPD	1a	LDV/SOF +VDV+RBV	None	Q30R (1.13%)	None	None	None	None

GT = genotype; NI = nucleotide inhibitor
Source: Appendix 16.2, Virology Listings 1-6

Pharmacokinetic Results: No PK analyses were performed for this report.

Safety Results:

The mean (SD) duration of exposure to study regimen was 8.2 (0.08) weeks in the LDV/SOF+VDV group and 8.0 (0.83) weeks in the LDV/SOF+VDV+RBV group. All 22 subjects (100.0%) in the LDV/SOF+VDV group and 23 of 24 subjects (95.8%) in the LDV/SOF+VDV+RBV group received 8 weeks of study regimen (Section 15.1, Table 6).

Adverse Events and Serious Adverse Events

The majority of subjects experienced at least 1 AE: 14 of 22 subjects (63.6%) in the LDV/SOF+VDV group and 13 of 24 subjects (54.2%) in the LDV/SOF+VDV+RBV group. The most frequently reported AEs were headache (13.6%, 3 of 22), rash and sinusitis (9.1%, 2 of 22, each) in the LDV/SOF+VDV group and headache (20.8%, 5 of 24), rash and sinusitis (12.5%, 3 of 24, each) in the LDV/SOF+VDV+RBV group (Section 15.1, Tables 19, 20, and 36). Most AEs were either Grade 1 (mild) or Grade 2 (moderate) in severity. Overall, 1 subject experienced a Grade 3 AE (rash in a subject in the LDV/SOF+VDV+RBV group), and no Grade 4 AEs were reported. The Grade 3 rash, considered related to study drug (RBV), led to discontinuation of RBV on Day 3; the rash resolved on Day 33 after the subject received antihistamine and corticosteroid treatment. An additional subject in the LDV/SOF+VDV+RBV group experienced a Grade 2 AE of anemia that led to discontinuation of RBV on Day 19; the AE resolved on Day 57 (Section 15.1, Tables 23, 24, and 27 and Appendix 16.2, Listings 9, 12, 18, 19, and 20).

No subjects experienced AEs leading to discontinuation of LDV/SOF or VDV (Section 15.1, Tables 28 and 29 and Appendix 16.2, Listing 20). No SAEs, pregnancies, or deaths were reported (Section 15.1, Tables 19 and 30 and Appendix 16.2, Listings 22 and 23).

All AE results are provided in Section 15.1, Tables 19 to 38, and Appendix 16.2, Listings 17 to 23.

Clinical Laboratory Results

Most subjects experienced at least 1 laboratory abnormality. The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Grade 3 laboratory abnormalities were reported for 3 of 22 subjects (13.6%) in the LDV/SOF+VDV group and for 7 of 24 subjects

(29.2%) in the LDV/SOF+VDV+RBV group; no Grade 4 laboratory abnormalities were reported (Section 15.1, Table 40).

The most common Grade 3 laboratory abnormality was hyperglycemia, reported for 1 of 22 subjects (4.5%) in the LDV/SOF+VDV group and 3 of 24 subjects (12.5%) in the LDV/SOF+VDV+RBV group, all of whom had a medical history of diabetes. Three of 24 subjects (12.5%) in the LDV/SOF+VDV+RBV group experienced Grade 3 decreases in hemoglobin (1 of which was recorded as the Grade 2 AE of anemia that led to discontinuation of RBV), 2 of whom had postbaseline hemoglobin values < 10 g/dL. Hemoglobin values for these 3 subjects were returning towards baseline values by posttreatment Week 4. An additional subject in the LDV/SOF+VDV group, who had a medical history of anemia, had a postbaseline hemoglobin value < 10 g/dL; no subjects had postbaseline hemoglobin values < 8.5 g/dL. Grade 3 increases in total bilirubin were reported for 2 of 24 subjects (8.3%) in the LDV/SOF+VDV+RBV group; total bilirubin levels for these 2 subjects returned to normal by posttreatment Week 4. The decreases in hemoglobin and increases in total bilirubin in the RBV-containing group were consistent with the expected safety profile of RBV {24149}. No other Grade 3 laboratory abnormalities were reported for more than 1 subject (Section 15.1, Tables 39.9 and 40 and Appendix 16.2, Listings 8, 16, 17, and 25).

All laboratory results are provided in Section 15.1, Tables 39.1 to 41, Figures 8 to 17, and Appendix 16.2, Listings 16 and 24 to 33.

Vital Signs Measurements and Electrocardiograms (ECGs)

No notable changes in vital signs measurements, and no clinically significant ECG results at baseline were reported (Section 15.1, Tables 42 to 45 and Appendix 16.2, Listings 34 to 36).

CONCLUSIONS:

- In treatment-experienced subjects with genotype 1 HCV infection with cirrhosis, 8 weeks of treatment with LDV/SOF+VDV with or without RBV resulted in high SVR12 rates of 87.5% and 95.5%, respectively.
- NS5A RAVs were detected in all 3 subjects who relapsed.
- Treatment with LDV/SOF+VDV with or without RBV was generally well tolerated, with no deaths, SAEs, discontinuations of LDV/SOF or VDV due to AEs; there were few Grade 3 AEs or Grade 3 laboratory abnormalities and no Grade 4 AEs or laboratory abnormalities.