FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin for 8 Weeks and Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 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-337-0108 (ION-3)
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	115268 Not applicable
Study Start Date:	06 May 2013 (First Subject Screened)
Study End Date:	07 March 2014 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Kris Kowdley, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Phil Pang, MD, PhD Telephone: PPD Fax: PPD
Report Date:	16 June 2014
Previous Report Date(s):	05 March 2014 (Interim Clinical Study Report Errata); 17 January 2014 (Interim Clinical Study Report)

STUDY SYNOPSIS
Study GS-US-337-0108
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/Ledipasvir Fixed-Dose Combination ± Ribavirin for 8 Weeks and Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 59 sites in the United States.

Publications:

Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. N Engl J Med 2014; 370:1879-1888.

Kowdley KV, Stuart GC, Reddy, KR, Rossaro L, Bernstein DE, An D, et al. Sofosbuvir/ledipasvir with and without ribavirin for 8 weeks compared to sofosbuvir/ledipasvir for 12 weeks in treatment-naïve non-cirrhotic genotype-1 HCV-infected patients: the phase 3 ION-3 study. J Hepatol 2014; 60 (1): S23.

Study Period:

06 May 2013 (First Subject Screened)
07 March 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 therpy (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 evaluate the efficacy of LDV/SOF FDC+RBV for 8 weeks versus LDV/SOF FDC for 12 weeks, in hepatitis C virus (HCV) genotype 1 treatment-naive subjects without cirrhosis

- To evaluate the efficacy of LDV/SOF FDC for 8 weeks versus LDV/SOF FDC for 12 weeks, in HCV genotype 1 treatment-naive subjects without cirrhosis
- To evaluate the efficacy of LDV/SOF FDC for 8 weeks versus LDV/SOF FDC+RBV for 8 weeks, in HCV genotype 1 treatment-naive subjects without cirrhosis
- 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 circulating HCV ribonucleic acid (RNA) during treatment and after treatment discontinuation
- To evaluate the emergence of viral resistance to LDV and SOF during treatment and after treatment discontinuation

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, virologic response to therapy, and/or tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics) in subjects who provided 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 LDV/SOF+RBV for 8 weeks and LDV/SOF (without RBV) for 8 and 12 weeks in treatment-naive subjects with chronic genotype 1 HCV infection.

Approximately 600 subjects were to be randomized (1:1:1) to 1 of the following 3 treatment groups:

- **LDV/SOF 12 Week group (Group 1):** LDV/SOF FDC (90 mg/400 mg) tablet once daily for 12 weeks
- **LDV/SOF +RBV 8 Week group (Group 2):** LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day in a divided daily dose [BID]) for 8 weeks
- **LDV/SOF 8 Week group (Group 3):** LDV/SOF FDC (90 mg/400 mg) tablet once daily for 8 weeks

Randomization was stratified by genotype (1a or 1b; subjects with mixed genotype 1a/1b were stratified as 1a). Investigators and the sponsor were blinded to posttreatment HCV RNA results. All subjects were to complete the posttreatment Week 4 and Week 12 visits, regardless of treatment duration or response. Subjects who had HCV RNA less that the lower limit of quantitation (LLOQ) at the posttreatment Week 12 visit were to complete the posttreatment Week 24 visit, unless a confirmed viral relapse occurred.

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

This final synoptic clinical study report (CSR) summarizes the results of the final analysis of data collected throughout the course of the study. Analysis of data collected for the primary efficacy endpoint (SVR12) was also reported in the interim CSR (dated 17 January 2014).

Number of Subjects (Planned and Analyzed):
Planned: Approximately 600 subjects (200 in each treatment group)

Analyzed:

- Full analysis set: 647 subjects
- Safety analysis set: 647 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 absence of cirrhosis; and had a body mass index (BMI) ≥ 18 kg/m^2.

Duration of Treatment: Treatment duration was 12 weeks for Group 1 and 8 weeks for Groups 2 and 3

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 Group 2 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:** DK1206B2 and DK1208B1R
- **RBV:** A97943Z

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

Criteria for Evaluation:

Efficacy: This CSR provides analyses of HCV RNA levels at posttreatment Week 24. Efficacy analyses at all other scheduled assessment time points were described in the interim CSR. The COBAS® TaqMan® HCV Test v2.0 for use with the High Pure System assay was used to quantify HCV RNA in this study, with an LLOQ of 25 IU/mL.

Pharmacokinetics: The interim CSR describes details on the collection of blood samples for population pharmacokinetic (PK) analyses.

Safety: The interim CSR provides analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, physical examinations, vital signs measurements, and 12-lead electrocardiograms (ECGs). This final synoptic CSR summarizes any new treatment emergent AEs or changes to previously reported treatment-emergent AEs between the data cuts for the interim CSR and the final CSR. Additionally, all serious adverse events (SAEs) collected after the data cut off for the interim CSR to the end of the study (posttreatment Week 24) are summarized. Serious adverse events occurring > 30 days after the last dose of study drug were considered nontreatment emergent.

Quality of Life: The interim CSR provided analyses of the quality-of- life questionnaires (Short Form Health Survey [SF-36], Chronic Liver Disease Questionnaire [CLDQ]-HCV, Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F], and Work Productivity and Activity Impairment [WPAI]: Hepatitis C) to assess the effect of treatment on health related quality of life. This final CSR summarizes additional data at posttreatment Weeks 12 and 24 and any changes to data that were previously reported in the interim between the data cut offs for the interim CSR and the final CSR.

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 of this report and described in detail in Section 7.7 of the interim CSR.

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the full analysis set. In the primary efficacy analysis, the SVR12 rates in each of the 3 treatment groups were compared to the adjusted historical SVR null rate of 60% for superiority using the 2 sided, 1 sample, binomial test. The basis for the 60% SVR null rate is described in the interim CSR.

A sequential testing procedure was used to control the family wise type I error rate at the 0.05 level. If the primary test for SVR12 rate in Group 1 was statistically significant at the 0.05 significance level, the SVR12 rates in Group 2 and Group 3 were to be compared to the null SVR rate, respectively, each at the 0.025 significance level. Given that the primary test for the SVR12 in Group 2 was statistically significant at the 0.025 significance level, the key secondary noninferiority analysis of Group 2 versus Group 1 was performed at the 0.025 significance level. Given that the primary test for the SVR12 in Group 3 was statistically significant at the 0.025 significance level, the key secondary noninferiority analysis of Group 3 versus Group 1 was performed at the 0.025 significance level. Given that both of the noninferiority tests were statistically significant, the key secondary noninferiority analysis of Group 3 versus Group 2 was performed at the 0.05 significance level. Noninferiority was assessed using the conventional confidence interval (CI) approach, and a noninferiority margin of 12% was applied. The 2-sided 97.5% CIs (for the differences between Group 2 and Group 1, and between Group 3 and Group 1) and the 2-sided 95% CIs (for the differences between Group 3 and Group 2) were constructed using stratum-adjusted Mantel-Haenszel (MH) proportions, stratified by the randomization stratification factor (i.e., genotype 1a or 1b). The 2 sided 95% exact CIs, based on the Clopper Pearson method, were also provided for the SVR12 rates in each of the 3 treatment groups.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and 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.

Secondary efficacy endpoints included SVR4 and SVR24. If a subject achieved SVR12 and had no further HCV RNA measurement, the subject was counted as a success for SVR24 due to the high correlation between these 2 endpoints {24697}. In addition, an analysis to assess the

concordance of SVR12 with SVR24 was performed.

Pharmacokinetics: Single plasma samples were collected at all scheduled on treatment study visits. Population PK models were developed to characterize the PK of LDV, SOF, and SOF's major metabolite GS-331007. Results for all PK analyses 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 date of the first dose of any study drug through the date of the last dose of study drug plus 30 days. Additionally, SAEs were collected on or after the first dose of study drug through the end of the study. Adverse events were coded using the Medical Dictionary for Regulatory Activities, 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, and 12 (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:

A total of 647 randomized subjects received treatment in this study and were included in the safety and full analysis sets (Section 15.1, Table 3). Full details on subject disposition, demographics, and baseline disease characteristics are reported in Section 8 of the interim CSR, and subject disposition at posttreatment Week 24 is summarized in Section 15.1, Table 3.

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, Listing 4). There were a small number of changes to concomitant medications that did not change the interpretation of the study results (Section 15.1, Table 6, and Appendix 16.2, Listing 7). Analyses related to disposition, demographics, and exposure are presented in Section 15.1, Tables 1 through 7 and Figure 1, and Appendix 16.2, Listings 1 through 7. In addition, an updated Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

Efficacy Results:

Analysis of the primary efficacy endpoint is reported in Section 9 of the interim CSR. Results for SVR24, a secondary efficacy endpoint, are summarized in this final CSR.

The proportion of subjects with SVR12 and SVR24 is presented in the table below. At the final analysis, the SVR12 and SVR24 rates were the same for all treatment groups, with a 100% positive predictive value between SVR12 and SVR24 (Section 15.1, Tables 8, 10.1, and 10.2, and Appendix 16.2, Listing 8.1). In the LDV/SOF 12 Week group, at the interim analysis, the posttreatment Week 12 visit was pending for 2 subjects (PPD PPD who were

considered to have not achieved SVR12 for the interim CSR; for the final analysis, these 2 subjects had HCV RNA < LLOQ at the posttreatment Week 12 and 24 visits (Section 15.1, Figure 1, and Appendix 16.2, Listing 8.1). Therefore, the proportion of subjects who achieved SVR12 at the final SVR24 analysis increased from 95.4% (206 of 216) to 96.3% (208 of 216).

There were 10 subjects who achieved SVR12 and did not have HCV RNA measurements at the posttreatment Week 24 visit who were imputed to achieve SVR24 based on the high correlation between SVR12 and SVR24 {24697} (Section 15.1, Table 11, and Appendix 16.2, Listing 8.1).

	LDV/SOF 8 Weeks (N = 215)	**LDV/SOF+RBV 8 Weeks (N = 216)**	**LDV/SOF 12 Weeks (N = 216)**
SVR12 (interim)	202/215 (94.0%)	201/216 (93.1%)	206/216 (95.4%)
95% CI	89.9% to 96.7%	88.8% to 96.1%	91.7% to 97.8%
SVR12 (final)	202/215 (94.0%)	201/216 (93.1%)	208/216 (96.3%)
95% CI	89.9% to 96.7%	88.8% to 96.1%	92.8% to 98.4%
SVR24	202/215 (94.0%)	201/216 (93.1%)	208/216 (96.3%)
95% CI	89.9% to 96.7%	88.8% to 96.1%	92.8% to 98.4%

TND = target not detected.
Note: HCV RNA was analyzed using Roche TaqMan v2.0 assay for use with the High Pure System assay with an LLOQ of 25 IU/mL.
Note: SVR12 and SVR24 were sustained virologic response (HCV RNA < LLOQ) 12 and 24 weeks after stopping study treatment, respectively.
Note: 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'); a missing SVR24 was imputed as a success if SVR12 was a success; otherwise, the missing SVR value was imputed as a failure.
Note: The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Section 15.1, Tables 8 and 10.2 and GS-US-337-0108 Interim CSR, Section 15.1, Table 8

Although the SVR12 rate for the 12-week regimen increased from the interim analysis to the final analysis, the 8-week RBV-free LDV/SOF regimen remained noninferior to the 8-week RBV-containing regimen and the 12-week LDV/SOF regimen. This is demonstrated by the lower bound 95.0% CI of −3.9% and lower bound 97.5% CI of −7.2%, respectively, based on the requirement that the lower bound of the CI of the difference between two treatment groups be greater than −12% as prespecified by the noninferiority margin (Section 15.1, Table 8). Thus, neither the addition of RBV to the 8-week LDV/SOF regimen, nor extending the duration of LDV/SOF from 8 to 12 weeks, substantially increased the observed SVR rates.

No subject in any group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse) (Section 15.1, Table 9, and Appendix 16.2, Listing 8.2).

A total of 36 of 647 subjects (6%) did not achieve SVR12 or SVR24: 13 in the LDV/SOF 8 Week group, 15 in the LDV/SOF+RBV 8 Week group, and 8 in the LDV/SOF 12 Week group. In the LDV/SOF 8 Week group, 11 subjects relapsed, 1 withdrew consent, and 1 was lost to follow-up. In the LDV/SOF+RBV 8 Week group, 9 subjects relapsed, 1 withdrew consent, and 5 were lost to follow-up. In the LDV/SOF 12 Week group, 3 subjects relapsed and 5 were lost to follow-up (Section 15.1, Table 11). Most relapses (17 of 23) occurred by the posttreatment

Week 4 visit; 3 subjects in the LDV/SOF 8 Week group and 3 subjects in the LDV/SOF+RBV 8 Week group relapsed between posttreatment Weeks 4 and 12 (Appendix 16.2, Listing 8.2). No subjects relapsed between posttreatment Weeks 12 and 24, and all subjects who had achieved SVR12 also achieved SVR24 (Section 15.1, Table 10.1, and Appendix 16.2, Listings 8.1 and 8.5). All efficacy analyses are provided in Section 15.1, Tables 8 through 15 and Figures 2 through 4.4, and Appendix 16.2, Listings 8.1 through 8.3 and 8.5.

The change in the overall SVR12 led to minor changes in the SVR12 by subgroup, SVR12 by early viral response, and SVR12 by dose modifications (Section 15.1, Tables 12.1, 12.2, and 12.3).

Full details on the resistance analysis are reported in Section 9.3.2 of the interim CSR. No additional resistance analyses were performed since no subjects relapsed during the posttreatment Week 12 through Week 24 (Appendix 16.2, Listing 8.5). However, the change in the overall SVR12 led to a minor change in SVR12 in subjects with resistance-associated variants (RAV) at baseline. In the LDV/SOF 12 Week group, one of the subjects whose posttreatment Week 12 visit was pending at the interim analysis (Subject PPD with genotype 1a HCV infection had a baseline NS5A RAV (Appendix 16.2.6, GS-US-337-0108 Virology Listings 1 and 2). Therefore, the proportion of subjects with nonstructural protein 5A (NS5A) RAVs at baseline who achieved SVR12 in the LDV/SOF 12 Week group at the final analysis increased from 95.0% (38 of 40) to 97.5% (39 of 40) and from 89.7% (104 of 116) to 90.5% (105 of 116) for all subjects with NS5A RAVs in the study (Appendix 16.2, Listing 8.1).

Pharmacokinetic Results:

Results of the PK analyses for this study are presented in separate population PK reports.

Safety Results:

All AEs and laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as AEs and laboratory abnormalities in this report, unless otherwise specified. Evaluations of safety data through 30 days after the last dose of study drugs were summarized in Section 11 of the interim CSR.

Adverse Events and Serious Adverse Events

A small number of updates were made to previously reported AE data due to the ongoing nature of the study and data reconciliation. These changes were primarily associated with AE resolution dates or minor clarifications to AE terms and newly reported Grade 1 or 2 AEs (Appendix 16.2, Listing 10 and Adhoc Listing 6589). These changes did not impact the overall interpretation or conclusions of the safety profile of LDV/SOF with or without RBV in this study.
Adhoc Listing 6589 provides a detailed listing of any newly reported AEs and AEs that had changes in reported or preferred term, onset date, or relationship to study drug between the data cuts taken at the posttreatment Week 12 and posttreatment Week 24 time points.

There were no additional treatment emergent SAEs. Six additional nontreatment emergent SAEs in 4 subjects were reported, none of which were considered related to study drug: 3 in the LDV/SOF 8 Week group and 1 in the LDV/SOF 12 Week group (Appendix 16.2, Listings 10, 13, and Adhoc Listing 6589). In the LDV/SOF 8 Week group, Subject PPD had a Grade 3 event of hemorrhagic anemia on posttreatment Day 95 (ongoing at the completion of the study)

and a Grade 3 event of influenza on posttreatment Day 150 (resolved on posttreatment Day 159). Subject PPD had a Grade 3 event of arthritis on posttreatment Day 108, which resolved on posttreatment Day 143. Subject PPD had a Grade 2 event of arthralgia, which was reported approximately 2 months after the subject's last dose of study drug and was ongoing at the completion of the study. In the LDV/SOF 12 Week group, Subject PPD had Grade 3 events of chest pain and dyspnea on posttreatment Day 131, both of which resolved on posttreatment Day 132.

A pregnancy was reported for Subject PPD (LDV/SOF 12 Week group) approximately 4.5 months after the subject's last dose of study drug (Appendix 16.2, Listing 14); the pregnancy is ongoing. No deaths were reported in this study (Appendix 16.2, Listing 15).

Narratives for all SAEs, AEs leading to discontinuation of study drugs, and subject and partner pregnancies from the first dose of study drug through the end of the study (ie, the posttreatment Week 24 visit) are provided in Section 15.2. All AE results are provided in Section15.1, Tables 16 through 30, and Appendix 16.2, Listings 10 through 15.

Clinical Laboratory Results

Blood samples for clinical laboratory analyses were not collected at the posttreatment Week 24 visit. Overall, no clinically meaningful changes in the clinical laboratory results were observed (Section 15.1, Tables 31.1 to 31.12 and 32 to 34, and Appendix 16.2, Listings 8.4 and 16 through 22.2).

All laboratory results are provided in Section 15.1, Tables 31.1 to 31.12 and 32 to 34, Figures 5.1 through 5.10, and Appendix 16.2, Listings 8.4 and 16 through 22.2.

Vital Signs Measurements and ECGs

Vital signs measurements (systolic and diastolic blood pressure and pulse) and weight were collected at the posttreatment Week 24 visit. No notable changes were observed (Section 15.1, Tables 36.1 through 36.4, and Appendix 16.2, Listings 24.1 and 24.2).

All vital signs measurement and ECG results are provided in Section 15.1, Tables 35 through 36.4, and Appendix 16.2, Listings 23 through 24.2.

Special Situations

Special situations including medication error, misuse, overdose, and product complaints with associated AEs were collected during the study; no new safety concerns were identified from reports of special situations.

Quality of Life:

Full details on the quality-of-life questionnaires (SF 36, CLDQ-HCV, FACIT F, and WPAI: Hepatitis C) through posttreatment Week 4 are reported in Section 12 of the interim CSR. All quality-of-life survey analyses are provided in Section 15.1, Tables 37.1 through 37.4, Figures 6.1 through 6.4, and Appendix 16.2, Listings 9.1 through 9.4.

Overall, results from the quality-of-life questionnaires remained consistent between posttreatment Week 4 and posttreatment Week 24 (Section 15.1, Tables 37.1 through 37.4, Figures 6.1 through 6.4, and Listings 9.1 through 9.4). These results indicated that, in contrast to the RBV-free LDV/SOF 8 Week and LDV/SOF 12 Week groups, which generally saw no

on-treatment decrements in quality of life; the RBV-containing LDV/SOF+RBV 8 Week group had statistically significant ($p < 0.05$) worsening in health related quality of life between baseline and end of treatment for most responses for the SF 36, FACIT F and WPAI: Hep C questionnaires. The mean scores for most scales improved from end of treatment to 24 weeks following treatment, with the greatest improvement generally occurring between end of treatment and posttreatment Week 4. At 4 weeks following treatment, there was a persistent statistically significant difference in mean changes from baseline for the SF-36 mental component score between the LDV/SOF 8 Week and LDV/SOF+RBV 8 week treatment groups, which remained statistically significant at 12 weeks following treatment but not at 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:

- LDV/SOF administered once daily with or without food as a FDC tablet for 8 weeks to treatment-naive subjects without cirrhosis, resulted in high SVR12 rates.
- The addition of RBV to an 8-week treatment course of LDV/SOF or extending the LDV/SOF treatment duration from 8 to 12 weeks did not substantially increase the observed SVR12 rates. Relapse rates were similar in the 8-week treatment groups, but were lower in the LDV/SOF 12 Week group.
- At the final analysis, the SVR12 and SVR24 rates were the same within each treatment group, with a 100% positive predictive value between SVR12 and SVR24.
- Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no impact on SVR12 rates.
- The virologic failure rate was low (LDV/SOF 8 Weeks: 5.1%, LDV/SOF+RBV 8 Weeks: 4.2%, and LDV/SOF 12 Weeks: 1.4%). No resistance to SOF or LDV was detected in 21 and 7 of the 23 relapsed subjects, respectively. Virologic failure was associated with single class LDV resistance in 16 (69.6%) of the relapse subjects. The substitutions V320A and L159F in NS5B were each detected in 1 subject with genotype 1a HCV infection at low levels at relapse.
- Treatment with LDV/SOF±RBV was generally well tolerated in this study, with no deaths, few permanent study drug discontinuations due to AEs, few SAEs, few Grade 3 or 4 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 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 LDV/SOF+RBV 8 Week group, as measured by patient-reported outcomes.