FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	An Open-Label, Multicenter Study To Evaluate The Efficacy And Safety Of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin For 12 or 24 Weeks In Chronic Genotype 1 HCV Infected Subjects Who Participated In A Prior Gilead-Sponsored HCV Treatment Study
Name of Test Drug:	Ledipasvir/Sofosbuvir fixed-dose combination (FDC)
Dose and Formulation:	Ledipasvir/Sofosbuvir FDC (90 mg/400 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-337-1118
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	115268 2014-001245-24
ClinicalTrials.gov Identifier:	NCT01987453
Study Start Date:	30 July 2014 (First Subject Screened)
Study End Date:	12 November 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Eric Lawitz, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Chohee Yun, MD Telephone: PPD Fax: PPD
Report Date:	05 April 2016
Previous Report Date(s):	05 February 2015 (Interim Synoptic Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-337-1118
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: An Open-Label, Multicenter Study To Evaluate The Efficacy And Safety Of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin For 12 or 24 Weeks In Chronic Genotype 1 HCV Infected Subjects Who Participated In A Prior Gilead-Sponsored HCV Treatment Study

Investigators: This was a multicenter study.

Study Centers: 45 centers, including 43 in the US, 1 in Australia, and 1 in Spain

Publications:

Lawitz E, Flamm S, Yang JC, Pang PS, Zhu Y, Svarovskaia E, et al. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks [Abstract 1627]. Presented at: The 50th Annual Congress of the European Association for the Study of Liver: The International Liver Congress (EASL); 2015 April 22-26; Vienna, Austria.

Lawitz E, Pockros PJ, Yang JC, Pang PS, Zhu Y, Svarovskaia E, et al. Ledipasvir/sofosbuvir regimens for the retreatment of patients who failed sofosbuvir-based regimens [Abstract 10868]. Presented at: The 25th Conference of the Asian Pacific Association for the Study of Liver (APASL); 2016 February 20-24; Tokyo, Japan.

Wyles, D, Pockros P, Morelli G, Younes Z, Svarovskaia E, Yang JC, et al. (2015) Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens. Hepatology. 61(6): 1793-1797.

Study Period:

30 July 2014 (First Subject Screened)
12 November 2015 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To determine the efficacy of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) ± ribavirin (RBV) as measured by the proportion of subjects with sustained viral response (SVR) at 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of LDV/SOF FDC ± RBV 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 evaluate the kinetics of plasma hepatitis C virus (HCV) RNA during and after treatment discontinuation
- To evaluate the emergence of viral resistance to LDV and SOF during and after treatment discontinuation

Methodology: This open-label Phase 2 study assessed the efficacy, safety, and tolerability of treatment with LDV/SOF±RBV for 12 or 24 weeks in subjects with chronic genotype 1 HCV infection that failed prior treatment in a previous Gilead-sponsored HCV treatment study.

Approximately 100 subjects were enrolled to 1 of 3 treatment groups:

- **LDV/SOF+RBV 12 Week group (Group 1)**: Subjects who failed a prior SOF+RBV±Peg-IFN regimen received LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided twice daily) for 12 weeks
- **LDV/SOF 24 Week group (Group 2)**: Subjects who failed a prior LDV/SOF±RBV regimen received LDV/SOF FDC (90 mg/400 mg) tablet once daily for 24 weeks
- **LDV/SOF+RBV 24 Week group (Group 3)**: Subjects with advanced compensated or decompensated cirrhosis who failed a prior SOF+RBV regimen received LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (adjusted for hemoglobin and renal status) for 24 weeks

All subjects were to complete the posttreatment Week 4 visit regardless of treatment duration. Subjects who had HCV RNA less than the lower limit of quantitation (< LLOQ) at the posttreatment Week 4 visit were also to complete the posttreatment Week 12 and 24 visits unless a confirmed viral relapse occurred.

After completing the current study, eligible subjects could enroll into 1 of 3 follow-on studies: the SVR Registry Study (GS-US-248-0122), the Sequence Registry Study (GS-US-248-0123), or the Cirrhosis SVR Registry Study (GS-US-337-1431).

The analysis of the LDV/SOF+RBV 12 Week group (Group 1) was conducted when all subjects in this group completed the posttreatment Week 24 visit or had prematurely discontinued from study. All data collected by the data finalization date (16 September 2014) were included in the interim clinical study report (CSR) (05 February 2015). This final synoptic CSR summarizes the

results from the analysis of the LDV/SOF 24 Week (Group 2) and the LDV/SOF+RBV 24 Week (Group 3) groups. This final analysis was conducted when subjects in Groups 2 and 3 completed the posttreatment Week 24 visit or prematurely discontinued from the study.
Number of Subjects (Planned and Analyzed): **Planned:** Approximately 100 subjects **Analyzed:** A total of 100 subjects were included in the Full and Safety Analysis Sets, including: 51 subjects in the LDV/SOF+RBV 12 Week group (Group 1), 41 subjects in the LDV/SOF 24 Week group (Group 2), and 8 subjects in the LDV/SOF+RBV 24 Week group (Group 3).
Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females ≥ 18 years of age, with chronic genotype 1 HCV infection, who had screening HCV RNA levels > LLOQ, were HCV treatment experienced, had participated in a previous Gilead-sponsored HCV treatment study, and had a Child-Pugh-Turcotte (CPT) score ≤ 12 (only LDV/SOF+RBV 24 Week group [Group 3]). Subjects were enrolled from the following Gilead-sponsored studies: P7977-0221, P7977-0422 (PROTON), P7977-0724 (ATOMIC), GS-US-334-0110 (NEUTRINO), and P2938-0721 (QUANTUM) for the LDV/SOF+RBV 12 Week group (Group 1); GS-US-337-0118 (LONESTAR), GS-US-337-0133 (LONESTAR 3), GS-US-337-0102 (ION-1), GS-US-337-0108 (ION-3), and GS-US-337-0109 (ION-2) for the LDV/SOF 24 Week group (Group 2); and GS-US-334-0125 for the LDV/SOF+RBV 24 Week group (Group 3).
Duration of Treatment: Treatment duration was LDV/SOF+RBV for 12 weeks (Group 1), LDV/SOF for 24 weeks (Group 2), and LDV/SOF+RBV for 24 weeks (Group 3), with 24 weeks of posttreatment follow-up
Test Product, Dose, Mode of Administration, and Lot No.: • **LDV/SOF** was administered orally to all subjects at a dose of 90/400 mg (1 FDC 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 twice daily). The lot numbers of study drugs administered in this study were as follows: • **LDV/SOF**: DK1209B1R, DK1304B1, and DK1313B3 • **RBV**: AA2773Z, A77416Y, and AB1933Z A list of the lot numbers of study drug administered to each subject is provided in Appendix 16.1.6.
Reference Therapy, Dose, Mode of Administration, and Lot No.: None

Criteria for Evaluation:

Efficacy: This CSR provides analyses of HCV RNA levels at posttreatment Weeks 12 and 24 for the LDV/SOF 24 Week (Group 2) and LDV/SOF+RBV 24 Week (Group 3) groups. In addition, any changes to previously reported efficacy analyses between the data cutoff (16 September 2014) for the primary analysis presented in the interim CSR (05 February 2015) and the final analysis presented in this CSR for the LDV/SOF+RBV 12 Week group (Group 1) are summarized.

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

Pharmacokinetics: No PK assessments were performed for this report.

Safety: The interim CSR (05 February 2015) provides analyses of adverse events (AEs), concomitant medications, clinical laboratory analyses, and vital sign measurements for the LDV/SOF+RBV 12 Week group (Group 1). This final CSR summarizes safety data for the LDV/SOF 24 Week (Group 2) and LDV/SOF+RBV 24 Week (Group 3) groups, and any new treatment-emergent AEs or changes to previously reported treatment-emergent AEs between the data cutoff for the interim CSR (16 September 2014) and the final analysis presented in this CSR for the LDV/SOF+RBV 12 Week group. Additionally, all serious adverse events (SAEs) collected after the data cutoff for the interim CSR to the end of the study (posttreatment Week 24) for the LDV/SOF+RBV 12 Week group (Group 1) are summarized. Serious adverse events occurring > 30 days after the last dose of study drug were considered nontreatment emergent.

Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital sign measurements, and physical examinations. CPT and the Model for End-Stage Liver Disease (MELD) scores were also evaluated at screening, Day 1, Weeks 12 and 24 (or upon early termination), and posttreatment Weeks 4, 12 (if applicable), and 24 (if applicable) for subjects in the LDV/SOF+RBV 24 Week group (Group 3) only.

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.

Efficacy: This study was not designed to evaluate formal statistical hypotheses. No statistical inference was performed. The primary efficacy endpoint was SVR12 (defined as HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the Full Analysis Set. In the primary efficacy analysis, the 2-sided 95% exact CI based on the Clopper-Pearson exact method was provided for the SVR12 rate in each of the treatment groups {Clopper et al 1934}.

Secondary efficacy endpoints included the proportion of subjects who achieved SVR4 and SVR24, the proportion of subjects with HCV RNA < LLOQ (ie, < 15 IU/mL) by study visit, HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through Week 8, the proportion of subjects with on-treatment virologic failure or relapse, and characterization of HCV drug resistance substitutions at baseline, during, and after therapy with LDV/SOF±RBV.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum). All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definition.

Pharmacokinetics: No PK analyses were performed for this report.

Safety: All enrolled 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, CPT and MELD scores (LDV/SOF+RBV 24 Week group [Group 3] only), vital signs measurements, 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 any study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

Subject disposition is summarized in Section 15.1, Table 2. Overall, 100 subjects were enrolled, received at least 1 dose of study drug, and were included in the Full and Safety Analysis Sets (Section 15.1, Table 2).

Analyses related to disposition, demographics, and exposure are presented in Section 15.1, Tables 1 to 7, Figure 1, and Appendix 16.2, Listings 1 to 7.1. In addition, an updated Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

LDV/SOF+RBV 12 Week Group (Group 1): For the 51 subjects in the LDV/SOF+RBV 12 Week group, full details on subject disposition, demographics and baseline disease characteristics are reported in the interim CSR (05 February 2015). No differences in demographic or baseline disease characteristics were observed between the interim analyses and the final analyses (Section 15.1, Table 4, and Appendix 16.2, Listings 4.1, 4.2). There were a small number of changes to concomitant medications that did not change the interpretation of the study results (Section 15.1, Tables 6 and Appendix 16.2, Listings 7 and 7.1).

LDV/SOF 24 Week Group (Group 2): A total of 41 treatment-experienced subjects who had failed a prior LDV/SOF±RBV regimen were enrolled to the LDV/SOF 24 Week group (Group 2) and included in the Full and Safety Analysis Sets. A total of 40 subjects (97.6%) completed study treatment. One subject (2.4%) discontinued study treatment due to lack of efficacy (Section 15.1, Table 2, Figure 1 and Appendix 16.2, Listings 3 and 8.2).

The mean age of subjects was 58 years (range: 35 to 71 years). Most subjects were male (82.9%), white (75.6%), and not of Hispanic or Latino ethnicity (87.8%). The mean BMI was 28.9 kg/m^2 (range: 18.5 to 45.0). Most subjects had genotype 1a (82.9%) HCV infection and had non-CC IL28B alleles (92.7%). A total of 46.3% of subjects had cirrhosis. The overall mean (SD) baseline HCV RNA value was 6.2 (0.62) log_{10} IU/mL, and most subjects had baseline HCV RNA ≥ 800,000 IU/mL (73.2%) (Section 15.1, Table 4).

All subjects had been treated in a prior Gilead-sponsored HCV study; 18 subjects (43.9%) had previously received LDV/SOF, 15 subjects (36.6%) had previously received LDV/SOF+RBV,

and 8 subjects (19.5%) had previously received treatment with LDV/SOF+GS-9669. All 41 subjects (100.0%) had experienced virologic failure (relapse or nonresponse) in the prior Gilead-sponsored study.

LDV/SOF+RBV 24 Week Group (Group 3): A total of 8 treatment-experienced subjects with advanced compensated or decompensated cirrhosis who failed a prior SOF+RBV regimen were enrolled to the LDV/SOF+RBV 24 Week group (Group 3). All 8 subjects were included in the Full and Safety Analysis Sets, and completed study treatment. One subject (2.4%) discontinued the study due to death (cause of death renal failure) on posttreatment Day 95 (Section 15.1, Table 2, Figure 1 and Appendix 16.2, Listings 3 and 14).

The mean age of subjects was 61 years (range: 51 to 70 years). Most subjects were male (87.5%), white (87.5%), and not of Hispanic or Latino ethnicity (100.0%). The mean BMI was 28.2 kg/m^2 (range: 21.5 to 36.4). Most subjects had genotype 1b (62.5%) HCV infection and had non-CC IL28B alleles (100.0%). All 8 subjects (100.0%) had cirrhosis; most subjects had MELD score ≤ 10 (62.5%) and had CPT Class B (7−9) score (62.5%). The overall mean (SD) baseline HCV RNA value was 5.6 (0.44) $\log_{10}$ IU/mL, and most subjects had baseline HCV RNA < 800,000 IU/mL (75.0%) (Section 15.1, Table 4).

All subjects (8 subjects, 100.0%) had been treated with LDV/SOF in a prior Gilead-sponsored HCV study and had experienced virologic failure (relapse or nonresponse) in the prior Gilead-sponsored study.

Efficacy Results:

Analysis of the primary efficacy endpoint for the LDV/SOF+RBV 12 Week group (Group 1) is reported in the interim CSR (05 February 2015), which included results for SVR12 and SVR24 (a secondary efficacy endpoint). In this final CSR, results through SVR24 for the LDV/SOF 24 Week (Group 2) and LDV/SOF+RBV 24 Week (Group 3) groups are summarized.

All efficacy analyses for all groups are provided in Section 15.1, Tables 8 to 15 and Figures 2 to 4.4 and Appendix 16.2, Listings 8.1 to 8.3 and 8.5.

LDV/SOF+RBV 12 Week Group (Group 1): There were no changes to the SVR12 and SVR24 results for subjects in the LDV/SOF+RBV 12 Week group as reported in the interim CSR (05 February 2015) (Section 15.1, Tables 8-15, and Appendix 16.2, Listings 8.1).

Virologic Resistance Analysis

Full details on the virologic resistance analysis are reported in the interim CSR (05 February 2015). No additional resistance analyses were performed since no subjects relapsed after the data cutoff for the interim CSR (16 September 2014).

LDV/SOF 24 Week Group (Group 2): Table 1 presents the proportion of subjects with SVR12 and virologic outcomes following 24 weeks of treatment with LDV/SOF. A total of 29 of 41 subjects (70.7%) achieved SVR12; 11 subjects (27.5%) relapsed and 1 subject (2.4%) had on-treatment virologic failure at Week 16 and discontinued the study due to lack of efficacy (Appendix 16.2, Listings 3 and 8.2). The on-treatment virologic failure subject (Subject PPD was believed to be adherent to study drug (Appendix 16.2, Listings 6.2 and 8.2). Of the 11 subjects who relapsed, all subjects achieved HCV RNA < LLOQ on treatment (10 subjects relapsed at posttreatment Week 4 and 1 subject relapsed at posttreatment Week 12) (Appendix 16.2, Listing 8.2).

Table 1. GS-US-337-1118. Proportion of Subjects with SVR12 and Virologic Outcomes (Full Analysis Set)

	LDV/SOF 24 Weeks (Group 2) (N = 41)	LDV/SOF+RBV 24 Weeks (Group 3) (N = 8)
SVR12	29/41 (70.7%)	8/8 (100.0%)
95% CI	54.5% to 83.9%	63.1% to 100.0%
Overall Virologic Failure	12/41 (29.3%)	0/8
Relapse	11/40 (27.5%)	0/8
Completed Study Treatment	11/40 (27.5%)	0/8
Discontinued Study Treatment	0/0	0/0
On-Treatment Virologic Failure	1/41 (2.4%)	0/8
Other	0/41	0/8

TND = target not detected
HCV RNA analyzed using Roche TaqMan V 2.0 assay for use with the Ampliprep system with limit of quantitation 15 IU/mL.
SVR12 is sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
A missing SVR12 value is imputed as a success if it is bracketed by values that are termed successes (ie, '<LLOQ TND' or '<LLOQ detected'); otherwise, the missing SVR12 value is imputed as a failure.
The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.
Relapse = confirmed HCV RNA >=LLOQ during the posttreatment period having achieved HCV RNA <LLOQ at 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 Non-response (HCV RNA persistently >=LLOQ through 8 weeks of treatment). Other = subject who did not achieve SVR12 and did not meet virologic failure criteria.
Source: Section 15.1, Tables 8 and 9

No subjects relapsed between posttreatment Weeks 12 and 24; the concordance between SVR12 and SVR24 was 100% (Section 15.1, Tables 10.1 and 10.2; Appendix 16.2, Listings 8.2 and 8.5).

Virologic Resistance Analysis

Table 2 presents the SVR12 rates in subjects with and without baseline nonstructural protein 5A (NS5A) LDV resistance-associated variants (RAVs). Successful full-length NS5A and NS5B deep sequencing results at baseline were obtained for all 41 subjects enrolled in the LDV/SOF 24 Week group (Group 2) (Appendix 16.2, Virology Listings 1 and 2). NS5A LDV RAVs were present at baseline in 30 of 41 subjects (73%) consistent with previous exposure to NS5A inhibitor (Appendix 16.2, Virology Listing 1). All 11 subjects without baseline NS5A LDV RAVs were previously treated with LDV/SOF±RBV for 8 weeks, and all achieved SVR12. The SVR12 rate in subjects with baseline NS5A LDV RAVs was 60% (18 of 30 subjects). All subjects who experienced virologic failure due to on-treatment breakthrough (1 subject, Subject PPD or relapse (11 subjects) had baseline NS5A LDV RAVs (Table 3) that conferred > 1000 fold-shift in susceptibility to LDV. Two subjects had new emergent NS5A LDV RAVs detected at virologic failure (Subjects PPD and PPD (Table 3).

Table 2. GS-US-337-1118. SVR12 Rates in Subjects with and without Baseline NS5B LDV RAVs

	LDV/SOF 24 Weeks (Group 2) (N = 41)
Subjects with NS5A sequencing data	41
Subjects with baseline NS5A LDV RAVs	30/41 (73%)
SVR12 rate in subjects with baseline NS5A LDV RAVs	18/30 (60%)
SVR12 rate in subjects without baseline NS5A LDV RAVs	11/11 (100%)

Source: Appendix 16.2, Virology Listing 1

Baseline NS5B nucleoside inhibitor (NI) RAVs were detected in 2 of 41 subjects. E237G (> 99%) was detected in Subject PPD with genotype 1a HCV infection. This subject was previously treated with LDV/SOF for 8 weeks and also had Q30Y (> 99%) Y93H (> 99%) NS5A LDV RAVs. Despite presence of double-class RAVs, this subject achieved SVR12. V321I (> 99%) was detected in Subject PPD with genotype 1b HCV infection. This subject was previously treated with LDV/SOF for 12 weeks and also had L31I (54.3%), L31M (45.1%), and Y93H (95.9%) NS5A LDV RAVs. This subject relapsed 4 weeks posttreatment.

Baseline NS5B NI RAVs were detected in 1 of 12 subjects with virologic failure. Treatment-emergent NS5B NI RAVs were detected in 6 of 12 subjects at the time of failure (Table 3).

Subject PPD who experienced on-treatment breakthrough, developed a double mutant L159F (97.5%) and S282T (> 99%). Phenotypic testing showed that this double mutant conferred 22-fold reduced susceptibility to SOF in replicon system (Appendix 16.2, Virology Listing 5).

In subjects with virologic relapse: E237G /S282T emerged in 1 subject, S282T emerged in 1 subject, E237G alone emerged in 2 subjects, and L159F emerged in 1 subject (Table 3).

Table 3. GS-US-337-1118. Resistance Analyses in Subjects with Virologic Failure

Subject	GT	Cirrhotic	Baseline: NS5A LDV RAVs	Virologic Failure: NS5A LDV RAVs	Baseline: NS5B SOF RAVs	Virologic Failure: NS5B SOF RAVs
PPD	1a	No	Y93N (> 99%)	Y93N (> 99%)	None	None
PPD	1a	No	Q30R (98.7%) L31M (> 99%)	Q30R (> 99%) L31M (> 99%)	None	None
PPD	1a	No	S38F (98.4%) Y93H (98.5%)	S38F (> 99%) Y93H (> 99%)	None	None
PPD	1a	No	Y93H (98.8%)	Y93H (>99%)	None	None
PPD	1b	No	Y93H (> 99%)	Y93H (> 99%)	None	None
Subject	**GT**	**Cirrhotic**	**Baseline: NS5A LDV RAVs**	**Virologic Failure: NS5A LDV RAVs**	**Baseline: NS5B SOF RAVs**	**Virologic Failure: NS5B SOF RAVs**
PPD	1a	Yes	Q30K (10.1%) Q30R (3.8%) Q30T (73.9%)	K24N (> 99%) Q30K (> 99%)	None	L159F (97.7%) S282T (> 99%)
PPD	1a	Yes	M28T (> 99%) Q30R (> 99%)	M28T (> 99%) Q30R (> 99%)	None	FU-4: E237G (3.6%) S282T (1.7%)
						FU-4 retest: E237G (1.7%)
						FU-12: None
PPD	1a	No	Y93N (> 99%)	Y93N (> 99%)	None	S282T (14.6%)
PPD	1a	Yes	Q30H (92.8%) L31M (> 99%)	Q30H (> 99%) L31M (> 99%)	None	E237G (2.6%)
PPD	1a	Yes	L31M (> 99%)	K24R (1.2%) M28T (2.2%) Q30H (51.9%) Q30K (2.3%) Q30R (5.5%) L31M (63.7%) L31V (35.1%)	None	E237G (1.7%)
PPD	1b	Yes	L31I (54.3%) L31M (45.1%) Y93H (95.9%)	L31I (1.8%) L31M (97.7%) Y93H (> 99%)	V321I (> 99%)	L159F (4.7%) V321I (> 99%)

FU = follow-up; GT = genotype
Source: Appendix 16.2, Virology Listings 1, 2, 3, and 4

LDV/SOF+RBV 24 Week Group (Group 3): Table 1 presents the proportion of subjects with SVR12 and virologic outcomes following 24 weeks of treatment with LDV/SOF+RBV. Of the 8 subjects with advanced compensated or decompensated cirrhosis who failed a prior SOF+RBV regimen, all achieved SVR12 (100.0%, 8 of 8 subjects) (Section 15.1, Table 8). SVR4 and SVR24 results were the same as SVR12 results (Section 15.1, Tables 10.1 and 10.2). No subject had virologic failure (Section 15.1, Table 9). No subjects relapsed between posttreatment Weeks 12 and 24; the concordance between SVR12 and SVR24 was 100% (Section 15.1, Tables 10.1 and 10.2; Appendix 16.2, Listings 8.2 and 8.5).

Virologic Resistance Analysis
Successful full-length NS5A and NS5B deep sequencing results at baseline were obtained for all 8 subjects enrolled in Group 3 (Appendix 16.2, Virology Listings 1 and 2). Baseline NS5A LDV RAV (K24R, at 2% of viral population) was observed in 1 of 8 subjects (12.5%). Baseline NS5B NI RAV (L159F, at > 99% of viral population) was observed in 1 of 8 subjects (12.5%). All subjects in this group achieved SVR12.

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. Evaluations of safety data through 30 days after the last dose of study drugs for the LDV/SOF+RBV 12 Week group (Group 1) were summarized in the interim CSR (05 February 2015). In this final CSR, safety results for the LDV/SOF 24 Week (Group 2) and LDV/SOF+RBV 24 Week (Group 3) groups are summarized.

Narratives for all SAEs, deaths, and AEs leading to discontinuation of study drugs from the first dose of study drug through the end of the study are provided in Section 15.2. All AE results are provided in Section 15.1, Tables 18 to 32 and Appendix 16.2, Listings 9 to 14.

All blood samples for clinical laboratory analyses collected through the posttreatment Week 24 visit are provided in Section 15.1, Tables 33.1-36, Figures 5.1-5.10, and Appendix 16.2, Listings 8.4, 16, 17.2-20.3.

All vital signs collected through the posttreatment Week 24 visit are provided in Section 15.1, Tables 37.1 to 37.4 and Appendix 16.2, Listings 21.1-21.2.

LDV/SOF+RBV 12 Week Group (Group 1): 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 (Appendix 16.2, Listing 9 and Ad Hoc Listing 1). Ad Hoc Listing 1 provides a detailed listing of one AE with a change in the preferred term between the data cutoffs at the interim CSR and the final CSR time points. These changes did not impact the overall interpretation or conclusions of the safety profile of LDV/SOF+RBV for 12 weeks in this study. No additional treatment-emergent Grade 3 or 4 AEs, SAEs, deaths, or pregnancies were reported (Appendix 16.2, Listings 10, 12, 13, and 14).

LDV/SOF 24 Week Group (Group 2): The mean (SD) duration of exposure to LDV/SOF was 24.0 (0.67) weeks and 36 subjects received at least 24 weeks of study regimen (Section 15.1, Table 5).

Approximately half of subjects who received LDV/SOF for 24 weeks (48.8%, 20 of 41 subjects) reported at least 1 AE (Section 15.1, Table 19). Treatment-related AEs were observed in 24.4% (10 of 41) of subjects (Section 15.1, Table 20). No AEs leading to permanent discontinuation, modification, or interruption of study drugs were reported (Section 15.1, Tables 30.1-30.4).

The majority of AEs reported were Grade 1 or Grade 2 in severity. No Grade 4 AEs were reported. Grade 3 AEs were reported in 3 subjects (7.3%), none were experienced by more than 1 subject (Section 15.1, Table 21). No treatment-related Grade 3 AEs were reported (Section 15.1, Table 22). Serious AEs were reported in 2 subjects (4.9%). The SAEs, hepatocellular carcinoma and intervertebral disc protrusion, were not considered by the investigator to be related to study drug (Section 15.1, Tables 26-27). No deaths or pregnancies were reported (Appendix 16.2, Listings 13-14).

Most laboratory abnormalities were Grade 1 or Grade 2 in severity (Section 15.1, Table 34). No Grade 4 laboratory abnormalities were reported; 2 subjects (4.9%) had one Grade 3 laboratory abnormality each (decreased hemoglobin following an SAE of intervertebral disc protrusion, and transient elevated lipase [no pancreatitis was reported]) (Section 15.1, Table 35; Section 15.2; Appendix 16.2, Listing 16).

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) or BMI were observed during the study (Section 15.1, Tables 37.1-37.4).

LDV/SOF+RBV 24 Week Group (Group 3): The mean (SD) duration of exposure to LDV/SOF+RBV was 24.0 (0.13) weeks and 5 subjects received at least 24 weeks of study regimen (Section 15.1, Table 5). One subject had an RBV dose reduction due to decreased hemoglobin (Appendix 16.2, Listings 6.1 and 9).

Most subjects (87.5%, 7 of 8 subjects) reported at least 1 AE (Section 15.1, Table 19). The majority of AEs reported were Grade 1 or Grade 2 in severity (Section 15.1, Table 21). Treatment-related AEs were observed in 50.0% (4 of 8) of subjects (Section 15.1, Table 20). No AEs leading to permanent discontinuation of study drugs were reported (Section 15.1, Tables 30.1-30.2).

Serious AEs were reported in 2 subjects (25.0%). The reported SAEs, anal abscess, genital edema, and renal failure, were not considered by the investigator to be related to study drug (Section 15.1, Table 26-27). Subject PPD experienced serious, Grade 4 renal failure on posttreatment Day 26, which led to the subject's death on posttreatment Day 95; this event was not considered related to study drug by the investigator (Appendix 16.2, Listings 9 and 14). No pregnancies were reported (Appendix 16.2, Listing 13). No Grade 3 AEs were reported (Section 15.1, Table 21).

The majority of the on-treatment laboratory abnormalities were consistent with the expected safety profile of RBV or the advanced liver disease status of these subjects, including decreases in hemoglobin, lymphocytes, and platelets, and elevations of total bilirubin {Inc 2013}. Four (50.0%) subjects had at least one Grade 3 laboratory abnormality and 1 subject (12.5%) had a Grade 4 laboratory abnormality (elevated lipase) (Section 15.1, Table 34; Appendix 16.2,

Listing 16). No Grade 4 hematology laboratory abnormalities were reported. Grade 3 hematology laboratory abnormalities were reported for lymphocytes (2 subjects, 25.0%), hemoglobin (1 subject, 12.5%), neutrophils (1 subject, 12.5%), platelets (1 subject, 12.5%), and white blood cells (1 subject, 12.5%). A Grade 4 chemistry laboratory abnormality was reported in 1 subject for lipase; the lipase elevation was transient and no pancreatitis was reported in this subject (Appendix 16.2, Listings 9 and 16). Grade 3 chemistry laboratory abnormalities were reported for serum glucose (hyperglycemia; 1 subject, 12.5%) and total bilirubin (hyperbilirubinemia; 1 subject, 12.5%) (Section 15.1, Table 35).

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) or BMI were observed during the study (Section 15.1, Tables 37.1-37.4).

At the end of treatment, 6 of 8 subjects (75.0%) had no change or an improvement from baseline in their CPT score (Section 15.1, Table 16). Likewise, at the end of treatment, 6 of 8 subjects (75.0%) had no change from baseline in their MELD score (Section 15.1, Table 17; Appendix 16.2, Listing 22).

CONCLUSIONS: The overall conclusions from Study GS-US-337-1118 are as follows:

LDV/SOF+RBV 12 Week Group (Group 1):

- Treatment with LDV/SOF+RBV for 12 weeks in treatment-experienced subjects, of whom 27.5% had cirrhosis, resulted in an SVR12 rate of 98%.
  - The 1 subject who experienced virologic failure (relapse) had genotype 3a HCV infection. Therefore, the SVR12 rate was 100% in subjects with genotype 1 HCV infection.
  - The SVR rate among subjects with genotype 1 HCV infection who had previously failed a SOF+Peg-IFN+RBV regimen was 100%.
  - The SVR rate among subjects with genotype 1 HCV infection who had previously failed a SOF+RBV regimen was 100%.
- All subjects with genotype 1 HCV infection with NS5A RAVs (n = 6) or the NS5B L159F variant (n = 2) at baseline achieved SVR12.
- Retreatment of prior SOF failures with LDV/SOF+RBV resulted in a durable SVR: all subjects who achieved SVR12 also achieved SVR24.
- Treatment with LDV/SOF+RBV for 12 weeks was safe and well tolerated.
- These data support retreatment of patients, with and without cirrhosis, who have failed a SOF+Peg-IFN+RBV or SOF+RBV regimen with LDV/SOF+RBV for 12 weeks.

LDV/SOF 24 Week Group (Group 2):

- Treatment with LDV/SOF for 24 weeks in 41 treatment-experienced subjects, of whom 46.3% had cirrhosis, resulted in an SVR12 rate of 70.7%.
  - Retreatment of LDV/SOF-experienced subjects without baseline NS5A RAVs achieved an SVR12 rate of 100%.
  - LDV/SOF for 24 weeks achieved a suboptimal SVR12 rate of 60% in LDV/SOF-experienced subjects with baseline NS5A RAVs.

- Baseline NS5A RAVs that were selected during previous NS5A-containing regimen reduced the SVR12 rate for LDV/SOF 24 week retreatment regimen
  - NS5A RAVs were detected in all subjects with virologic failure at baseline and at the time of failure
- NS5B NI RAVs were detected in a subset of subjects at virologic failure
  - Emergence of SOF-associated variant, S282T, was observed in 3 of 12 virologic failure subjects
- Retreatment with LDV/SOF in subjects who had previously received LDV/SOF and had virologic failure resulted in a durable SVR: all subjects who achieved SVR12 also achieved SVR24.
- Treatment with LDV/SOF for 24 weeks was safe and well tolerated. There were no new safety signals.
- These data support retreatment of LDV/SOF-experienced patients without baseline NS5A RAVs, with and without cirrhosis with LDV/SOF for 24 weeks. Other treatment regimens should be evaluated for NS5A inhibitor-experienced patients with baseline NS5A RAVs.

LDV/SOF+RBV 24 Week Group (Group 3):

- Treatment with LDV/SOF+RBV for 24 weeks in 8 treatment-experienced subjects with compensated or decompensated cirrhosis resulted in an SVR12 rate of 100.0%.
- Retreatment with LDV/SOF+RBV in subjects who had previously received SOF and had virologic failure resulted in a durable SVR: all subjects who achieved SVR12 also achieved SVR24
- Treatment with LDV/SOF+RBV for 24 weeks was safe and well tolerated. There were no new safety signals.
- These data provide proof of principle that retreatment of patients with advanced liver disease (eg, decompensated cirrhosis) who have failed a SOF+RBV regimen with LDV/SOF+RBV for 24 weeks is safe and efficacious.