FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir, With or Without Ribavirin, in HCV Infected Subjects Who Have Failed Prior Treatment With Sofosbuvir-based Therapies
Name of Test Drug:	Ledipasvir/Sofosbuvir Fixed-Dose Combination (FDC)
Dose and Formulation:	Ledipasvir/Sofosbuvir FDC (90 mg/400 mg) tablet Ribavirin 200 mg tablet
Indication:	Hepatitis C Virus Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-337-1746 (RESCUE)
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	115268 2015-001247-36
ClinicalTrials.gov Identifier:	NCT02600351
Study Start Date:	11 November 2015 (First Subject Screened)
Study End Date:	21 March 2017 (Last Subject Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Edward Tam, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Lorenzo Rossaro, MD Telephone: PPD Fax: PPD
Report Date:	26 October 2017

STUDY SYNOPSIS

Study GS-US-337-1746
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
United States

Title of Study: A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir, With or Without Ribavirin, in HCV Infected Subjects Who Have Failed Prior Treatment With Sofosbuvir-based Therapies

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 42 study sites in the United States (including 1 site in Puerto Rico), and Canada.

Publications:

Tam E, Brown RS, Satapathy S, Shen X, Camus G, Copans A, et al. Efficacy and Safety of Ledipasvir/Sofosbuvir (LDV/SOF), with or without Ribavirin (RBV), for Treatment of HCV-mono and HIV/HCV Co-infected Patients Who Have Failed Prior Treatment with Non-NS5A, SOF-based Therapies [Poster THU-265]. The International Liver Congress™ 2017: European Association for the Study of the Liver (EASL); 2017 19-23 April; Amsterdam, the Netherlands.

Tam E, Mantry PS, Satapathy SK, Ghali P, Shen X, Han LL, et al. A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir (LDV/SOF), with or without Ribavirin (RBV), in HCV Infected Subjects Who Have Failed Prior Treatment with Non-NS5A, SOF-based Therapies (RESCUE) [Poster PP0217]. Asian Pacific Association for the Study of the Liver (APASL); 2017 15-19 February; Shanghai, China.

Tam E, Brown RS, Satapathy S, Camus G, Copans A, Rossaro L, et al. Ledipasvir/Sofosbuvir ± Ribavirin in HCV and HIV/HCV Prior SOF-based Virologic Failures (RESCUE and ACTG A5348 Studies) [Poster 568LB]. Conference on Retroviruses and Opportunistic Infections (CROI); 2017 13-16 February; Seattle, WA.

Study Period:

11 November 2015 (First Subject Screened)
21 March 2017 (Last Subject Last Observation for the Primary Endpoint)
29 May 2017 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To evaluate the efficacy of treatment with ledipasvir (LDV)/sofosbuvir (SOF) fixed-dose combination (LDV/SOF FDC; Harvoni®) for 12 weeks with or without ribavirin (RBV) in subjects without cirrhosis, and LDV/SOF FDC for 12 weeks with RBV or LDV/SOF FDC for 24 weeks without RBV in subjects with cirrhosis, as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of LDV/SOF FDC for 12 weeks with or without RBV in subjects without cirrhosis, and LDV/SOF FDC for 12 weeks with RBV or LDV/SOF FDC for 24 weeks without RBV in subjects with cirrhosis, 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 attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)
- To determine the proportion of subjects with virologic failure
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation among subjects with virologic failure

The exploratory objectives of this study were as follows:

- To determine the proportion of subjects with pre-existing NS5A and NS3/4A resistance-associated variants (RAVs) at baseline
- To evaluate the change in NS3/4A RAVs from available historical resistance tests to baseline
- To assess the effect of LDV/SOF FDC treatment on health-related quality of life (QOL)

Methodology: This was a Phase 3b, multicenter, open-label study in adult male and female subjects with chronic genotype 1 or genotype 4 hepatitis C virus (HCV) infection who have failed prior SOF-based HCV therapy, specifically, SOF in combination with simeprevir (SMV) ± RBV or with RBV ± pegylated interferon (Peg-IFN).

Approximately 50% of subjects enrolled may have had prior treatment with SOF+SMV±RBV. Approximately 5% of subjects may have been infected with genotype 4 HCV.

Enrollment of approximately 430 subjects was planned; however, the study was terminated after 87 subjects were enrolled due to the lack of feasibility of enrolling the originally planned number of subjects.

Subjects were enrolled into 2 cohorts:

Cohort 1: Subjects without cirrhosis were randomized in a 1:1 ratio into the following 2 treatment groups:

- **LDV/SOF 12 Weeks (Group 1):** LDV/SOF FDC (90 mg/400 mg) tablet once daily for 12 weeks
- **LDV/SOF+RBV 12 Weeks (Group 2):** LDV/SOF FDC (90 mg/400 mg) tablet once daily plus RBV (1000 or 1200 mg/day divided twice daily) for 12 weeks

Cohort 2: Subjects with compensated cirrhosis were randomized in a 1:1 ratio into the following 2 treatment groups:

- **LDV/SOF+RBV 12 Weeks (Group 3):** LDV/SOF FDC (90 mg/400 mg) tablet once daily plus RBV (1000 or 1200 mg/day divided twice daily) for 12 weeks
- **LDV/SOF 24 Weeks (Group 4):** LDV/SOF FDC (90 mg/400 mg) tablet once daily for 24 weeks

Randomization was stratified by the following parameters:

- Genotype 1 or 4
- Prior SOF therapy: with or without SMV

All subjects were required to complete the posttreatment Week 4 and 12 visits. All subjects who achieved SVR12, defined as HCV RNA less than the lower limit of quantitation (< LLOQ) at posttreatment Week 12, completed the posttreatment Week 24 visit unless confirmed viral relapse occurred.

Subjects who provided separate and specific consent provided additional samples for optional future biomarker research. A blood sample was drawn at the baseline/Day 1 visit and at the end of treatment visit or early termination visit, as applicable.

Number of Subjects (Planned and Analyzed):

Planned: 430 subjects
Enrolled: 87 subjects
Analyzed: 82 subjects

- All Randomized/Enrolled Analysis Set: 87 subjects
- Full Analysis Set (FAS): 82 subjects
- Safety Analysis Set: 82 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females ≥ 18 years of age with chronic genotype 1 or 4 HCV infection, including subjects with or without compensated cirrhosis, with prior virologic failure after treatment with SOF in combination with SMV ± RBV or with RBV ± Peg-IFN. Prior therapy with an NS5A inhibitor was exclusionary.

Duration of Treatment: Treatment duration was 12 weeks (Groups 1, 2, and 3) or 24 weeks (Group 4), with up to 24 weeks of posttreatment follow-up.

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

- LDV/SOF was administered orally to all subjects at a dose of 90 mg/400 mg (1 FDC tablet, once daily). The batch number was DK1309B1.
- Ribavirin was administered orally to subjects in Group 2 and Group 3 at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided twice daily [BID]). The batch number was AC4297Z.

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

Criteria for Evaluation:

Efficacy: Blood samples to determine HCV RNA levels were collected from subjects at screening, Day 1 (predose), Weeks 1, 2, 4, 8, and 12 (all groups), and Weeks 16, 20, and 24 (Group 4) during treatment (or upon early termination), and posttreatment Weeks 4, 12, and 24 (if applicable). The COBAS® Ampliprep/COBAS® TaqMan® HCV Quantitative Test, v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: No PK assessments were performed for this study.

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

Quality of Life: Health-related quality of life was assessed with the Short Form Health Survey (SF-36), Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, and the Work Productivity and Activity Impairment: Hepatitis C (WPAI: Hep C) questionnaire.

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.

Analysis results are presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category is presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum are presented.

Data collected in the study is presented in by-subject listings for all subjects in the Safety Analysis Set, unless otherwise specified. All by-subject listings are presented by subject number in ascending order, unless otherwise specified.

Analysis Sets: The All Randomized/Enrolled Analysis Set includes all subjects who were randomized or enrolled in the study. Subjects were grouped within this analysis set according to the treatment to which they were randomized.

The FAS includes all enrolled subjects who received at least 1 dose of study drug (LDV/SOF FDC with or without RBV). A total of 4 subjects received incorrect study drug based on their randomized treatment assignment due to incorrect assessment of baseline cirrhosis status (n = 3) or lack of RBV dispensing by the local pharmacy (n = 1); these 4 subjects were reassigned treatment groups (Listing 16.2.2.4). Due to these randomization errors, 2 new FAS populations were defined for efficacy analyses: FAS by Randomized Treatment (grouped according to the treatment to which they were randomized) and FAS by Actual Treatment (grouped according to their cirrhotic status and the treatment/duration they actually received).

The Safety Analysis Set includes all subjects who received at least 1 dose of study drug. Subjects were grouped according to the treatment they actually received.

Efficacy: All efficacy analyses were conducted using the FAS by Randomized Treatment and the FAS by Actual Treatment, unless specified otherwise. The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ) 12 weeks after discontinuation of study drug). Efficacy analyses were performed separately for Cohorts 1 and 2.

In Cohort 1, a non-inferiority test of SVR12 rates comparing Groups 1 and 2 (noncirrhotic cohort) was planned. With a 10% non-inferiority margin, a sample size of 90 subjects per treatment group was required to provide at least 90% power to establish non-inferiority at the 1-sided 0.025 level, assuming the SVR12 rates were 98% for both groups.

In Cohort 2, a non-inferiority test of SVR12 rates comparing Groups 3 and 4 (compensated cirrhotic cohort) was planned. With a 10% non-inferiority margin, a sample size of 125 subjects per treatment group was required to provide at least 90% power to establish non-inferiority at the 1-sided 0.025 level, assuming the SVR12 rates were 95% for both groups.

However, the study was terminated after 87 subjects had been enrolled (34 subjects in Cohort 1 and 53 subjects in Cohort 2) due to the lack of feasibility of enrolling the originally planned number of subjects.

Although the non-inferiority comparisons of SVR12 in the non-cirrhotic cohort (Group 1 vs Group 2) and in the compensated cirrhotic cohort (Group 3 vs Group 4) were performed, the results are for exploratory purposes only and caution should be used in interpretation as the actual sample size was not sufficiently powered for the test.

The secondary efficacy endpoints included the proportion of subjects who achieved SVR4, SVR12, and SVR24, 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, and the proportion of subjects with virologic failure.

Pharmacokinetics: No PK assessments were performed for this study.

Safety: All safety analyses were conducted using the Safety Analysis Set, unless specified otherwise. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, electrocardiograms (ECGs), and physical examinations.

Safety data were analyzed by treatment group 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. 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) v20.0.

Quality of Life: The health-related quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) were completed at baseline/Day 1, Weeks 4 and 12 for all groups and Week 24 for Group 4, upon early termination (if applicable), and posttreatment Weeks 4 and 12. A Wilcoxon signed rank test explored within-treatment group changes in status from baseline to each postbaseline time point and from end of treatment to each posttreatment time point.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 87 subjects were randomized in the study, of which 82 subjects received at least 1 dose of study drug and were included in the FAS and Safety Analysis Set for their respective cohort. In Cohort 1 (noncirrhotic), a total of 33 subjects were randomized and received at least 1 dose of study drug: 16 subjects in the LDV/SOF 12 Week group and 17 subjects in the LDV/SOF+RBV 12 Week group. In Cohort 2 (cirrhotic), a total of 49 subjects were randomized and received at least 1 dose of study drug: 25 subjects in the LDV/SOF+RBV 12 Week group and 24 subjects in the LDV/SOF 24 Week group (Table 15.8.1.3). All 82 subjects (100.0%) completed study treatment. Ten subjects (12.2 %) discontinued due to lack of efficacy and 1 subject (1.2%) was lost to follow-up after achieving SVR12 (Listings 16.2.1.2 and 16.2.6.1).

Among subjects in the Safety Analysis Set (n = 82), the mean age of subjects was 59 years (range: 40 to 71 years); the majority of subjects were < 65 years of age (86.6%). The majority of subjects were male (74.4%), white (70.7%), and of non-Hispanic/Latino ethnicity (80.5%) (Table 15.8.3.1). The mean baseline BMI was 31.0 (range: 19.3–50.1) kg/m^2 and 53.7% of subjects had BMI $\geq$ 30 kg/m^2. The majority of subjects had genotype 1 HCV infection (89.0% [1a = 65.9%, 1b = 20.7%, unconfirmed subtype = 2.4%]), and most of the subjects (95.1%) had a non-CC IL28B genotype (CT = 68.3%, TT = 26.8%). The mean (SD) baseline HCV RNA was 6.2 (0.67) log_{10} IU/mL, and most subjects had baseline HCV RNA $\geq$ 800,000 IU/mL (75.6%) (Table 15.8.3.3).

Overall, 33 subjects (40.24%) were noncirrhotic (enrolled in Cohort 1), while 49 subjects (59.76%) had cirrhosis (enrolled in Cohort 2). All subjects in this study were treatment-experienced, with 41.5% having most recently received SOF+RBV+Peg-IFN as their HCV treatment regimen, 36.6% having most recently received SOF+SMV, and 22.0% having most recently received SOF+RBV. The response to prior HCV treatment was relapse or breakthrough for 81 subjects (98.8%), and early treatment discontinuation for 1 subject (1.2%) (Table 15.8.3.3).

Analyses related to disposition, demographics, and exposure are presented in Tables 15.8.1.1 to 15.8.4, Figures 15.8.1 and 15.8.2, and Listings 16.2.1.1 to 16.2.5.2. In addition, an Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

Efficacy Results:

The study was terminated after 87 subjects had been enrolled due to the lack of feasibility of enrolling the originally planned number of subjects. The proportions of subjects with SVR12 by treatment group for the FAS by Actual Treatment are presented in Table 1. The proportions of subjects with SVR12 by treatment group for the FAS by Randomized Treatment are presented in Tables 15.9.1.1 and 15.9.2.1.1.

Overall, a total of 72 of 82 subjects (87.8% [95% CI: 78.7%-94.0%]) achieved SVR12. Overall, a total of 10 of 82 subjects (12.2%) did not achieve SVR12, all 10 (100.0%) of whom relapsed. No subjects in any group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse). No subjects relapsed between posttreatment Weeks 12 and 24, and for both cohorts, the overall concordance between SVR12 and SVR24 was 100.0% (Tables 15.9.2.3 and 15.9.2.4, and Listings 16.2.6.1 and 16.2.6.4).

For noncirrhotic subjects (Cohort 1), 13 of 16 subjects (81.3%) in the LDV/SOF 12 Week group and 17 of 17 subjects (100.0%) in the LDV/SOF+RBV 12 Week group achieved SVR12. One subject (LDV/SOF+RBV 12 Week group) did not have HCV RNA measurements at the posttreatment Week 12 visit and was imputed to achieve SVR12 based on bracketed success (achieving SVR4 and having observed HCV RNA values < LLOQ obtained after the posttreatment Week 12 visit window) (Table 15.9.2.1.6). A total of 3 noncirrhotic subjects did not achieve SVR12; all 3 subjects were in the LDV/SOF 12 Week group and relapsed. One subject relapsed at the posttreatment Week 4 visit, and 2 subjects relapsed at the posttreatment Week 12 visit (Listing 16.2.6.2).

For cirrhotic subjects (Cohort 2), 20 of 25 subjects (80.0%) in the LDV/SOF+RBV 12 Week group and 22 of 24 subjects (91.7%) in the LDV/SOF 24 Week group achieved SVR12. One subject (LDV/SOF+RBV 12 Week group) did not have HCV RNA measurements at the posttreatment Week 12 visit and was imputed to achieve SVR12 based on bracketed success (Table 15.9.2.1.6). A total of 7 cirrhotic subjects (5 in the LDV/SOF+RBV 12 Week group and 2 in the LDV/SOF 24 Week group) did not achieve SVR12. For the subjects in the LDV/SOF+RBV 12 Week group, 3 subjects relapsed at the posttreatment Week 4 visit, and 2 subjects relapsed at the posttreatment Week 12 visit. For the subjects in the LDV/SOF 24 Week group, 1 subject relapsed at the posttreatment Week 4 visit and 1 subject relapsed at the posttreatment Week 12 visit (Listing 16.2.6.2).

Table 1. GS-US-337-1746: Proportions of Subjects with SVR12 and Virologic Outcomes (Full Analysis Set by Actual Treatment)

	Cohort 1 (Noncirrhotic)		Cohort 2 (Cirrhotic)		
	LDV/SOF 12 Weeks (N = 16)	LDV/SOF+RBV 12 Weeks (N = 17)	LDV/SOF+RBV 12 Weeks (N = 25)	LDV/SOF 24 Weeks (N = 24)	Total (N = 82)
SVR12	13/16 (81.3%)	17/17 (100.0%)	20/25 (80.0%)	22/24 (91.7%)	72/82 (87.8%)
95% CI	54.4% to 96.0%	80.5% to 100.0%	59.3% to 93.2%	73.0% to 99.0%	78.7% to 94.0%
Overall Virologic Failure	3/16 (18.8%)	0/17	5/25 (20.0%)	2/24 (8.3%)	10/82 (12.2%)
Relapse	3/16 (18.8%)	0/17	5/25 (20.0%)	2/24 (8.3%)	10/82 (12.2%)
Completed Study Treatment	3/16 (18.8%)	0/17	5/25 (20.0%)	2/24 (8.3%)	10/82 (12.2%)
On-Treatment Virologic Failure	0/16	0/17	0/25	0/24	0/82
Other	0/16	0/17	0/25	0/24	0/82

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: Tables 15.9.1.2 and 15.9.2.1.2

For both cohorts, HCV RNA levels (log_{10} IU/mL) declined rapidly with similar decreases in HCV RNA observed throughout treatment (Table 15.9.2.6). Time to virologic suppression was not associated with treatment outcome overall or treatment regimen (Table 15.9.2.5).

All efficacy analyses are provided in Tables 15.9.1.1 to 15.9.4.8, Figures 15.9.1 to 15.9.7, and Listings 16.2.6.1 to 16.2.6.4.

Virologic Resistance Analysis:

The full-length NS3, NS5A, and NS5B coding regions were successfully deep sequenced at pretreatment (baseline) for all 82 subjects included in the Full Analysis Set (Virology Listings 1 to 3), and at posttreatment for all 10 subjects who relapsed (Virology Listings 4 to 6). Baseline and posttreatment analyses were conducted with a 15% cutoff.

Overall, 12 of the 82 (14.6%) subjects had NS5A RAVs at baseline: 6 of 73 (8.2%) subjects with genotype 1 HCV infection, and 6 of 9 (66.7%) subjects with genotype 4 HCV infection. Ten of 12 (83.3%) achieved SVR12, compared to 62 of 70 subjects (88.6%) without NS5A RAVs (Table 2). The 2 subjects who relapsed were infected with HCV genotype 1a or genotype 1b; both had NS5A RAVs at baseline and received LDV/SOF for 12 or 24 weeks in the absence of RBV. All subjects with genotype 4 HCV infection, with or without NS5A RAVs, achieved SVR12.

Five subjects had a baseline NS5B nucleoside inhibitor RAS (L159F in 2 subjects with genotype 1b and V321I in 3 subjects with genotype 4r HCV infection); all 5 subjects achieved SVR12 (Virology Listing 3).

Forty-three subjects (52.4%) had baseline NS3/4A Class RAVs: 26 of 36 subjects (72.2%) who were previously treated with NS3 protease inhibitors and 17 of 46 subjects (37.0%) who never received NS3 protease inhibitors. Of the 43 subjects with baseline NS3 RAVs, 37 (86.0%) achieved SVR12, compared with 35 of 39 subjects (89.7%) without NS3 RAVs (Virology Listings 1 and 4).

Table 2. GS-US-337-1746: Prevalence of Baseline NS5A RAVs and SVR Rates

	Cohort 1 (Noncirrhotic)		Cohort 2 (Cirrhotic)		
	LDV/SOF 12 Weeks (N = 16)	LDV/SOF+RBV 12 Weeks (N = 17)	LDV/SOF+RBV 12 Weeks (N = 25)	LDV/SOF 24 Weeks (N = 24)	Total (N = 82)
Subjects with NS5A RAVs, n/N (%)	3/16 (18.8%)	4/17 (23.5%)	1/25 (4.0%)	4/24 (16.7%)	12/82 (14.6%)
SVR12 for Subjects with NS5A RAVs, n/N (%)	2/3 (66.7%)	4/4 (100.0%)	1/1 (100.0%)	3/4 (75.0%)	10/12 (83.3%)
SVR12 for Subjects without NS5A RAVs, n/N (%)	11/13 (84.6%)	13/13 (100.0%)	19/24 (79.2%)	19/20 (95.0%)	62/70 (88.6%)

Source: Virology Listings 2 and 5

A total of 10 subjects experienced virologic failure (all viral relapses). Table 3 presents the baseline and posttreatment NS5A RAVs in the 10 subjects who relapsed. Two of these 10 subjects (20.0%) had preexisting NS5A RAVs at baseline. NS5A RAVs emerged posttreatment in all 10 subjects with single NS5A RAVs in 6 of 10 subjects. The emergent NS5A RAVs were Q30H/R/K/E or Y93H/C. None of the subjects who relapsed had NS5B NI RAVs at baseline or posttreatment (Virology Listing 6).

Table 3. GS-US-337-1746: NS5A RAVS in Subjects with Virologic Failure

Subject ID	GT	Treatment	NS5A RAVs at Baseline	NS5A RAVs at Posttreatment
PPD	1a	Cohort 1, Group 1 LDV/SOF 12 Weeks	L31M	L31M, Q30R
PPD	1a	Cohort 1, Group 1 LDV/SOF 12 Weeks	None	Q30Q/H, Y93Y/H
PPD	1a	Cohort 1, Group 1 LDV/SOF 12 Weeks	None	Q30H, Y93H
PPD	1a	Cohort 2, Group 3 LDV/SOF+RBV 12 Weeks	None	Q30K
PPD	1a	Cohort 2, Group 3 LDV/SOF+ RBV 12 Weeks	None	Q30R
PPD	1a	Cohort 2, Group 3 LDV/SOF+ RBV 12 Weeks	None	Y93C
PPD	1a	Cohort 2, Group 3 LDV/SOF+ RBV 12 Weeks	None	Q30R
PPD	1a	Cohort 2, Group 3 LDV/SOF+ RBV 12 Weeks	None	Q30E
PPD	1a	Cohort 2, Group 4 LDV/SOF 24 Weeks	None	Q30E
PPD	1b	Cohort 2, Group 4 LDV/SOF 24 Weeks	L31M	L31M, Y93H

GT = genotype
Source: Virology Listing 5

Pharmacokinetic Results: No PK assessments were performed for this 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.

Adverse Events and Serious Adverse Events

Table 4 presents the overall summary of AEs by treatment group. Overall, the majority of subjects (64 of 82 subjects [78.0%]) experienced at least 1 AE. AEs assessed by the investigator as related to study treatment were reported for a total of 47 subjects (57.3%). The proportions of subjects experiencing at least 1 AE was similar in the LDV/SOF 12 Week and LDV/SOF 24 Week groups (68.8% and 70.8%, respectively), despite the difference in duration of treatment,

and were lower than those for the LDV/SOF+RBV 12 Week groups (82.4% and 88.0% for Cohorts 1 and 2, respectively). In addition, a lower proportion of subjects in the 2 non-RBV-containing treatment groups had AEs that were assessed as related to study drug (43.8% and 45.8% in the LDV/SOF 12 Week and LDV/SOF 24 Week groups, respectively), compared with the 2 RBV-containing treatment groups (70.6% and 68.0% in the Cohort 1 and Cohort 2 LDV/SOF+RBV 12 Week groups, respectively).

Overall, the most frequently reported AEs (reported for ≥ 10% of subjects overall) included the following: headache (23 subjects, 28.0%), fatigue (19 subjects, 23.2%), insomnia (12 subjects, 14.6%), rash (10 subjects, 12.2%), and nausea (9 subjects, 11.0%) (Table 15.11.2.1.3). Most AEs were either Grade 1 (mild) or Grade 2 (moderate) in severity. A total of 6 subjects (7.3%) reported Grade 3 AEs, none of which were reported for more than 1 subject, and no Grade 4 AEs were reported (Table 15.11.2.2.2). Grade 3 AEs for 2 subjects were considered related to study drug by the investigator: headache and increased blood bilirubin. The AE of headache was reported for 1 noncirrhotic subject who received LDV/SOF for 12 weeks, which resolved without a change in study drug dosing. The AE of increased blood bilirubin was reported for 1 cirrhotic subject who received LDV/SOF+RBV for 12 weeks, which was consistent with RBV-induced hemolysis, led to RBV dose reduction, and was ongoing as of the end of the study (Table 15.11.2.3.3 and Listing 16.2.7.2).

Serious adverse events (SAEs) were reported for 1 subject (1.2%) with underlying cirrhosis and a history of esophageal varices and portal hypertensive gastropathy, who received LDV/SOF for 24 weeks: Grade 3 upper gastrointestinal hemorrhage and Grade 2 gastrointestinal hemorrhage (Table 15.11.4.1 and Listing 16.2.4.3.1). Neither event was considered related to study drug by the investigator and resolved after treatment in the hospital without discontinuation of LDV/SOF (Listing 16.2.7.4). A narrative for this subject is presented in Section 15.2.

No subjects experienced AEs leading to discontinuation of LDV/SOF or RBV (Table 15.11.5.1 and Listing 16.2.7.5). A total of 2 subjects had AEs leading to modification or interruption of RBV: Grade 1 dyspnea, fatigue, and insomnia in a noncirrhotic subject who received LDV/SOF+RBV for 12 weeks, and Grade 1 dyspnea exertional and Grade 3 increased blood bilirubin in a cirrhotic subject who received LDV/SOF+RBV for 12 weeks (described above); these AEs are consistent with the known toxicity profile of RBV. There were no AEs leading to modification or interruption of LDV/SOF (Tables 15.11.2.4.1, 15.11.2.4.2, and Listing 16.2.7.6).

No deaths or pregnancies were reported (Listings 16.2.7.3 and 16.2.8.3).

Table 4. GS-US-337-1746: Overall Summary of Adverse Events (Safety Analysis Set)

Number (%) of Subjects Experiencing Any	Cohort 1 (Noncirrhotic)		Cohort 2 (Cirrhotic)		Total (N = 82)
	LDV/SOF 12 Weeks (N = 16)	LDV/SOF+RBV 12 Weeks (N = 17)	LDV/SOF+RBV 12 Weeks (N = 25)	LDV/SOF 24 Weeks (N = 24)	
AE	11 (68.8%)	14 (82.4%)	22 (88.0%)	17 (70.8%)	64 (78.0%)
Grade 3 or Above AE	2 (12.5%)	0	2 (8.0%)	2 (8.3%)	6 (7.3%)
Treatment-Related AE	7 (43.8%)	12 (70.6%)	17 (68.0%)	11 (45.8%)	47 (57.3%)
Grade 3 or Above Treatment-Related AE	1 (6.3%)	0	1 (4.0%)	0	2 (2.4%)
SAE	0	0	0	1 (4.2%)	1 (1.2%)
Treatment-Related SAE	0	0	0	0	0
AE Leading to Premature Discontinuation of Any Study Drug	0	0	0	0	0
AE Leading to Modification or Interruption of Any Study Drug	0	1 (5.9%)[a]	1 (4.0%)[a]	0	2 (2.4%)[a]
All Deaths	0	0	0	0	0

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
a AE led to modification or interruption of RBV.
Source: Table 15.11.2.1.1

All AE results are provided in Tables 15.11.2.1.1 to 15.11.5.5 and Listings 16.2.7.1 to 16.2.7.6 and 16.2.8.3).

Clinical Laboratory Results

Overall, 67 of 82 subjects (81.7%) experienced at least 1 laboratory abnormality (Table 15.11.6.2). The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Grade 3 laboratory abnormalities were reported for 10 subjects (12.2%) overall, and 1 subject (1.2%) experienced Grade 4 laboratory abnormalities.

The most common Grade 3 laboratory abnormality was decreased hemoglobin, reported for 2 subjects (11.8%) in the LDV/SOF+RBV 12 week group (Cohort 1), 1 subject (4.0%) in the LDV/SOF+RBV 12 week group (Cohort 2), and 2 subjects (8.3%) in the LDV/SOF 24 week group (Cohort 2). The decreases in hemoglobin for the 3 subjects in the RBV-containing groups were consistent with the expected safety profile of RBV, and hemoglobin values for all 3 subjects returned to Grade 0 by posttreatment Week 4. One of the subjects in the LDV/SOF 24 week group, with cirrhosis, had Grade 3 decreased hemoglobin at Week 8 and 12 following SAEs of upper gastrointestinal hemorrhage and gastrointestinal hemorrhage; hemoglobin values for this subject returned to Grade 0 by Week 20. The second subject in the LDV/SOF 24 week group, with cirrhosis, had Grade 3 decreased hemoglobin at Weeks 12 through posttreatment Week 4 (excluding Week 16), and had a postbaseline hemoglobin value < 8.5 g/dL; the Grade 3 abnormality was recorded as a Grade 1 AE of anemia. This subject also had Grade 4 increased aspartate aminotransferase and Grade 4 increased creatine kinase at the Week 2 visit (both reported as Grade 1 AEs), both of which returned to Grade 0 by Week 4. One additional subject

had a postbaseline hemoglobin value < 10 g/dL; this subject had cirrhosis and was treated with LDV/SOF+RBV for 12 weeks. Grade 3 decreased platelets was experienced by 2 subjects (8.3%) with cirrhosis in the LDV/SOF 24 week group; both subjects had graded platelets at baseline and at every study visit. No other Grade 3 laboratory abnormalities were reported for more than 1 subject (Listings 16.2.7.1, 16.2.8.1.1, and 16.2.8.1.3).

All laboratory results are provided in Tables 15.11.6.1.1 to 15.11.6.3, Figures 15.10.1 to 15.10.2, and Listings 16.2.8.1.1 to 16.2.8.1.8.

Vital Signs Measurements and Electrocardiograms (ECGs)

No notable changes in vital signs measurements, and no clinically significant ECG results at baseline were reported (Tables 15.11.7.1 to 15.11.7.3 and 15.11.7.5, and Listings 16.2.8.2.1, 16.2.8.2.2, and 16.2.8.4).

Quality of Life Results:

No notable changes in the analyses of the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C questionnaires were observed (Tables 15.12.1.1 to 15.12.4.2, Figures 15.11.1.1 to 15.11.4.2, and Listings 16.2.6.5 to 16.2.6.8).

CONCLUSIONS: The conclusions for this study in subjects with HCV infection who had not received previous treatment with an NS5A inhibitor are as follows:

- Treatment with LDV/SOF with or without RBV for 12 weeks in noncirrhotic subjects who had failed prior SOF-based therapy resulted in high SVR12 rates of 81.3% and 100.0%, respectively.
- Treatment with LDV/SOF+RBV for 12 weeks in cirrhotic subjects who had failed prior SOF-based therapy resulted in a high SVR12 rate of 80.0%.
- Treatment with LDV/SOF for 24 weeks in cirrhotic subjects who had failed prior SOF-based therapy resulted in a high SVR12 rate of 91.7%.
- The addition of RBV to the12-week regimen for the noncirrhotic subjects and the prolongation of LDV/SOF treatment duration from 12 to 24 weeks for the cirrhotic subjects appeared to improve efficacy.
- The presence of NS5A, NS5B, or NS3 RAVs did not appear to impact treatment outcome.
- LDV/SOF for 12 or 24 weeks was generally well tolerated. The addition of RBV to the 12-week regimen increased the incidence of AEs and laboratory abnormalities, but did not affect the overall high rates of treatment completion. No treatment-emergent deaths, treatment-related Grade 4 AEs, or treatment-related SAEs were observed.