FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Open-Label Study to Assess the Efficacy and Safety of Oral Regimens for the Treatment of Chronic HCV Infection
Name of Test Drug:	Ledipasvir (LDV)/sofosbuvir (SOF) Fixed-Dose Combination (FDC) (Harvoni®) SOF/Velpatasvir (VEL; GS-5816) FDC (Epclusa®) Voxilaprevir (VOX; GS-9857)
Dose and Formulation:	LDV/SOF FDC (90/400 mg) tablet SOF/VEL FDC (400/100 mg) tablet VOX 100 mg (1 × 100-mg tablet or 2 × 50-mg tablets)
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-337-1468 (LEPTON)
Phase of Development:	Phase 2
IND No.:	Not Applicable
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02202980
Study Start Date:	04 August 2014 (First Subject Screened)
Study End Date:	09 May 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Edward Gane, MB ChB, MD, FRACP Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	26 August 2016
Previous Report Date:	24 March 2015

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-337-1468
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Open-Label Study to Assess the Efficacy and Safety of Oral Regimens for the Treatment of Chronic HCV Infection

Investigators: Edward Gane, MB ChB, MD, FRACP; Catherine Stedman, MB ChB, FRACP, PhD

Study Centers: 2 sites in New Zealand

Publications:

Gane EJ, Svarovskaia ES, Hyland RH, Stamm LM, Osinusi A, Brainard DM, Chodavarapu K, Miller MD, Mo H, Schwabe C. Resistance Analysis of Treatment-Naive and DAA-Experienced Genotype 1 Patients with and without Cirrhosis Who Received Short-Duration Treatment with Sofosbuvir/GS-5816+ GS-9857 [Poster 713]. J Hepatol 2015;62:563A

Gane EJ, Schwabe C, Hyland RH, Yang Y, Svarovskaia E, Stamm LM, Brainard DM, McHutchison JG, Stedman CA. Efficacy of the Combination of Sofosbuvir, Velpatasvir, and the NS3/4A Protease Inhibitor GS-9857 in Treatment-naïve or Previously Treated Patients with HCV Genotype 1 or 3 Infections. Gastroenterology 2016 May 27; pii: S0016-5085(16)34513-9. doi: 10.1053/j.gastro.2016.05.021. [Epub ahead of print]

Study Period:

04 August 2014 (First Subject Screened)
16 March 2016 (Last Subject Observation for the Primary Endpoint)
09 May 2016 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To evaluate the antiviral efficacy of combination therapy with oral regimens for the treatment of chronic hepatitis C virus (HCV) infection as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of oral regimens administered for up to 24 weeks

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attained SVR at 4 and 24 (as applicable) weeks after discontinuation of therapy (SVR4 and SVR24)

- To evaluate the proportion of subjects with virologic failure
- To evaluate the emergence of viral resistance to ledipasvir (LDV), sofosbuvir (SOF), and other oral direct-acting antivirals (DAA) during treatment and after treatment discontinuation
- To characterize viral dynamics during treatment and after treatment discontinuation

The exploratory objectives of this study were as follows:

- To identify or validate genetic markers that may be predictive of the natural history of disease, virologic response to therapy and/or the tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics), in subjects who provided a separate and specific consent
- To characterize any changes in the extrahepatic manifestations of subjects following treatment for HCV infection
- To characterize steady-state pharmacokinetics (PK) of study drugs

Methodology: This Phase 2, multicenter, open-label study evaluated the safety, tolerability, and antiviral efficacy of oral DAA regimens administered for up to 24 weeks in subjects with chronic HCV infection. Two hundred seventy-three subjects were enrolled into 1 of 5 cohorts.

Cohort 1

Cohort 1 of the study offered additional treatment options to patients who previously received a SOF-containing regimen through participation in P7977-0523, GS-US-337-0122, or GS-US-337-1468 (Cohort 2) studies without achieving SVR. Cohort 1 consisted of 2 groups:

- **Group 1:** Fourteen subjects with HCV received an LDV/SOF tablet once daily and ribavirin (RBV) 1000 or 1200 mg divided twice daily (weight-based) for 24 weeks.
- **Group 2:** Zero subjects with HCV received an LDV/SOF tablet once daily and ribavirin (RBV) 1000 or 1200 mg divided twice daily (weight-based) for 12 weeks.

Subjects in this cohort were initially assigned to Group 1 (24 week duration) or to Group 2 (12 week duration) at the investigator's discretion; however, all subjects in Group 2 following enrollment were moved to Group 1 to receive the 24-week treatment duration.

Cohort 2

Cohort 2 explored the potential efficacy of LDV/SOF in subjects with genotype 2 HCV infection. Up to 40% of the subjects may have been treatment experienced and up to 25% may have been cirrhotic in each group. Cohort 2 consisted of two groups:

- **Group 1:** Twenty-six subjects with genotype 2 HCV infection received an LDV/SOF tablet once daily for 12 weeks.
- **Group 2:** Twenty-seven subjects with genotype 2 HCV infection received an LDV/SOF tablet once daily for 8 weeks.

Group 2 was enrolled only if the SVR4 rate for Group 1 was > 90%.

Cohort 3

Cohort 3 assessed the potential of LDV/SOF treatment to provide symptomatic relief to subjects with extrahepatic manifestations of HCV in addition to offering the potential to achieve SVR. Cohort 3 consisted of two groups:

- **Group 1:** Thirty-two subjects with genotype 1, 2, or 4 HCV infection and extrahepatic manifestations of chronic HCV infection received an LDV/SOF tablet once daily for 12 weeks.
- **Group 2:** Thirteen subjects with genotype 3 HCV infection and extrahepatic manifestations of chronic HCV infection received an LDV/SOF tablet once daily and RBV 1000 or 1200 mg divided twice daily (weight-based) for 12 weeks.

Extrahepatic manifestations included HCV-associated cases of non-Hodgkin's lymphoma, cryoglobulinemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, lichen planus, porphyria cutanea tarda (PCT), psoriasis, and cryoglobulin-negative HCV-related immune complex glomerulonephritis.

Cohort 4

Cohort 4 assessed the safety, efficacy, and PK of SOF/velpatasvir (VEL) + voxilaprevir (VOX) in subjects with genotype 1 HCV infection without cirrhosis to assist with the dose selection of VOX. Cohort 4 consisted of one group:

- **Group 1:** Fifteen treatment-naive subjects with genotype 1 HCV infection without cirrhosis received VOX 100 mg with food on Day 1. Following Day 1, subjects received SOF/VEL fixed-dose combination (FDC) (400/100 mg) + VOX 100 mg daily with food for 6 weeks.

Cohort 5

Cohort 5 assessed the safety and efficacy of SOF/VEL FDC (400/100 mg) + VOX 100 mg in subjects with genotype 1 or 3 HCV infection with or without cirrhosis. Data from Cohort 4 as well as the Phase 1b proof of concept study guided dose selection for Cohort 5. Cohort 5 consisted of 8 groups:

- **Group 1:** Fifteen treatment-naive subjects with genotype 1 HCV infection without cirrhosis received SOF/VEL+VOX once daily with food for 4 weeks.
- **Group 2:** Fifteen treatment-naive subjects with genotype 1 HCV infection with cirrhosis received SOF/VEL+VOX once daily with food for 6 weeks.
- **Group 3:** Eighteen treatment-naive subjects with genotype 3 HCV infection with cirrhosis received SOF/VEL+VOX once daily with food for 6 weeks.
- **Group 4:** Seventeen pegylated interferon (Peg-IFN) + RBV treatment-experienced subjects with genotype 1 HCV infection with cirrhosis received SOF/VEL+VOX once daily with food for 8 weeks.
- **Group 5:** Nineteen Peg-IFN+RBV treatment-experienced subjects with genotype 3 HCV infection with cirrhosis received SOF/VEL+VOX once daily with food for 8 weeks.

- **Group 6:** Twenty-eight nonstructural protein (NS)3/4A protease inhibitor (PI) treatment-experienced subjects with genotype 1 HCV infection with or without cirrhosis received SOF/VEL+VOX once daily with food for 8 weeks. Approximately 50% of subjects enrolled may have had cirrhosis.
- **Group 7:** Thirty DAA treatment-experienced subjects with genotype 1 HCV infection with or without cirrhosis received SOF/VEL+VOX once daily with food for 6 weeks. Approximately 50% of subjects enrolled may have had cirrhosis.
- **Group 8:** Four DAA treatment-experienced subjects with genotype 3 HCV infection with or without cirrhosis received SOF/VEL+VOX once daily with food for 8 weeks. Approximately 50% of subjects enrolled may have had cirrhosis.

A previously submitted interim synoptic clinical study report (24 March 2015) presented efficacy (SVR12) and safety results for subjects enrolled in Cohort 2, Group 1, collected through 19 February 2015.

Number of Subjects (Planned and Analyzed):
Planned: Up to 300 subjects
Analyzed:
Safety Analysis Set: 273 subjects
Full Analysis Set (FAS): 273 subjects

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

Duration of Treatment: Up to 24 weeks

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

- **LDV/SOF (90/400 mg)** was administered orally as 1 FDC tablet once daily.
- **VOX 50 mg** was administered orally as 2 tablets once daily.
- **VOX 100 mg** was administered orally as 1 tablet once daily.
- **SOF/VEL (400/100 mg)** was administered orally as 1 FDC tablet once daily.
- **RBV 1000 or 1200 mg** (generic) was administered orally as 5 × 200-mg tablets or 6 × 200-mg tablets, respectively, divided twice daily.

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

- **LDV/SOF**: DK1302B1, DK1304B1, DK1313B3, DK1309B1
- **VOX 50 mg**: DY1403B1
- **VOX 100 mg**: DY1407B1, DY1407B2
- **SOF/VEL**: DU1403B1
- **RBV**: A97943Z, AB7658Z

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

Criteria for Evaluation:

Efficacy: Efficacy was evaluated using scheduled assessments of HCV RNA performed using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: A single PK blood sample was collected at each on-treatment visit except on day 1 for all subjects in Cohorts 2, 3, 4, and 5.

Cohort 4 subjects participated in an intensive serial PK substudy performed on Day 0 to Day 3 and at the Week 2 on-treatment visit for additional intensive serial PK collection. Serial PK samples were collected over 24 hours postdose.

Cohort 5 subjects may have been eligible to participate in an optional intensive PK substudy performed at any time on or between the Week 2 or Week 4 on-treatment visits. Serial PK samples were collected over 24 hours postdose.

The PK of SOF (and its metabolites GS-566500 and GS-331007), LDV, VEL, and VOX were assessed.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, electrocardiograms (ECGs), vital sign measurements, physical examinations, and monitoring of extrahepatic manifestations (Cohort 3 only).

Statistical Methods:

Efficacy: The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) for the FAS. A 2-sided 95% CI based on the Clopper-Pearson method was provided for the SVR12 rate in each treatment group. Secondary efficacy endpoints included the proportion of subjects with SVR4 and SVR24, the proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline during treatment, the proportion of subjects with virologic failure, and the characterization of HCV drug resistance substitutions at baseline, during, and after treatment. An exploratory efficacy endpoint included changes in the extrahepatic manifestations of subjects following treatment for HCV infection compared with Day 1.

Pharmacokinetics: The pharmacokinetics of SOF, its metabolites (GS-566500 and GS-331007), VEL, and VOX were assessed over a 24-hour dosing interval in all subjects enrolled in Cohort 4 (Days 1, 2, and Week 2), and in subjects in Cohort 5 who participated in the optional PK substudy at the Week 2 or Week 4 on-treatment visit. Pharmacokinetic parameters were derived using noncompartmental methods using WinNonlin® software. For each subject, the following PK parameters were calculated: AUC_{tau}, C_{last}, C_{max}, C_{tau}, CL_{ss}/F, $t_{1/2}$, T_{last}, T_{max}, V_z/F, and λ_z.

Descriptive statistics (sample size, mean, SD, percent CV, median, first quartile, third quartile, minimum, maximum, and geometric mean and its 95% CI) were summarized for PK concentration data and PK parameter data by treatment group and day.

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, ECGs, vital sign measurements, physical examinations, and monitoring of extrahepatic manifestations (Cohort 3 only). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

Cohort 1: A total of 14 subjects who were treatment-experienced with a SOF-based regimen were enrolled in Cohort 1. All subjects completed study treatment of 24 weeks with LDV/SOF+RBV.

The majority of subjects were male (71.4%) and white (71.4%), and all (100%) were non-Hispanic/Latino. The mean age was 56 years with a range of 35 to 65 years. The mean baseline BMI was 27.0 kg/m^2, and 28.6% of subjects had a BMI $\geq$ 30 kg/m^2.

Half of the subjects had genotype 2 HCV infection (50.0%) and did not have cirrhosis (71.4%). One-half of the subjects had the IL28B CC genotype and one-half had the CT genotype. The mean baseline HCV RNA was 6.5 $\log_{10}$ IU/mL. Most subjects had baseline HCV RNA $\geq$ 800,000 IU/mL (92.9%) and most had baseline alanine aminotransferase (ALT) values $\leq$ 1.5 × the upper limit of normal (ULN) (57.1%). The mean baseline estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation was 121.1 mL/min. Seven subjects had previously been treated with LDV/SOF for 8 weeks, 2 subjects had previously been treated with LDV/SOF for 12 weeks, and 5 subjects had previously been treated with LDV/SOF+RBV for 12 weeks.

Cohort 2: A total of 53 treatment-naive and treatment-experienced subjects with genotype 2 HCV infection with and without cirrhosis were enrolled and randomized in Cohort 2. Twenty-six subjects in Group 1 received LDV/SOF for 12 weeks, and 27 subjects in Group 2 received LDV/SOF for 8 weeks. Twenty-five of the enrolled subjects (96.2%) in Group 1 completed 12 weeks of treatment with LDV/SOF; 1 subject withdrew consent and prematurely discontinued from the study after receiving 1 dose of study drug. All subjects in Group 2 completed study treatment.

Overall in Cohort 2, the majority of subjects were male (67.9%) and white (84.9%), and all (100.0%) were non-Hispanic/Latino. The mean age was 54 years with a range of 28 to 75 years. The mean baseline BMI of subjects was 26.0 kg/m^2, and 18.9% of subjects had a BMI $\geq$ 30 kg/m^2.

All subjects in Cohort 2 had genotype 2 HCV infection. Across treatment groups, 2 subjects (3.8%), both in Group 1, had cirrhosis. Approximately one-half of the subjects had the IL28B CC genotype (45.3%) and approximately one-half had the CT genotype (47.2%). The mean baseline HCV RNA value of subjects was 6.3 $\log_{10}$ IU/mL, and 37 (69.8%) had HCV RNA $\geq$ 800,000 IU/mL. The majority of subjects were naive to prior HCV treatment (77.4%).

Cohort 3: Cohort 3 consisted of treatment-naive and treatment-experienced subjects with genotypes 1, 2, 3, or 4 HCV infection with extrahepatic manifestations of chronic HCV infection. A total of 45 subjects were enrolled in Cohort 3, Groups 1 and 2. Thirty-two subjects in Group 1 had genotype 1, 2, or 4 HCV infection, and 13 subjects in Group 2 had genotype 3 HCV infection. All subjects completed study treatment.

Overall in Cohort 3, the majority of subjects were male (71.1%) and white (84.4%), and all (100.0%) were non-Hispanic/Latino. The mean age was 57 years with a range of 39 to 79 years.

The mean baseline BMI of subjects was 26.7 kg/m^2, and 22.2% of subjects had a BMI ≥ 30 kg/m^2.

The majority of subjects in Group 1 had genotype 1 HCV infection (96.9%) without cirrhosis (71.9%), and all subjects in Group 2 had genotype 3 HCV infection, the majority of whom had cirrhosis (76.9%). The majority of subjects across both groups had IL28B non-CC genotypes (75.6%). The mean baseline HCV RNA was 6.1 log_{10} IU/mL. Most subjects had baseline HCV RNA ≥ 800,000 IU/mL (73.3%). The majority of subjects with genotype 1 or 4 HCV infection in Group 1 had baseline ALT values ≤ 1.5 × ULN (65.6%), whereas most subjects with genotype 3 HCV infection in Group 2 had baseline ALT values > 1.5 × ULN (69.2%). Overall, the mean baseline eGFR using the Cockcroft-Gault equation was 106.0 mL/min.

The majority of subjects in Group 1 were treatment-naive (53.1%). The treatment-experienced subjects had primarily been treated with Peg-IFN+RBV (80.0%). Of these subjects, 58.3% had a relapse/breakthrough outcome, and 41.7% were nonresponders. The majority of subjects in Group 2 were treatment-experienced (76.9%), most of whom had been treated with Peg-IFN+RBV (80.0%). Of these subjects, 62.5% had a relapse or breakthrough outcome, and 37.5% were nonresponders. All subjects for whom data was available, with the exception of 3 subjects in Group 1 and 1 subject in Group 2, had been treated for > 12 weeks with the most recent prior HCV treatment.

The most frequent extrahepatic manifestations of HCV were PCT (33.3%), psoriasis (31.1%) and cryoglobulinemia (28.9%).

Cohorts 4 and 5: Cohorts 4 and 5 enrolled 161 treatment-naive and treatment-experienced subjects with genotypes 1 or 3 HCV infection with or without cirrhosis at 2 sites in New Zealand. All subjects completed study treatment. Of the 161 subjects who completed study treatment, 1 subject had HCV RNA results at the posttreatment Week 4 visit but not at the posttreatment Week 12 visit; this subject withdrew consent. A total of 128 subjects (79.5%) completed the study and 33 subjects (20.5%) prematurely discontinued the study: 29 subjects (18.0%) discontinued due to lack of efficacy, 3 subjects (1.9%) were lost to follow-up, and 1 subject (0.6%) withdrew consent.

Across treatment groups, the majority of subjects were male (70.2%; range: 46.7%−100.0%), white (87.0%; range: 66.7%−94.7%), and non-Hispanic/Latino (99.4%; range: 93.3%−100.0%). The mean age was 55 years (range: 50−59 years). The mean baseline BMI was 27.3 kg/m^2, and 27.3% of subjects had a BMI ≥ 30 kg/m^2. In treatment groups with genotype 1 HCV infection, the majority of subjects had the genotype 1a subtype (range: 70.0%−88.2%), followed by the genotype 1b subtype (range: 6.7%−26.7%). In the groups with a plan to enroll approximately 50% of subjects with cirrhosis (Cohort 5, Groups 6 through 8), 16.7% to 50.0% had cirrhosis. Across all treatment groups, the majority of subjects had IL28B non-CC genotypes (65.8%). The mean baseline HCV RNA was 6.2 log_{10} IU/mL (range: 6.0−6.9 log_{10} IU/mL) and most subjects across treatment groups had HCV RNA ≥ 800,000 IU/mL (75.8%). The mean baseline eGFR using the Cockcroft-Gault equation across treatment groups was 114.8 mL/min (range: 100.8−126.6 mL/min).

All 63 subjects in Cohort 4 and Cohort 5, Groups 1, 2, and 3, were treatment-naive. All 36 subjects in Cohort 5, Groups 4 and 5, previously received treatment with a Peg-IFN+RBV regimen. The majority of these subjects had received > 12 weeks of their most recent prior HCV

treatment (88.2%−100.0%). All 28 subjects in Cohort 5, Group 6, had previously received treatment with an NS3/4A PI. The majority of subjects had received > 12 weeks of their most recent prior HCV treatment (85.7%). All 34 subjects in Cohort 5, Groups 7 and 8, had previously been treated with at least 2 DAAs. The majority of subjects with genotype 1 HCV infection in Group 7 (86.7%; 26 of 30 subjects) had received treatment with an NS5B inhibitor and an NS3/4A PI. The majority of these subjects had received ≤ 12 weeks of their most recent prior HCV treatment (73.3%). Of the 4 subjects with genotype 3 HCV infection in Group 8, 2 subjects received previous treatment with an NS5A inhibitor with an NS5B inhibitor (50.0%), 1 subject received an NS5A inhibitor alone (25.0%), and 1 subject received an NS5B inhibitor alone (25.0%). The majority had received ≤ 12 weeks of their most recent prior HCV treatment (75.0%).

Efficacy Results:

Cohort 1: Cohort 1 consisted of subjects who had previously received LDV/SOF in Studies P7977-0523, GS-US-337-0122, or Cohort 2 in GS-US-337-1468 without achieving SVR. These treatment-experienced subjects were treated with LDV/SOF+RBV for 24 weeks. In this population, 13 of 14 subjects (92.9%) achieved SVR12. One subject with genotype 3 infection without cirrhosis who previously failed treatment with LDV/SOF+RBV relapsed after achieving SVR2. The SVR4, SVR12, and SVR24 rates were 100% concordant.

Potent and rapid suppression of HCV RNA while on treatment was observed. All subjects had HCV RNA < LLOQ by Week 4 of treatment. The 1 subject that relapsed had experienced breakthrough at Week 16 and subsequently had HCV RNA < LLOQ at Week 24. All subjects had HCV RNA < LLOQ at the end of treatment.

The small number of subjects precludes meaningful interpretation of subgroup analyses.

Virologic Resistance Analysis:

Ten of 14 subjects had pretreatment NS5A LDV-specific resistance-associated variants (RAVs) and all achieved SVR12.

The 1 subject who relapsed had NS5B nucleoside inhibitor (NI) RAVs L159F and E237G that emerged at the time of virologic failure in the parental study. This subject relapsed after retreatment with LDV/SOF+RBV for 24 weeks at which time L159F was enriched at relapse. No other NS5B NI or NS5A LDV-specific RAVs were detected in this subject.

Cohort 2: Among treatment-naive and treatment-experienced subjects with genotype 2 HCV infection with and without cirrhosis SVR rates were higher in those who received LDV/SOF for 12 weeks (96.2%; 25 of 26 subjects) compared to those who received LDV/SOF for 8 weeks (74.1%; 20 of 27 subjects).

No subjects had virologic failure after receiving treatment with LDV/SOF for 12 weeks; all subjects achieved SVR12 except for 1 subject who withdrew consent and discontinued the study after receiving a single dose of LDV/SOF. Six subjects relapsed after receiving treatment with LDV/SOF for 8 weeks. One additional subject who received LDV/SOF for 8 weeks, who did not achieve SVR12, had not achieved HCV RNA < LLOQ at the end of treatment and therefore was not part of the relapse population.

For all subjects, treatment with LDV/SOF led to rapid reduction of HCV RNA which was maintained through the end of treatment.

The SVR4 and SVR24 results for subjects receiving treatment with LDV/SOF for 12 weeks were the same as the SVR12 results. Two of the virologic relapses in subjects receiving treatment with LDV/SOF for 8 weeks occurred between posttreatment Weeks 4 and 12. For both treatment durations, SVR12 was 100% concordant with SVR24.

The small number of subjects precludes meaningful interpretation of subgroup analyses.

Virologic Resistance Analysis

All subjects with HCV genotype 2 infection and pretreatment NS5A and NS5B RAVs who received LDV/SOF for 12 weeks achieved SVR12. Numerically lower SVR12 rates were observed in subjects infected with genotype 2a HCV infection (33.3%, 2 of 6 subjects) compared with genotype 2b HCV infection (94.7%, 18 of 19 subjects) in subjects treated for 8 weeks. There was a higher prevalence of NS5A LDV-specific RAVs in subjects with genotype 2a infection compared with genotype 2b HCV infection, therefore, it is not clear whether lower SVR12 in subjects who were treated for 8 weeks was associated with genotype 2a or pretreatment NS5A LDV-specific RAVs, or both due to the small number of subjects treated for 8 weeks. No NS5A and NS5B RAVs emerged in any the subjects at virologic failure.

Cohort 3: All 32 subjects with genotype 1, 2, or 4 HCV infection achieved SVR12 following 12 weeks of treatment with LDV/SOF, and 10 of 13 subjects with genotype 3 HCV infection (76.9%) achieved SVR12 following 12 weeks of treatment with LDV/SOF+RBV. The 3 subjects, treated with LDV/SOF+RBV that did not achieve SVR, relapsed.

For all subjects, treatment with LDV/SOF or LDV/SOF+RBV led to rapid reduction of HCV RNA which was maintained through Week 12.

Improvements were reported in the extrahepatic manifestations of PCT and psoriasis at Week 12 and posttreatment Week 12. For the other classes of extrahepatic manifestation, the small number of subjects precluded meaningful interpretation of any changes in symptoms.

The small number of subjects precludes meaningful interpretation of subgroup analyses.

Virologic Resistance Analysis

Pretreatment NS5A LDV-specific RAVs were detected in 4 of 39 subjects in Cohort 3. All subjects with NS5A LDV-specific RAVs achieved SVR12 after receiving 12 weeks of LDV/SOF (2 subjects with genotype 1 HCV infection) or LDV/SOF+RBV (2 subjects with genotype 3 HCV infection). No NS5B NI RAVs were detected in any subjects.

There were no virologic failures in Cohort 3, Group 1. There were 3 subjects with genotype 3 with virologic failure after receiving 12 weeks of LDV/SOF+RBV in Cohort 3, Group 2. No pretreatment or posttreatment NS5A LDV-specific RAVs were detected in the 3 subjects with virologic failure. One subject had treatment emergent NS5B NI RAVs L159F (1.6%) and V321A (2.0%) at relapse. No other NS5B NI RAVs were detected in the other two subjects who relapsed.

Cohorts 4 and 5: Across groups, SVR12 rates ranged from 26.7% to 100.0% and relapse was more common with the shorter treatment durations of 4 or 6 weeks.

- Fourteen of 15 noncirrhotic treatment-naive subjects (93.3%) with genotype 1 HCV infection and who received SOF/VEL+VOX for 6 weeks achieved SVR12 (Cohort 4).

- Four of 15 noncirrhotic treatment-naive subjects (26.7%) with genotype 1 HCV infection and who received SOF/VEL+VOX for 4 weeks achieved SVR12 (Cohort 5, Group 1).
- Thirteen of 15 cirrhotic treatment-naive subjects (86.7%) with genotype 1 HCV infection and who received SOF/VEL+VOX for 6 weeks achieved SVR12 (Cohort 5, Group 2).
- Fifteen of 18 cirrhotic treatment-naive subjects (83.3%) with genotype 3 HCV infection and who received SOF/VEL+VOX for 6 weeks achieved SVR12 (Cohort 5, Group 3).

The SVR12 rate for treatment-experienced subjects ranged from 66.7% to 100.0%.

- All subjects who had received prior treatment with a Peg-IFN+RBV (36 of 36 subjects), with either genotype 1 or 3 HCV infection, and who received SOF/VEL+VOX for 8 weeks achieved SVR12 (Cohort 5, Groups 4 and 5).
- Twenty-five of 28 subjects with genotype 1 HCV infection who had received prior treatment with an NS3/4A PI and who received SOF/VEL+VOX for 8 weeks achieved SVR12 (Cohort 5, Group 6).
- Twenty of 30 subjects with genotype 1 HCV infection who had received prior treatment with 2 or more DAAs and who received SOF/VEL+VOX for 6 weeks achieved SVR12 (Cohort 5, Group 7).
- All subjects (4 of 4) with genotype 3 HCV infection who received prior treatment with 2 or more DAAs and who received SOF/VEL+VOX for 8 weeks achieved SVR12 (Cohort 5, Group 8).

Seventeen treatment-naive subjects did not achieve SVR12. Eleven subjects relapsed who received treatment with SOF/VEL+VOX for 4 weeks, and 5 subjects relapsed who received treatment with SOF/VEL+VOX for 6 weeks. One subject who received SOF/VEL+VOX for 6 weeks and did not achieve SVR12 withdrew consent in the posttreatment period.

Thirteen treatment-experienced subjects did not achieve SVR12. Three subjects relapsed who had received prior treatment with an NS3/4A PI and received treatment with SOF/VEL+VOX for 8 weeks, and 9 subjects relapsed who had received prior treatment with 2 or more DAAs and received treatment with SOF/VEL+VOX for 6 weeks. For all subjects, treatment with SOF/VEL+VOX led to rapid reduction of HCV RNA. One treatment-experienced subject who did not achieve SVR12 had not achieved HCV RNA < LLOQ at the end of treatment. All other subjects achieved HCV RNA < LLOQ at the last on-treatment visit.

The small number of subjects precludes meaningful interpretation of subgroup analyses.

Virologic Resistance Analysis

Seventy-nine of 159 subjects (49.7%) had baseline RAVs in at least 1 of the 3 target genes (NS3, NS5A, or NS5B). The presence of baseline RAVs did not impact the SVR12 rates in the treatment-naive or treatment-experienced subjects of Cohorts 4 and 5.

None of the 26 subjects who relapsed had NS5B NI treatment-emergent RAVs. One subject had an NS3 RAV V55A emerge at the time of relapse, and 1 had an NS5A RAV Y93H emerge at the time of relapse. NS3 V55A does not confer any reduced susceptibility to VOX in the genotype 1a replicon assay. NS5A Y93H confers reduced susceptibility to VEL.

Pharmacokinetics Results:

Cohorts 4 and 5: PK results from Cohort 4, Days 1 and 2, indicated that the drug-drug interaction observed between VOX and SOF/VEL in Study GS-US-338-1130 (Cohort 1, fasted healthy volunteers), which resulted in decreased VOX exposure, was not observed when SOF/VEL and VOX were coadministered with food to subjects with HCV infection.

For 72 subjects in Cohorts 4 and 5 who participated in the intensive PK substudy, steady-state SOF, GS-566500, GS-331007, and VEL exposures were similar in subjects regardless of cirrhosis status. Mean steady-state VOX exposure was modestly higher (< 2-fold) in subjects with cirrhosis than in subjects without cirrhosis (mean [%CV] AUC_{tau} 4613.8 [69.9] h•ng/mL vs 2498.4 [55.1] h•ng/mL and C_{max} 549.4 [73.5] ng/mL vs 333.3 [66.2] ng/mL, respectively).

Safety Results:

Cohort 1: The majority of LDV/SOF-experienced subjects who received LDV/SOF+RBV for 24 weeks had at least 1 AE (85.7%; 12 of 14 subjects), all of which were Grade 1 or 2. The most common AEs were headache (42.9%; 6 of 14 subjects), and nausea and upper respiratory tract infection (28.6% each; 4 of 14 subjects). Two subjects (14.3%) had serious adverse events (SAEs). One subject had 2 SAEs of nausea and gastroenteritis; the nausea was assessed as related to study drug by the investigator and led to premature discontinuation of RBV. One subject had an SAE of a fall that was considered by the investigator to be unrelated to study drug. No Grade 3 or 4 AEs, deaths, or pregnancies were reported.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Grade 3 decreased hemoglobin was reported in 2 of 14 subjects (14.3%). There were no Grade 4 hematology laboratory abnormalities and no other Grade 3 hematology abnormalities were observed. Grade 4 ALT and Grade 3 aspartate aminotransferase increased levels were experienced by 1 subject in the context of virologic relapse, and 1 subject had a Grade 3 increased creatine kinase attributed by the investigator to exercise. No other Grade 3 or Grade 4 chemistry abnormalities were observed. There were no AEs associated with the Grade 3 or Grade 4 hematology or chemistry laboratory values. No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study. No clinically significant abnormal 12-lead ECGs were reported.

Cohort 2: The majority of treatment-naive and treatment-experienced subjects with genotype 2 HCV infection with and without cirrhosis who received LDV/SOF for 8 or 12 weeks experienced at least 1 AE (75.5%; 40 of 53 subjects). Overall, the most common AEs were headache (24.5%; 13 of 53 subjects), fatigue (20.8%; 11 of 53 subjects), and nausea (17.0%; 9 of 53 subjects).

There were 3 Grade 3 or Grade 4 AEs reported, all of which were also SAEs and were assessed as unrelated to study drug by the investigator. One subject receiving LDV/SOF for 8 weeks experienced Grade 3 bipolar I disorder and 1 subject receiving LDV/SOF for 12 weeks experienced Grade 3 gastroesophageal reflux disease. One subject receiving LDV/SOF for 8 weeks experienced Grade 4 atrial fibrillation. No AEs led to permanent discontinuation from LDV/SOF and no deaths or pregnancies were reported.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. An unconfirmed Grade 3 decreased hemoglobin was reported in 1 of 53 subjects (1.9%). which was not associated with an AE. There were no Grade 4 hematology laboratory abnormalities. There were no Grade 3 or 4 chemistry laboratory abnormalities reported during the study.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study. No clinically significant abnormal 12-lead ECGs were reported.

Cohort 3: The majority of subjects with genotype 1, 2, 3, or 4 HCV infection who received LDV/SOF or LDV/SOF+RBV for 12 weeks experienced at least 1 AE (86.7%; 39 of 45 subjects). The most common AEs were upper respiratory tract infection (17.8%; 8 of 45 subjects), headache (15.6%; 7 of 45 subjects), and nausea and fatigue (13.3% each; 6 of 45 subjects).

Five subjects had 7 SAEs. Three subjects with genotype 1, 2, or 4 HCV infection receiving LDV/SOF experienced one SAE each (Grade 2 Meniere's disease, Grade 2 pneumonia, and Grade 2 renal colic). Two subjects with genotype 3 HCV infection receiving LDV/SOF+RBV experienced SAEs; 1 subject experienced Grade 2 lower respiratory tract infection, and 1 subject experienced Grade 3 acute kidney injury, Grade 3 hyperglycemia, and Grade 2 confusional state. All SAEs were assessed as unrelated to study drug by the investigator. No AEs led to permanent discontinuation from LDV/SOF and/or RBV and no deaths or pregnancies were reported.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. All Grade 3 or 4 hematology laboratory abnormalities were reported in subjects receiving LDV/SOF+RBV. Grade 3 decreased hemoglobin was reported in 2 of 45 subjects (4.4%). Grade 4 decreased lymphocytes was reported in 2 of 45 subjects (4.4%). AEs of hemolytic anemia were associated with 2 of the decreased hemoglobin abnormalities. One subject with genotype 3 HCV infection and a medical history of diabetes mellitus receiving LDV/SOF+RBV experienced a Grade 3 increased glucose level at posttreatment Week 4. No other Grade 3 or 4 laboratory abnormalities were observed.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study. There were no clinically significant abnormal 12-lead ECGs.

Cohorts 4 and 5: The majority of treatment-naive and treatment-experienced subjects with genotypes 1 or 3 HCV infection with or without cirrhosis who received SOF/VEL+VOX for 4, 6, or 8 weeks subjects reported at least 1 AE (79.5%; 128 of 161 subjects). The most common AEs for both treatment-naive and treatment-experienced subjects across all treatment groups were headache (23.0%; 37 of 161 subjects), nausea (20.5%; 33 of 161 subjects), and fatigue (17.4%; 28 of 161 subjects). There were no Grade 3 or 4 AEs. Treatment-related AEs were observed in 42.9% of subjects across all treatment groups. There was no trend in AEs with regard to prior treatment experience, cirrhosis status, or treatment duration.

Three SAEs were reported. One treatment-experienced subject with genotype 1 HCV infection receiving SOF/VEL+VOX for 8 weeks experienced Grade 2 atrial fibrillation, 1 subject with genotype 3 HCV infection and cirrhosis receiving SOF/VEL+VOX for 8 weeks experienced Grade 1 bladder transitional cell carcinoma, and 1 subject with genotype 3 HCV infection and cirrhosis receiving SOF/VEL+VOX for 8 weeks experienced Grade 2 hepatocellular carcinoma. All SAEs were assessed as unrelated to study drug by the investigator. No AEs led to permanent discontinuation of SOF/VEL+VOX and no deaths or pregnancies were reported.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Eighteen of

161 subjects (11.1%) in Cohorts 4 and 5 had at least 1 Grade 3 or 4 laboratory abnormality. The majority of these abnormalities were Grade 3 (15 subjects; 9.3%) and 3 subjects (1.9%) had Grade 4 laboratory abnormalities. No Grade 3 or 4 laboratory abnormality was reported as an AE.

Four subjects had 5 Grade 3 hematology laboratory abnormalities, including decreased neutrophils, decreased platelets, and decreased white blood cells. There were no clinically meaningful changes in hemoglobin or reticulocyte values during treatment with SOF/VEL+VOX. Chemistry laboratory abnormalities included 7 subjects with Grade 3 (6 subjects) or Grade 4 (1 subject) increased lipase, none of which were associated with symptoms of pancreatitis; 6 subjects with Grade 3 increased glucose, all but one of whom had a medical history of diabetes; 2 subjects with Grade 4 increased creatine kinase, both attributed by the investigator to exercise; and 1 subject with a single Grade 3 increased AST associated with a concurrent Grade 4 exercise-induced creatine kinase elevation. There were no clinically meaningful changes in ALT or total bilirubin values during treatment with SOF/VEL+VOX.

No notable changes from baseline in vital signs were observed during the study. No clinically significant abnormal 12-lead ECGs were reported.

CONCLUSIONS:

Cohort 1

- Retreatment with LDV/SOF+RBV for 24 weeks in subjects who had previously received an LDV/SOF±RBV regimen for 8 or 12 weeks resulted in 13 of 14 subjects (92.9%) achieving SVR12.
- All subjects (10 of 14, 71.4%) with preexistent NS5A LDV-specific RAVs achieved SVR12 following treatment with LDV/SOF+RBV for 24 weeks. NS5B NI RAVs, but not NS5A RAVs, were detected in the single subject who relapsed.
- Treatment with LDV/SOF+RBV for 24 weeks was generally safe and well tolerated.

Cohort 2

- The SVR12 rate for subjects with genotype 2 HCV infection who received LDV/SOF for 12 weeks was 96.2% (25 of 26 subjects). No subject experienced virologic failure.
- SVR12 rate for subjects with genotype 2 HCV infection who received LDV/SOF for 8 weeks was 74.1% (20 of 27 subjects). Six of 27 subjects relapsed after receiving treatment with LDV/SOF for 8 weeks.
- Among subjects treated for 12 weeks with LDV/SOF, high rates of SVR12 were observed with or without baseline LDV-specific RAVs. Lower SVR12 rates were observed in subjects treated with 8 weeks infected with genotype 2a HCV infection (33.3%, 2 of 6 subjects) compared with genotype 2b HCV infection (94.7%, 18 of 19 subjects) possibly due to the higher prevalence of NS5A LDV-specific RAVs in subjects with genotype 2a HCV infection.
- Treatment with LDV/SOF for 8 or 12 weeks was generally safe and well tolerated.

Cohort 3

- All 32 subjects with genotype 1, 2, or 4 HCV infection achieved SVR12 following 12 weeks of treatment with LDV/SOF, and 10 of 13 subjects (76.9%) with genotype 3 HCV infection achieved SVR12 following 12 weeks of treatment with LDV/SOF+RBV.

- Improvements were observed in the extrahepatic manifestations of PCT and psoriasis at Week 12 and posttreatment Week 12. For the other classes of extrahepatic manifestation, the small number of subjects precluded meaningful interpretation of any changes in symptoms.
- Among the 3 subjects with genotype 3 HCV infection who relapsed following treatment with LDV/SOF+RBV, no NS5A LDV-specific RAVs were detected at baseline or posttreatment and 1 of 3 subjects had NS5B NI RAVs (L159F and V321A) that emerged posttreatment.
- Treatment with LDV/SOF with or without RBV for 12 weeks in subjects with extrahepatic manifestations of HCV was generally safe and well tolerated.

Cohorts 4 and 5

- For treatment-naive subjects without cirrhosis and with genotype 1 HCV infection, treatment with SOF/VEL+VOX for 4 and 6 weeks resulted in SVR12 rates of 26.7% (4 of 15 subjects) and 93.3% (14 of 15 subjects), respectively.
- For treatment-naive subjects with cirrhosis, treatment with SOF/VEL+VOX for 6 weeks resulted in SVR12 rates of 86.7% (13 of 15 subjects) and 83.3% (15 of 18 subjects) in subjects with genotype 1 and genotype 3 HCV infection, respectively.
- SOF/VEL+VOX administered for 8 weeks to subjects with cirrhosis and previously treated with Peg-IFN+RBV resulted in 100% SVR12 for subjects with genotype 1 or genotype 3 HCV infection (17 of 17 and 19 of 19 subjects, respectively).
- SOF/VEL+VOX administered for 8 weeks to subjects with genotype 1 HCV infection with or without cirrhosis and previously treated with an NS3/4A PI resulted in an SVR12 rate of 89.3% (25 of 28 subjects).
- In subjects previously treated with 2 or more DAAs with or without cirrhosis, 6 weeks of treatment with SOF/VEL+VOX resulted in an SVR12 rate of 66.7% (20 of 30 subjects) for subjects with genotype 1 HCV infection, and 8 weeks of treatment with SOF/VEL+VOX resulted in an SVR12 rate of 100% (4 of 4 subjects) for subjects with genotype 3 HCV infection.
- The presence of baseline RAVs did not impact SVR12 rates for treatment-naive or treatment-experienced subjects who received SOF/VEL+VOX for 4, 6, or 8 weeks.
- None of the subjects who experienced virologic relapse had treatment-emergent NS5B NI RAVs. At the time of relapse, 1 subject had a treatment-emergent NS3 RAV (V55A) and 1 subject had a treatment-emergent NS5A RAV (Y93H).
- SOF, GS-566500, GS-331007 and VEL steady-state exposures were similar in all subjects in the intensive PK substudy, regardless of cirrhosis status. Mean steady-state VOX exposure was modestly higher (< 2-fold) in subjects with cirrhosis relative to subjects without cirrhosis.
- Treatment with SOF/VEL+VOX for 4, 6, or 8 weeks in treatment-naive and treatment-experienced subjects with genotypes 1 or 3 HCV infection with or without cirrhosis was generally safe and well tolerated.