FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection
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-337-0102 (ION-1)
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	115268 2012-003387-43
Study Start Date:	26 September 2012 (First Subject Screened)
Study End Date	30 April 2014 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Nezam H. Afdhal, MD Affiliation: PPD
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Report Date:	28 July 2014
Previous Report Dates:	05 March 2014 (Interim Clinical Study Report Errata) 08 January 2014 (Interim Clinical Study Report)

STUDY SYNOPSIS
Study GS-US-337-0102:
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 100 sites: 62 in the United States, 10 in Germany, 7 in France, 7 in the United Kingdom, 6 in Spain, and 8 in Italy.

Publications:

Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. NEJM 2014; 370: 1889-1898.

Mangia A, Marcellin P, Kwo P, Foster GR, Buti M, Bräu N, et al. All oral fixed-dose combination sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-naïve genotype 1 HCV-infected patients: the phase 3 ION-1 study. J Hepatol 2014; 60 (1): S523-524.

Study Period:

26 September 2012 (First Subject Screened)
30 April 2014 (Last Subject Observation)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To determine the antiviral efficacy of combination treatment with ledipasvir/sofosbuvir (LDV/SOF; formerly SOF/LDV) fixed-dose combination (FDC) ± ribavirin (RBV) as measured by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of each treatment regimen 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 attained SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)
- To evaluate the kinetics of circulating hepatitis C virus (HCV) ribonucleic acid (RNA) during treatment and after treatment discontinuation
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation
- To characterize steady-state pharmacokinetics (PK) of study drugs

The exploratory objectives of this study were as follows:

- To identify or validate genetic markers that may have been predictive of the natural history of disease, response to therapy and/or tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics) in subjects who provide their separate and specific consent
- To assess the effect of treatment on health-related quality of life

Methodology: This Phase 3, randomized, open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF±RBV treatment in treatment-naive subjects with chronic genotype 1 HCV infection.

Approximately 800 subjects were randomized in a 1:1:1:1 ratio to 1 of the following 4 treatment groups:

- LDV/SOF 24 Week group (Group 1): LDV/SOF FDC (90 mg/400 mg) tablet once daily for 24 weeks
- LDV/SOF+RBV 24 Week group (Group 2): LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided twice daily [BID]) for 24 weeks
- LDV/SOF 12 Week group (Group 3): LDV/SOF FDC (90 mg/400 mg) tablet once daily for 12 weeks
- LDV/SOF+RBV 12 Week group (Group 4): LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

Randomization was stratified by genotype (1a, 1b, or mixed 1a/1b) and the presence or absence of cirrhosis at screening. Approximately 20% of the subjects enrolled may have had evidence of compensated cirrhosis at screening. Posttreatment HCV RNA results were blinded to the investigator and sponsor.

Subject enrollment occurred in 2 parts. Part A enrolled and randomized approximately 200 subjects (50 subjects per treatment group; up to 20% may have evidence of compensated cirrhosis at screening). Enrollment was halted in all 4 treatment groups once Part A was fully enrolled. After subjects in Groups 3 and 4 (12-week treatment groups) reached posttreatment Week 4, the data monitoring committee (DMC) reviewed safety data from the first 12 weeks of dosing for all subjects (Groups 1 to 4) and SVR4 efficacy data for Groups 3 and 4. If the predefined interim futility criteria were met, Groups 3 and/or 4 were to be discontinued. As futility criteria were not met, the study was continued as planned. Part B commenced enrollment after this interim futility analysis was complete. Approximately 600 additional subjects (approximately 150 subjects per group) were enrolled in Part B.

During a Type C meeting with the US Food and Drug Administration (FDA) on 03 June 2013, it was agreed that if 12 weeks of LDV/SOF±RBV was able to achieve an SVR12 ≥ 90% in subjects with and without cirrhosis separately, efficacy data from the 24-week treatment groups would not be necessary for the initial LDV/SOF new drug application (NDA) filing. Based upon meeting the prespecified criteria in the interim analysis, results from the primary efficacy analysis for Groups 3 and 4 and all subjects in Part A were summarized in the interim clinical study report (CSR). This final CSR summarizes the results of the final analysis, which was conducted when all subjects completed the posttreatment Week 24 visit or prematurely discontinued from the study.

After completing the current study, eligible subjects could have enrolled into 1 of 2 follow-on studies: the SVR Registry Study (GS-US-248-0122) or the Sequence Registry Study (GS-US-248-0123).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 800 subjects (200 in each treatment group)

Analyzed:

- All randomized subjects: 870 subjects
- Full analysis set (FAS): 865 subjects
- Safety analysis set: 865 subjects

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 ≥ 10^4 IU/mL; were HCV treatment naive; had documentation of the presence or absence of cirrhosis; and had a body mass index (BMI) ≥ 18 kg/m^2.

Duration of Treatment: Treatment duration was 24 weeks for Groups 1 and 2, and 12 weeks for Groups 3 and 4.

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

- **LDV/SOF** was administered orally to all subjects at a dose of 90 mg/400 mg (1 FDC tablet once daily).
- **RBV** was administered orally to subjects in Groups 2 and 4 at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided BID).

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

- **LDV/SOF:** DK1202B2, DK1204B2, DK1205B2-A, DK1205B2-B, and DK1209B1R
- **RBV:** A77418Z and A77420Z

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

Criteria for Evaluation:

Efficacy: Blood samples to determine serum HCV RNA levels were collected from subjects at screening, Day 1 (predose), Weeks 1, 2, 4, 6, 8, 10, and 12 (all groups), and Weeks 16, 20, and 24 (Groups 1 and 2) during treatment (or upon early termination), and posttreatment Weeks 4, 12, and 24 (if applicable). The COBAS® TaqMan® HCV 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 25 IU/mL.

Pharmacokinetics: A single PK blood sample was collected at each on-treatment visit for all subjects. An optional PK substudy was performed at the Week 2 or 4 on-treatment visit in a subset of subjects (target 15 per group). Serial PK samples were collected over 24 hours postdose. The PK of SOF, GS-566500, GS-331007, LDV, and RBV (if appropriate) was assessed.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital signs measurements, electrocardiograms (ECGs), and physical examinations through the posttreatment Week 4 visit.

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:

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the FAS. In the primary efficacy analysis, the SVR12 rates in each of the 4 treatment groups were compared with the adjusted historical SVR null rate of 60% using a 2-sided exact 1-sample binomial test. The Bonferroni correction method was used to strongly control the family-wise type I error rate at the 0.05 level and individual type I error rate at the 0.0125 level for each primary hypothesis. Secondary efficacy endpoints included SVR4 and SVR24.

After the first 200 subjects were enrolled (Part A), futility in the 12-week treatment groups (Groups 3 and 4), was assessed using an interim futility stopping procedure that utilized a conditional power approach under the observed trend. Stopping for futility was triggered when the conditional power was less than 5% (which was equivalent to an observed response rate of 60% or less).

Based on meeting the prespecified criteria agreed at a Type C meeting with the FDA, an interim analysis was conducted when all subjects in the 12-week treatment groups (ie, Groups 3 and 4) completed the posttreatment Week 12 visit or prematurely discontinued from the study. The final analysis was conducted when all subjects completed the posttreatment Week 24 visit or prematurely discontinued from the study.

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

Pharmacokinetics: Steady-state PK over a 24-hour dosing interval was determined in subjects who participated in the PK substudy at the Week 2 or 4 on-treatment visit. The interim CSR describes details on the statistical methods for PK analyses. In addition, a population PK model was developed to characterize the PK of LDV, SOF, and SOF's major metabolite GS-331007, results of which are presented in separate population PK reports.

Safety: All randomized subjects who received at least 1 dose of study drug were included in the safety analysis set. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs, ECGs, and physical examinations. Safety data were analyzed by treatment group and included all data collected on or after the first dose of any study drug up to the date of the last dose of study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0.

Quality of Life: The health-related quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) were completed at Day 1 (baseline), Weeks 2, 4, 8, 12 and 24 (if applicable), early termination (if applicable), and posttreatment Weeks 4, 12, and 24 (if applicable). A Wilcoxon signed rank test explored within-treatment group changes from baseline to each of the time points, and from end of treatment (EOT) to each posttreatment time point. A Wilcoxon rank sum test explored between-treatment group differences in change from baseline to each of the time points.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Of the 870 randomized subjects, 865 received at least 1 dose of study drug and were included in the safety and full analysis sets. Of the 865 randomized and treated subjects, 27 (3.1%) prematurely discontinued study treatment: A total of 2 subjects (0.9%) in the LDV/SOF 12 Week group, 4 subjects (1.8%) in the LDV/SOF+RBV 12 Week group, 9 subjects (4.1%) in the LDV/SOF 24 Week group, and 12 subjects (5.5%) in the LDV/SOF+RBV 24 Week group prematurely discontinued study treatment. The reasons for premature discontinuation of study treatment were AE (1.2%, 10 subjects), withdrawal of consent (0.8%, 7 subjects), lost to follow up (0.5%, 4 subjects), protocol violation (0.5%, 4 subjects), lack of efficacy associated with noncompliance (0.1%, 1 subject in the LDV/SOF 24 Week group), and pregnancy (0.1%, 1 subject).

Demographics were generally balanced across the 4 treatment groups. The majority of subjects were male (59.3%), white (85.0%), and non-Hispanic/Latino (88.1%), with a mean age of 52 years (ranging from 18–80 years). Overall, 12.5% of subjects were black or African-American race. Of the subjects enrolled in the United States (US), 19.5% were black or African-American race. The overall mean (SD) baseline BMI value for subjects was 26.5 (5.00) kg/m^2, and 20.0% of subjects had a BMI $\geq$ 30 kg/m^2.

Baseline disease characteristics were also generally balanced across the 4 treatment groups. The majority of subjects in the safety analysis set had genotype 1a HCV infection (67.2%), non-CC (CT or TT) IL28B alleles (70.4%), HCV RNA $\geq$ 800,000 IU/mL (79.0%), with a mean (SD) baseline HCV RNA value of 6.4 (0.66) $\log_{10}$ IU/mL. A total of 15.7% of subjects had cirrhosis at screening. The mean (SD) baseline alanine aminotransferase (ALT) value was 81 (62.6) U/L, and 53.2% of subjects had baseline ALT values > 1.5 × the upper limit of the normal range (ULN).

The majority of subjects were interferon (IFN) eligible (92.3%). Of the 67 subjects (7.7%) who were IFN ineligible, the primary reasons for ineligibility were significant psychiatric disease (53.7%, 36 subjects) and autoimmune disorders (17.9%, 12 subjects).

Efficacy Results: All 4 treatment groups met the primary efficacy endpoint of an SVR12 rate that was superior to the historical control rate of 60% ($p < 0.001$). For the LDV/SOF 12 Week group, a small number of updates were made to previously reported data in the interim CSR due to the ongoing nature of the study and data reconciliation. These changes did not impact the overall interpretation or conclusions of efficacy results. The SVR12 rates were:

- LDV/SOF 12 Week group: 98.6% (95% CI: 96.0% to 99.7%) of subjects (211 of 214) achieved SVR12
- LDV/SOF+RBV 12 Week group: 97.2% (95% CI: 94.1% to 99.0%) of subjects (211 of 217) achieved SVR12
- LDV/SOF 24 Week group: 98.2% (95% CI: 95.3% to 99.5%) of subjects (213 of 217) achieved SVR12
- LDV/SOF+RBV 24 Week group: 99.1% (95% CI: 96.7% to 99.9%) of subjects (215 of 217) achieved SVR12

Cirrhotic subjects in all 4 treatment groups achieved SVR12 rates of 94% to 100%. The addition of RBV to LDV/SOF and/or extending the duration of the regimen to 24 weeks did not have an impact on the SVR12 rate. Furthermore, there was no clinical impact on SVR12 whether subjects took LDV/SOF with or without food.

A total of 15 subjects failed to achieve SVR12 in the study, 12 subjects were lost to follow-up or withdrew consent, and 3 subjects were virologic failures. One subject in the LDV/SOF 24 Week group had on-treatment virologic failure (breakthrough) observed at Week 8, associated with documented study drug noncompliance. Pharmacokinetic results for this subject show GS-331007 and LDV plasma concentrations were below the limit of quantitation at the Week 8 and 10 visits, supportive of study drug noncompliance at or around these visits. Posttreatment virologic failure (relapse) was observed in 2 subjects: 1 subject in the LDV/SOF 12 Week group relapsed at posttreatment Week 4 and 1 in the LDV/SOF 24 Week group relapsed at posttreatment Week 12; no other virologic failure was observed after posttreatment Week 12 (SVR12). The concordance observed between SVR12 and SVR24 was 100% in all treatment groups.

Several host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, cirrhosis, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no impact on SVR12 rates, including the presence of baseline LDV-associated nonstructural protein 5A (NS5A) RAVs detected in 140 subjects.

HCV RNA levels (log_{10} IU/mL) declined rapidly in all 4 treatment groups. After 1 week of treatment, mean (SD) changes from baseline across all groups ranged from -4.44 (0.596) to -4.52 (0.626) log_{10} IU/mL, demonstrating that similar decreases in HCV RNA were observed in all groups, irrespective of inclusion of RBV in the treatment regimen. Accordingly, at Week 2, > 80% of subjects in each group had HCV RNA < LLOQ. At Week 4, 99.1% to 100% of subjects in each treatment group had HCV RNA< LLOQ.

Similar proportions of subjects had ALT > ULN at baseline in the 4 treatment groups (74.7%–83.4%). Normalization of ALT was observed in most of these subjects in all 4 treatment groups during treatment (87.1%–93.0% by end of treatment), coincident with suppression of viral replication.

Virologic Resistance Results: A total of 140 of 861 (16.3%) subjects were identified as having at least 1 baseline NS5A RAV by deep sequencing with a 1% assay cut off. These 140 subjects included 32 of 213 (15.0%) subjects in the LDV/SOF 12 Week group, 36 of 216 (16.7%) subjects in LDV/SOF+RBV 12 Week group, 34 of 216 (15.7%) subjects in the LDV/SOF 24 Week group, and 38 of 216 (17.6%) in the LDV/SOF+RBV 24 Week group.

Of these 140 subjects, 100 (71.4%) had at least 1 NS5A RAV conferring > 100-fold reduced susceptibility to LDV in vitro. Despite the presence of these NS5A RAVs, 136 of these 140 (97.1%) subjects with baseline NS5A RAVs achieved SVR12. Of the 4 subjects who did not achieve SVR12, 2 relapsed and 2 were lost to follow up.

Among the 865 subjects who were enrolled in the study, only 2 subjects relapsed. The first subject who relapsed was randomized to the LDV/SOF 12 Week group. This subject was cirrhotic, had genotype 1a HCV infection, had the IL28B TT allele and the NS5A RAV L31M (> 99%) at baseline. The other subject who relapsed was randomized to the LDV/SOF 24 Week

group, was cirrhotic, had genotype 1b HCV infection, the IL28B TT allele and the NS5A RAV Y93H (94.07%) at baseline. No additional NS5A RAVs were detectable at failure timepoint for either of the 2 relapsed subjects. Phenotypic analysis showed a reduced susceptibility to LDV at both baseline and at relapse. No NS5B nucleoside inhibitor (NI) RAVs or phenotypic change to SOF was detected at any timepoint tested for either subject.

Additionally, 1 subject in the LDV/SOF 24 Week group with genotype 1b HCV infection had on-treatment virologic failure (breakthrough), associated with documented study drug noncompliance. The viral breakthrough observed at Week 8 was associated with the detection of NS5A RAV Y93H and phenotypic resistance to LDV. No NI RAVs, including S282T, or any phenotypic change to SOF were detected in this subject.

Pharmacokinetics Results: Full details on the PK analysis are reported in Section 10 of the interim CSR and the interim CSR errata.

Safety Results: Overall, treatment with LDV/SOF±RBV was generally safe and well tolerated. The LDV/SOF 12 Week group had the lowest percentage of subjects experiencing any AE (80.8%, 173 of 214 subjects), including treatment-related AEs (51.4%, 110 of 214 subjects), and AEs leading to modification or interruption of any study drug (0.5%, 1 of 214 subjects). Increasing the treatment duration of LDV/SOF from 12 to 24 weeks had a minimal impact on the percentage of subjects experiencing any AE (80.8% vs 82.0%). However, inclusion of RBV in the LDV/SOF treatment regimen had a notable impact on the rate of observed AEs: higher percentages of subjects experiencing any AE were observed in the RBV-containing (LDV/SOF+RBV) groups (12 Week, 86.2% and 24 Week, 93.1%), including treatment-related AEs (12 Week, 70.5% and 24 Week, 79.3%) and AEs leading to modification or interruption of any study drug (12 Week, 16.1% and 24 Week, 17.5%). In the LDV/SOF 24 Week group, 82.0% of subjects experienced any AE, including treatment-related AEs (53.0%) and AEs leading to modification or interruption of any study drug (1.8%).

The 3 most commonly observed AEs in the RBV-free (LDV/SOF) groups were headache (25.1%), fatigue (23.0%), and nausea (12.3%). The 3 most commonly observed AEs in the RBV-containing (LDV/SOF+RBV) groups were fatigue (37.6%), headache (26.7%), and insomnia (21.0%). During 12 weeks of therapy, inclusion of RBV in the treatment regimen increased the incidence of fatigue, insomnia, nausea, cough, pruritus, anemia, dyspnea, and dry skin by ≥ 5%. Inclusion of RBV in the 12-week treatment regimen also increased the incidence of treatment-related AEs requiring medical intervention (required medication, hospitalization or prolongation of hospitalization, or other treatment [eg, procedures]) by approximately 9%.

Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. No treatment-emergent deaths or Grade 4 (life threatening) AEs were reported in the study. There was one nontreatment-emergent death in the study. Overall, Grade 3 (severe) AEs were rare (5.9%; 51 of 865 subjects). The LDV/SOF 12 Week group had the lowest percentage of subjects experiencing any Grade 3 AEs (1.9%, 4 subjects). An increase in the percentage of subjects experiencing any Grade 3 AE was observed when LDV/SOF treatment duration was extended to 24 weeks (LDV/SOF 24 Week, 9.7% [21 subjects]) or RBV was included in the treatment regimen (LDV/SOF+RBV 12 Week, 6.5% [14 subjects]; LDV/SOF+RBV 24 Week, 5.5% [12 subjects]). Fatigue, headache, anemia, and hypokalemia were the only Grade 3 AEs reported in > 1 subject in any treatment arm.

Three pregnancies were reported in study subjects (LDV/SOF 12 Week, LDV/SOF 24 Week and LDV/SOF+RBV 24 Week groups), 2 of which had induced abortions and 1 a spontaneous abortion. One additional pregnancy occurred in the female partner of a male study subject (LDV/SOF 12 Week group); the partner delivered a healthy infant.

Serious AEs (SAEs) were also rare (3.8%, 33 of 865 subjects). A total of 1 subject (0.5%) in the LDV/SOF 12 Week group, 7 subjects (3.2%) in the LDV/SOF+RBV 12 Week group, 18 subjects (8.3%) in the LDV/SOF 24 Week group, and 7 subjects (3.2%) in the LDV/SOF+RBV 24 Week group had an SAE.

The only SAEs reported in > 1 subject were cellulitis (1 subject each in the LDV/SOF 24 Week and the LDV/SOF+RBV 24 Week groups), chest pain (1 subject each in the LDV/SOF 12 Week and the LDV/SOF 24 Week groups), gastroenteritis (2 subjects in the LDV/SOF 24 Week group), hand fracture (2 subjects in the LDV/SOF 24 Week group), noncardiac chest pain (1 subject each in the LDV/SOF+RBV 12 Week and the LDV/SOF 24 Week groups), and pneumonia (1 subject each in the LDV/SOF+RBV 12 Week and the LDV/SOF+RBV 24 Week groups); all 12 of these SAEs were considered by investigators to be not related to study drug. Eleven of the 12 subjects completed treatment and 1 subject, who had experienced chest pain secondary to viral myocarditis, discontinued treatment early but still achieved SVR12 and SVR24.

Discontinuations of the treatment regimen due to AEs were also rare: 1.8% in the LDV/SOF 24-week group and 2.8% in the LDV/SOF+RBV 24-week group and no subjects in the 12-week groups permanently discontinuing treatment regimen due to an AE. Eleven subjects experienced AEs considered by the investigator to be related to study drugs that led to discontinuation of any drug (LDV/SOF and/or RBV). The only AEs that led to discontinuation of treatment reported in > 1 subject were anxiety (2 subjects in the LDV/SOF+RBV 24 Week group) and palpitations (1 subject each in the LDV/SOF 24 Week and the LDV/SOF+RBV 24 Week groups).

Most subjects had at least 1 laboratory abnormality reported. The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Few subjects had Grade 4 laboratory abnormalities (increased ALT/AST] in 1 subject, decreased hemoglobin in 1 subject, decreased lymphocytes in 1 subject, increased lipase in 9 subjects, and increased total bilirubin in 1 subject), with 0 to 2.3% of subjects experiencing Grade 4 abnormalities across the 4 treatment groups. A higher percentage of subjects in the LDV/SOF+RBV 12 Week (7.4%, 16 subjects), LDV/SOF 24 Week (8.3%, 18 subjects), and LDV/SOF+RBV 24 Week (12.4%, 27 subjects) groups had Grade 3 laboratory abnormalities compared with the LDV/SOF 12 Week group (2.8%, 6 subjects).

The most common Grade 3 or 4 laboratory abnormality across treatment groups was decreased hemoglobin, which was reported only in the RBV-containing (LDV/SOF+RBV) groups (12 Week, 4.6% [10 subjects] and 24 Week, 8.3% [18 subjects]), except for 1 subject (0.5%) in the RBV-free groups. The subject (LDV/SOF 12 Week group) experienced an unconfirmed Grade 3 hemoglobin decrease at Week 8 (11.3 g/dL) of unknown etiology; the subject was asymptomatic and the hemoglobin decrease resolved without any intervention while continuing LDV/SOF treatment.

No clinically meaningful changes from baseline in hematology parameters were observed in the LDV/SOF treatment groups. Consistent with the expected toxicity profile of RBV, decreases

from baseline in hemoglobin and increases in reticulocytes and platelets were observed in both RBV-containing (LDV/SOF+RBV) groups for the duration of treatment. In the RBV-containing groups, median hemoglobin, reticulocyte, and platelet values returned towards baseline values within 4 weeks after the last dose of study drug. Twenty subjects (9.2%) in the LDV/SOF+RBV 12 Week group and 16 subjects (7.4%) in the LDV/SOF+RBV 24 Week group had clinically significant anemia (ie, postbaseline hemoglobin < 10 g/dL); of these, 1 subject (0.5%) in the LDV/SOF+RBV 12 Week group had on-treatment hemoglobin values < 8.5 g/dL and received blood transfusions. No other subjects required a blood transfusion and no subjects required the use of erythropoietin in this study. Hemoglobin values < 10 g/dL were not observed in the RBV-free (LDV/SOF) groups. Decreases from baseline in median lymphocytes were also observed in both RBV-containing treatment groups; median lymphocytes returned towards baseline values within 4 weeks after the last dose of study drug. No clinically meaningful changes from baseline in neutrophils were observed in any treatment group.

The most common Grade 3 or 4 chemistry laboratory abnormality across treatment groups was increased lipase. Grade 3 or 4 increases in lipase were reported for 5 subjects (2.3%; Grade 4 in 3 subjects) in the LDV/SOF 12 Week group, 3 subjects (1.4%; Grade 4 in 2 subjects) in the LDV/SOF+RBV 12 Week group, 8 subjects (3.7%; Grade 4 in 4 subjects) in the LDV/SOF 24 Week group, and 4 subjects (1.8%; no Grade 4) in the LDV/SOF+RBV 24 Week group. No on-treatment trends in lipase were observed. Grade 3 and 4 lipase elevations were not sustained. None of the subjects with Grade 3 or 4 lipase elevations had an AE of clinical pancreatitis.

One subject (LDV/SOF 12 Week group) had a Grade 4 increase in ALT and AST, observed for the first time 4 weeks after the completion of dosing. While on treatment, the subject had minimally elevated ALT and AST at baseline and at most on-treatment visits. Four weeks after discontinuing LDV/SOF, the subject's ALT was 2103 U/L (Grade 4), AST was 2656 U/L (Grade 4), and total bilirubin was 1.3 mg/dL (Grade 1). The subject's ALT and AST decreased rapidly at subsequent visits; however, at posttreatment Day 67, increases in liver enzymes recurred. To date, all diagnostic workups have been negative and a biopsy suggested ongoing inflammation, but no etiology. The subject achieved SVR12. This event was reported as an AE of acute hepatitis ("unknown etiology") and was considered related to study drug by the investigator.

One subject (LDV/SOF+RBV 12 Week group) met the prespecified criterion of AST or ALT > 3 × ULN and total bilirubin > 2 × ULN. The subject had Grade 3 ALT and AST at baseline, which were decreasing with treatment when the subject experienced an elevation in total bilirubin at Week 1. The subject's AST and ALT levels normalized by Week 2, and remained within the reference range for the duration of treatment (Week 12). Total bilirubin levels declined after Week 2, but remained slightly elevated above baseline for the duration of treatment. Based on the sequence of these events, it was determined that no drug-related hepatotoxicity had occurred.

Coincident with suppression of viral replication, decreases from baseline in median ALT values were observed in all 4 treatment groups for the duration of treatment and at the posttreatment Week 4 visit. Laboratory results for AST were similar to those for ALT. Grade 3 or 4 increases in total bilirubin were reported in no subjects in the LDV/SOF 12 Week group, 9 subjects (4.1%) in the LDV/SOF+RBV 12 Week group (including 1 subject with a Grade 4 increase), 1 subject (0.5%) in the LDV/SOF 24 Week group, and 7 subjects (3.2%) in the LDV/SOF+RBV 24 Week

group. Total bilirubin > 2 × ULN was reported for 27 subjects (6.2%) in the RBV-containing groups and 1 subject (0.2%) in the RBV-free groups (24 week). The subject in the LDV/SOF 24 Week group with a Grade 3 increase in total bilirubin had a medical history of Gilbert's syndrome and an elevated (Grade 1) bilirubin at baseline. Consistent with RBV-associated hemolysis, increases from baseline in median total bilirubin values were observed in both RBV-containing treatment groups, which peaked at Week 1 and began to decrease towards baseline levels by Week 4.

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) were reported during the study. Two subjects (1 subject in LDV/SOF 12 Week group and 1 subject in LDV/SOF 24 group) had clinically significant ECGs changes from baseline (new onset, incomplete right bundle branch block; possible inferior infarct). Both subjects remained on study drug with subsequent ECGs that were deemed not clinically significant by the investigator, and both achieved SVR12 and SVR24.

Quality of Life: Overall, results from the SF-36 (Part B only), CLDQ-HCV, FACIT-F, and WPAI: Hep C quality of life questionnaires indicated that, in contrast to the RBV-free (LDV/SOF) groups, which had no on-treatment decrements in quality of life, the RBV-containing (LDV/SOF+RBV) 12- and 24-week treatment groups had a statistically significant ($p < 0.05$) worsening in health-related quality of life between baseline and the end-of-treatment for most responses for the SF-36, FACIT-F, and WPAI: Hep C questionnaires. The mean scores for all scales generally improved from end of treatment to 4, 12, and 24 weeks following treatment. These results should be interpreted with caution as multiple endpoints were tested, and the study was not powered to test these exploratory endpoints.

CONCLUSIONS: The conclusions from this final analysis are as follows:

- LDV/SOF, administered once daily with or without food as an FDC tablet for 12 weeks to treatment-naive subjects with and without cirrhosis, resulted in high SVR12 rates.
- The addition of RBV to LDV/SOF and/or extending treatment duration to 24 weeks did not increase the observed SVR12 rate.
- Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, cirrhosis, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no impact on SVR12 rates.
- In general, the PK of SOF, GS-566500, GS-331007 and LDV in the LDV/SOF±RBV groups was similar. Compensated cirrhosis had no clinically meaningful impact on SOF or LDV PK.
- The virologic failure rate was exceptionally low (0.35%, 3 of 865 subjects; 2 subjects relapsed; 1 had on-treatment virologic failure due to non-compliance). In the 2 subjects who relapsed, one had the L31M NS5A RAV and the other had the Y93H NS5A RAV detected at baseline and at the time of virologic failure. No genotypic or phenotypic resistance to SOF was detected at baseline or at the time of virologic failure.
- The presence of NS5A RAVs at baseline did not affect response to treatment with LDV/SOF.

- Treatment with LDV/SOF±RBV was generally well tolerated in this study, with no treatment-emergent deaths or Grade 4 AEs, few permanent study drug discontinuations due to AEs, few SAEs, few Grade 3 AEs, and few Grade 3 or 4 laboratory abnormalities.
- Inclusion of RBV in the LDV/SOF treatment regimen contributed substantially to the incidence of AEs (eg, anemia) and clinically significant laboratory abnormalities experienced by subjects; this is also indirectly reflected in the on-treatment decreases in quality of life observed for the RBV-containing groups, as measured by patient-reported outcomes.