FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Open-Label Study to Assess the Efficacy and Safety of Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection
Name of Test Drug:	Ledipasvir/Sofosbuvir fixed-dose combination (FDC); Sofosbuvir; Velpatasvir (GS-5816); GS-9669
Dose and Formulation:	Ledipasvir/Sofosbuvir FDC (90/400 mg) tablet; Sofosbuvir 400-mg tablet; Velpatasvir 25- and 100-mg tablets; GS-9669 250-mg tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-337-0122 (ELECTRON-2)
Phase of Development:	Phase 2
IND No.:	Not Applicable
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT01826981
Study Start Date:	03 April 2013 (First Subject Screened)
Study End Date:	25 May 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Edward Gane, MB ChB, MD, FRACP Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Phillip S. Pang, MD, PhD Telephone: PPD
Report Date:	25 August 2015
Previous Report Date(s):	06 March 2015 (Interim 2 Clinical Study Report) 06 January 2014 (Interim Synoptic Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-337-0122
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 Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection

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

Study Centers: 1 center in Auckland, New Zealand; 1 center in Christchurch, New Zealand

Publications:

Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia ES, Pang PS, Symonds WT. Once Daily Sofosbuvir/Ledipasvir Fixed-Dose Combination with or without Ribavirin: the ELECTRON Trial. Hepatology, 58: 4 (suppl) 243A. October 2013 (AASLD 2013).

Gane EJ, Hyland RH, An D, Pang PS, Symonds WT, McHutchison JG, Stedman CA. Sofosbuvir/Ledipasvir Fixed Dose Combination is Safe and Effective in Difficult-To-Treat Populations Including Genotype-3 Patients, Decompensated Genotype-1 Patients, and Genotype-1 Patients with Prior Sofosbuvir Treatment Experience. Hepatology, 60: 4 (suppl) S3-S4. April 2014 (EASL 2014).

Gane EJ, Hyland RH, An D, Svarovskaia ES, Pang PS, Symonds, WT, McHutchison JG, Stedman CA. High Efficacy of LDV/SOF Regimens for 12 Weeks for Patients with HCV Genotype 3 or 6 Infection. Hepatology, 60: 6 (suppl) 1274A-1275A. December 2014 (AASLD 2014).

Gane EJ, Hyland RH, An D, McNally J, Brainard DM, Symonds WT, McHutchison JG, Stedman DA. Once Daily Sofosbuvir with GS-5816 for 8 weeks with or without Ribavirin in Patients with HCV Genotype 3 without Cirrhosis Result in High Rates of SVR12: The ELECTRON2 Study. Hepatology, 60: 4 (suppl) 236A. October 2014 (AASLD 2014).

Bourlière M, Sulkowski MS, Omata M, Zeuzem S, Feld JJ, Lawitz E, Marcellin P, Hyland RH, Ding X, Yang JC, Knox SJ, Pang PS, Subramanian M, Symonds WT, McHutchison JG, Mangia A, Gane EJ, Reddy R, Mizokami M, Pol S, Afdhal NH. An Integrated Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with Ledipasvir/Sofosbuvir with or without Ribavirin. Hepatology, 60: 4 (suppl) 239A. October 2014 (AASLD 2014).

Gane EJ, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, Stedman CA. Efficacy of Ledipasvir and Sofosbuvir, With or Without Ribavirin, for 12 Weeks in Patients With HCV Genotype 3 or 6 Infection. Gastroenterology (2015), in press.

Study Period:

03 April 2013 (First Subject Screened)
25 May 2015 (Last Subject Observation)
16 December 2014 (Last Subject Observation for the Primary Endpoint)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To evaluate the antiviral efficacy of combination therapy with sofosbuvir (SOF)-containing regimens for the treatment of chronic hepatitis C virus (HCV) infection 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 SOF-containing regimens administered for up to 24 weeks

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attain sustained virologic response at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)
- To evaluate the emergence of viral resistance to SOF, ledipasvir (LDV), velpatasvir (VEL; GS-5816), and GS-9669 during treatment and after treatment discontinuation
- To characterize viral dynamics during treatment and after treatment discontinuation
- To characterize steady-state pharmacokinetics (PK) of study drugs

The exploratory objective of this study was 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 provide a separate and specific consent

Methodology: This Phase 2 multicenter, open-label study evaluated the safety, tolerability and antiviral efficacy of SOF-containing treatment regimens administered for up to 24 weeks in subjects with chronic HCV infection. This study was conducted in 3 parts: Part A (Cohorts 1, 2, and 3), Part B (Cohort 4), and Part C (Cohorts 5 and 6).

Cohort 1 consisted of 2 treatment groups to evaluate the safety and efficacy of LDV/SOF + ribavirin (RBV) or SOF + pegylated interferon (Peg-IFN) + RBV treatment in subjects with genotype 1, 2, or 3 HCV infection who had been previously treated in Study P7977-0523 (ELECTRON) and did not achieve SVR. For Cohort 1, up to 50 and 30 subjects were planned to be enrolled into Groups 1 and 2, respectively, to receive the following treatments:

- **Cohort 1, Group 1 (LDV/SOF+RBV 12 weeks)**: LDV/SOF (90 mg/400 mg) once daily + RBV 1000 or 1200 mg/day divided twice daily (BID) for 12 weeks in subjects with

genotype 1 HCV infection who had been previously treated in Study P7977-0523 and did not achieve SVR

- **Cohort 1, Group 2 (SOF+Peg-IFN+RBV 12 weeks)**: SOF 400 mg once daily + Peg-IFN 180 μg once weekly + RBV 1000 or 1200 mg/day divided BID for 12 weeks in subjects with genotype 2 or 3 HCV infection who had been previously treated in Study P7977-0523 and did not achieve SVR

Cohort 2 consisted of 6 treatment groups to evaluate the safety and efficacy of LDV/SOF alone or with GS-9669 or RBV in subjects with genotype 1, 3, or 6 HCV infection. Within this cohort, up to 40% of enrolled subjects in each group may have had compensated cirrhosis at screening.

For Cohort 2, Groups 1 and 2, approximately 50 subjects with genotype 1 HCV infection and advanced liver fibrosis or compensated cirrhosis were planned to be enrolled and randomized (1:1) into one of the following 2 treatments:

- **Cohort 2, Group 1 (LDV/SOF+RBV 12 weeks)**: LDV/SOF (90 mg/400 mg) once daily + RBV 1000 or 1200 mg/day divided BID for 12 weeks in treatment-experienced subjects with genotype 1 HCV infection and advanced liver fibrosis or compensated cirrhosis
- **Cohort 2, Group 2 (LDV/SOF+GS-9669 12 weeks)**: LDV/SOF (90 mg/400 mg) once daily + GS-9669 500 mg once daily for 12 weeks in treatment-experienced subjects with genotype 1 HCV infection and advanced liver fibrosis or compensated cirrhosis

For Cohort 2, Groups 3 and 4, approximately 50 treatment-naive subjects with genotype 3 HCV infection were planned to be enrolled and randomized (1:1) into one of the following 2 treatments:

- **Cohort 2, Group 3 (LDV/SOF 12 weeks)**: LDV/SOF (90 mg/400 mg) once daily for 12 weeks in treatment-naive subjects with genotype 3 HCV infection
- **Cohort 2, Group 4 (LDV/SOF+RBV 12 weeks)**: LDV/SOF (90 mg/400 mg) once daily + RBV 1000 or 1200 mg/day divided BID for 12 weeks in treatment-naive subjects with genotype 3 HCV infection

For Cohort 2, Groups 5 and 6, approximately 25 treatment-naive or treatment-experienced subjects with genotype 6 HCV infection and 50 treatment-experienced subjects with genotype 3 HCV infection were planned to be enrolled in Cohort 2, Group 5 and Cohort 2, Group 6, respectively, and assigned to receive the following treatments:

- **Cohort 2, Group 5 (LDV/SOF 12 weeks)**: LDV/SOF (90 mg/400 mg) once daily for 12 weeks in treatment-naive or treatment-experienced subjects with genotype 6 HCV infection
- **Cohort 2, Group 6 (LDV/SOF+RBV 12 weeks)**: LDV/SOF (90 mg/400 mg) once daily + RBV 1000 or 1200 mg/day divided BID for 12 weeks in treatment-experienced subjects with genotype 3 HCV infection

Cohort 3 was composed of 1 treatment group to evaluate the safety and efficacy of LDV/SOF in subjects with genotype 1 HCV infection and Child Pugh-Turcotte (CPT) B cirrhosis. Approximately 20 subjects were planned to be enrolled to receive the following treatment:

- **Cohort 3, Group 1 (LDV/SOF 12 weeks)**: LDV/SOF (90 mg/400 mg) once daily for 12 weeks in subjects with genotype 1 HCV infection and CPT B cirrhosis

Cohort 4 comprised 4 treatment groups to evaluate the safety and efficacy of SOF and one of 2 doses of VEL (25 and 100 mg) with and without RBV. Approximately 100 treatment-naive, noncirrhotic subjects with genotype 3 HCV infection were planned to be enrolled and randomized (1:1:1:1) into one of the following 4 treatments:

- **Cohort 4, Group 1 (SOF+ VEL 25 mg 8 weeks):** SOF 400 mg + VEL 25 mg once daily for 8 weeks in treatment-naive, noncirrhotic subjects with genotype 3 HCV infection
- **Cohort 4, Group 2 (SOF+VEL 25 mg+RBV 8 weeks):** SOF 400 mg + VEL 25 mg once daily + RBV 1000 or 1200 mg/day divided BID for 8 weeks in treatment-naive, noncirrhotic subjects with genotype 3 HCV infection
- **Cohort 4, Group 3 (SOF+VEL 100 mg 8 weeks):** SOF 400 mg + VEL 100 mg once daily for 8 weeks in treatment-naive, noncirrhotic subjects with genotype 3 HCV infection
- **Cohort 4, Group 4 (SOF+VEL 100 mg+RBV 8 weeks):** SOF 400 mg + VEL 100 mg once daily + RBV 1000 or 1200 mg/day divided BID for 8 weeks in treatment-naive, noncirrhotic subjects with genotype 3 HCV infection

Cohort 5 comprised 1 treatment group to evaluate the safety and efficacy of LDV/SOF+RBV treatment. Approximately 25 subjects with genotype 1 or 3 HCV infection with prior exposure to a SOF-containing regimen in either Study P7977-0523 or GS-US-337-0122 who did not achieve SVR were planned to be enrolled to receive the following treatment:

- **Cohort 5, Group 1 (LDV/SOF+RBV 24 weeks):** LDV/SOF (90 mg/400 mg) once daily + RBV 1000 or 1200 mg/day divided BID for 24 weeks in subjects with prior exposure to a SOF-containing regimen in either Study P7977-0523 or GS-US-337-0122 who did not achieve SVR.

Cohort 6 comprised 1 treatment group to evaluate the safety and efficacy of LDV/SOF treatment in HCV/hepatitis B virus (HBV)-coinfected subjects. Approximately 10 subjects with genotype 1 HCV and HBV coinfection were planned to be enrolled to receive the following treatment:

- **Cohort 6, Group 1 (LDV/SOF 12 weeks):** LDV/SOF (90 mg/400 mg) once daily for 12 weeks in subjects with genotype 1 HCV and HBV coinfection.

Results through the posttreatment Week 24 visit from Cohorts 1 (Groups 1-2), 2 (Groups 1-4), 3 (Group 1), and 4 (Groups 1-4) are provided in the interim clinical study reports (CSRs) (06 January 2014 and 06 March 2015). In addition, the second interim CSR (06 March 2015) included results for subjects in Cohorts 2 (Groups 5-6) and 6 (Group 1) through the posttreatment Week 12 visit, and for subjects in Cohort 5 (Group 1) through the end-of-treatment visit.

This final synoptic CSR summarizes the results of the final analysis of data collected throughout the course of the study, after all subjects had completed the posttreatment Week 24 visit or prematurely discontinued from the study.

Number of Subjects (Planned and Analyzed):
Planned: Up to 410 subject
Analyzed:

- Full Analysis Set (FAS): 358 subjects
- Safety Analysis Set: 358 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females ≥ 18 years of age, with chronic genotype 1, 2, 3, or 6 HCV infection, who had screening HCV RNA levels ≥ 10^4 IU/mL; 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 8 weeks for Cohort 4, Groups 1, 2, 3, and 4. Treatment duration was 12 weeks for Cohort 1, Groups 1 and 2; Cohort 2, Groups 1, 2, 3, 4, 5, and 6; Cohort 3, Group 1; and Cohort 6, Group 1. Treatment duration was 24 weeks for Cohort 5, Group 1. For all groups, there were 24 weeks of posttreatment follow-up.

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

- **Sofosbuvir 400 mg** was administered orally as 1 × 400-mg tablet once daily
- **LDV/SOF (90 mg/400 mg)** was administered orally as 1 × 90-mg/400-mg fixed-dose combination (FDC) tablet once daily
- **GS-9669 500 mg** was administered orally as 2 × 250-mg tablets once daily
- **VEL 25 or 100 mg** was administered orally as 1 × 25-mg tablet or 1 × 100-mg tablet, respectively, once daily
- **Ribavirin 1000 or 1200 mg** (generic) was administered orally as 5 × 200-mg tablets or 6 × 200-mg tablets, respectively, divided BID
- **Peg-IFN 180 μg** (Pegasys®) was administered via subcutaneous injection once weekly

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

- **Sofosbuvir**: DC1205B1 and DC1209B1
- **LDV/SOF**: DK1206B2, DK1209B1R, DK1208B1R, and DK1304B1
- **GS-9669**: CU1108B1
- **VEL 25 mg**: DL1301C1
- **VEL 100 mg**: DL1301D1
- **Ribavirin**: A97943Z and AA2773Z
- **Peg-IFN**: B1303B08

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 12 (Cohort 5 [Group 1]) and posttreatment Week 24 (Cohort 2 [Groups 5-6], Cohort 5 [Group 1], and Cohort 6 [Group 1]). In addition, any changes to previously reported efficacy analyses between the data cutoffs for the primary analysis presented in the second interim CSR (06 March 2015) and the final analysis presented in the final CSR for all treatment groups are summarized. Efficacy analyses at all other scheduled assessment time points were described in the 2 interim CSRs (06 January 2014 and 06 March 2015). The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to determine HCV RNA results in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: The interim CSRs (06 January 2014 and 06 March 2015) describe details on the collection of blood samples for the optional PK substudy.

Safety: The interim CSRs (06 January 2014 and 06 March 2015) provide analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, electrocardiograms (ECGs), and vital signs measurements. This final synoptic CSR summarizes any new treatment-emergent AEs or changes to previously reported treatment-emergent AEs between the data cutoffs for the second interim CSR (06 March 2015) and the final CSR for all treatment groups. Additionally, all serious adverse events (SAEs) collected after the data cutoff for the second interim CSR to the end of the study (posttreatment Week 24) for all treatment groups are summarized. Serious adverse events occurring > 30 days after the last dose of study drug were considered nontreatment emergent.

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 second interim CSR (06 March 2015).

Efficacy: This study was not designed to evaluate formal statistical hypotheses. No statistical inference was performed. The primary efficacy endpoint was SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the Full Analysis Set. The 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method was provided for the SVR12 rates in each efficacy analysis group. Secondary efficacy endpoints included SVR4, SVR24, the proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through Week 8, the proportion of subjects with virologic failure, and the characterization of HCV drug resistance substitutions at baseline, during, and after treatment. The proportion of subjects who had HCV RNA below the LLOQ (ie, < 15 IU/mL) by visit while on treatment and during the posttreatment follow-up period were summarized based on categorical imputation rules. Absolute values and change from baseline in HCV RNA (log_{10} IU/mL) by visit through Week 8 were summarized. No other imputation was performed for continuous data. Plots of the mean ± standard deviation (SD) and median (first quartile [Q1], third quartile [Q3]) change from baseline in HCV RNA through Week 8 were presented.

Virologic failure was summarized using descriptive statistics by category (on-treatment virologic failure and relapse).

Pharmacokinetics: The second interim CSR (06 March 2015) describes details on the statistical methods for the optional PK substudy.

Safety: All enrolled or 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 sign measurements, 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. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 358 subjects were enrolled/randomized and received treatment in this study and were included in the FAS and Safety Analysis Set (Section 15.1, Tables 2 and 2-C4). Full details on subject disposition for Cohorts 1, 2 (Groups 1-4), 3, and 4 through posttreatment Week 24 are reported in Section 8 of the second interim CSR (06 March 2015). Subject disposition at posttreatment Week 24 for all cohorts is summarized in Section 15.1, Tables 2 and 2-C4.

Full details on demographics and baseline disease characteristics for all cohorts are reported in Section 8 of the second interim CSR (06 March 2015). No differences in demographic or baseline disease characteristics were observed between the primary analyses and the final analyses (Section 15.1, Tables 3 and 3-C4, and Appendix 16.2, Listings 4.1, 4.2, 4.1-C4, and 4.2-C4). There were a small number of changes to concomitant medications that did not change the interpretation of the study results (Section 15.1, Tables 5 and 5-C4, and Appendix 16.2, Listings 7.1 and 7.1-C4).

Analyses related to disposition, demographics, and exposure are presented in Section 15.1, Tables 1 to 6, 1-C4 to 6-C4 and Figures 1 and 1-C4, and Appendix 16.2, Listings 1 to 7.2 and 1-C4 to 7.1 -C4. 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 second interim CSR (06 March 2015), which included results for SVR12 and SVR24 (a secondary efficacy endpoint) for Cohorts 1 (Groups 1-2), 2 (Groups 1-4), 3 (Group 1), and 4 (Groups 1-4), SVR12 results for subjects in Cohorts 2 (Groups 5-6) and 6 (Group 1), and available data as of the data cutoff for subjects in Cohort 5 (Group 1). In this final CSR, results through SVR24 for Cohorts 2 (Groups 5-6), 5 (Group 1), and 6 (Group 1) are summarized.

Cohorts 1 (Groups 1-2), 2 (Groups 1-4), 3 (Group 1), and 4 (Groups 1-4)

There were no changes to the SVR12 and SVR24 results for subjects in Cohorts 1 (Groups 1-2), 2 (Groups 1-4), 3 (Group 1), and 4 (Groups 1-4) as reported in the second interim CSR (06 March 2015) (Section 15.1, Tables 7, 9, 10, 7-C4, 9-C4, and 10-C4, and Appendix 16.2, Listings 8.1 and 8.1-C4).

Cohorts 2 (Groups 5-6), 5 (Group 1), and 6 (Group 1)

The proportions of subjects with SVR12 and SVR24 for subjects in Cohorts 2 (Groups 5-6), 5 (Group 1), and 6 (Group 1) are presented in Table 1.

Table 1. GS-US-337-0122: Proportion of Subjects with SVR12 and SVR24 (Cohorts 2 [Groups 5-6], 5 [Group 1], and 6 [Group 1]) (Full Analysis Set)

	Cohort 2		Cohort 5	Cohort 6
	Group 5	Group 6	Group 1	Group 1
	Treatment Naive or Treatment Experienced	Treatment Experienced	Treatment Experienced	HCV and HBV Coinfected
	Genotype 6	Genotype 3	Genotype 1 or 3	Genotype 1
	LDV/SOF 12 Weeks (N = 25)	LDV/SOF+RBV 12 Weeks (N = 50)	LDV/SOF+RBV 24 Weeks (N = 20)	LDV/SOF 12 Weeks (N = 8)
SVR12	24/25 (96.0%)	41/50 (82.0%)	15/20 (75.0%)	8/8 (100.0%)
95% CI	79.6% to 99.9%	68.6% to 91.4%	50.9% to 91.3%	63.1% to 100.0%
SVR24	24/25 (96.0%)	41/50 (82.0%)	15/20 (75.0%)	8/8 (100.0%)
95% CI	79.6% to 99.9%	68.6% to 91.4%	50.9% to 91.3%	63.1% to 100.0%

TND = target not detected.
HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, version 2.0 assay with an LLOQ of 15 IU/mL.
SVR12 and SVR24 were sustained virologic response (HCV RNA < LLOQ) 12 and 24 weeks after stopping study treatment, respectively.
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.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Section 15.1, Tables 7 and 9

Cohort 2, Groups 5-6: For this final analysis, the SVR12 and SVR24 rates were observed to be the same for both treatment groups (96.0% [95% CI: 79.6%-99.9%] and 82.0% [95% CI: 68.6%-91.4%], respectively). Of note, 1 subject was imputed to have achieved SVR24 based on the high correlation between SVR12 and SVR24 {24697} (Section 15.1, Tables 7, 9, and 10 and Appendix 16.2, Listing 8.1).

Of the subjects with genotype 6 HCV infection who received LDV/SOF for 12 weeks (Cohort 2, Group 5), the 1 subject (Subject PPD) who did not achieve SVR12 had withdrawn consent for treatment at Week 8 and then subsequently relapsed (Appendix 16.2, Listings 3 and 8.2).

Of the treatment-experienced subjects with genotype 3 HCV infection who received LDV/SOF+RBV for 12 weeks (Cohort 2, Group 6), 8 subjects relapsed and 1 subject (Subject PPD) had on-treatment virologic failure at the end of treatment visit, and subsequently discontinued the study due to lack of efficacy. Of the 8 subjects that relapsed, all subjects achieved HCV RNA < LLOQ on treatment (4 subjects relapsed at posttreatment

Week 2, 3 subjects relapsed at posttreatment Week 4, and 1 subject relapsed at posttreatment Week 8) (Appendix 16.2, Listings 3 and 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 and Appendix 16.2, Listings 8.2 and 8.5).

Cohort 5, Group 1: A total of 15 of 20 subjects (75.0% [95% CI: 50.9%-91.3%]) achieved SVR12. The SVR12 and SVR24 rates were the same. One subject who achieved SVR12 did not have HCV RNA measurements at the posttreatment Week 24 visit and was imputed to achieve SVR24 based on bracketed success (achieving SVR12 and having observed HCV RNA values < LLOQ obtained after the posttreatment Week 24 visit window) (Section 15.1, Tables 7, 9, and 10 and Appendix 16.2, Listing 8.1).

Of the 5 subjects who did not achieve SVR12, 3 subjects relapsed (all at posttreatment Week 4), and 2 subjects died: Subject PPD withdrew consent and died of hepatocellular carcinoma on posttreatment Day 55 and Subject PPD died on posttreatment Day 62 of upper gastrointestinal hemorrhage. No subjects relapsed between posttreatment Weeks 12 and 24, and all subjects who had achieved SVR12 also achieved SVR24 (Section 15.1, Table 10 and Appendix 16.2, Listings 3, 8.2, 8.3, 8.5, and 14).

Cohort 6, Group 1: For this final analysis, the SVR12 and SVR24 rates were the same (100.0% [95% CI: 63.1%-100.0%]). One subject who achieved SVR12 did not have HCV RNA measurements at the posttreatment Week 24 visit and was imputed to achieve SVR24 based on bracketed success, having had observed HCV RNA values < LLOQ obtained after the posttreatment Week 24 visit window. No subject had virologic failure (Section 15.1, Tables 7, 9, and 10 and Appendix 16.2, Listing 8.1).

All efficacy analyses for all cohorts and groups are provided in Section 15.1, Tables 7 to 13 and 7-C4 to 13-C4 and Figures 3 to 4.4 and 2-C4 to 4.4-C4, and Appendix 16.2, Listings 8.1 to 8.3, 8.5, 8.1-C4 to 8.3-C4, and 8.5-C4).

Full details on the virologic resistance analysis for all cohorts and groups are reported in Section 9 of the second interim CSR (06 March 2015). No additional resistance analyses were performed since no subjects relapsed after the data cutoff for the second interim CSR (06 March 2015).

Pharmacokinetic Results:

Results of the optional PK substudy analyses for this study are presented in Section 10 of the second interim CSR (06 March 2015). All PK results are provided in Section15.1, Tables 34.1 to 35.5 and 34.1-C4 to 35.5-C4, and Appendix 16.2, Listings 24 and 24-C4.

Safety Results:

All AEs and laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as AEs and laboratory abnormalities in this report, unless otherwise specified. Evaluations of safety data through 30 days after the last dose of study drugs for Cohorts 1-4 and 6, and all available safety data for Cohort 5 as of the data cutoff, were summarized in Section 11 of the second interim CSR (06 March 2015).

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. No additional treatment-emergent Grade 3 or 4 AEs were reported (Appendix 16.2, Listings 9, 9-C4, 10, 10-C4, and Adhoc Listings 1-C12356 and 1-C4). These changes did not impact the overall interpretation or conclusions of the safety profile of the study treatment in this study. Adhoc Listings 1-C12356 and 1-C provide detailed listings of any newly reported AEs and AEs that had changes in reported or preferred term, onset date, severity, relationship to study drug, or action(s) taken between the data cutoffs at the primary analysis and final analysis.

There were no additional treatment-emergent SAEs. One additional nontreatment-emergent SAE for a subject in Cohort 5, Group 1 (Subject PPD) was reported; this subject experienced Grade 4 upper gastrointestinal hemorrhage on Day 60, which led to the subject's death on Day 62 and was not considered related to study drug by the investigator. Aside from this subject's death, no additional new deaths were reported. No additional pregnancies were reported (Appendix 16.2, Listings 9, 12 to 14, 9-C4, 12-C4 to 14-C4, and Adhoc Listings 1-C12356 and 1-C).

Narratives for all SAEs, deaths, AEs leading to discontinuation of study drugs, and subject pregnancies from the first dose of study drug through the end of the study (ie, the SVR24 visit) are provided in Section 15.2. All AE results are provided in Section15.1, Tables 14 to 28 and 14-C4 to 28-C4, and Appendix 16.2, Listings 9 to 14 and 9-C4 to 14-C4.

Clinical Laboratory Results

Blood samples for clinical laboratory analyses were collected through the posttreatment Week 4 visit for Cohorts 1-5 and through the posttreatment Week 24 visit for Cohort 6. Therefore, updates were made to previously reported laboratory data for Cohort 5, Group 1 for the posttreatment Week 2 and 4 visits and new laboratory data are available for Cohort 6, Group 1 for visits occurring after the posttreatment Week 12 visit (Section 15.1, Tables 29.1 to 29.5 and 29.7 to 29.12). These additional data to not indicate any safety concerns. In particular, there were no HBV flares among the subjects with HBV and HCV coinfection treated with LDV/SOF in Cohort 6, Group 1 (Appendix 16.2, Listings 20.2, 20.4, and 20.5).

A small number of updates were made to previously reported graded laboratory abnormalities due to the ongoing nature of the study and data reconciliation. These changes were primarily associated with corrections in the toxicity grading which led to minor changes in Grade 1 or 2 laboratory abnormalities of international normalized ratio and albumin. No additional Grade 3 or 4 laboratory abnormalities were reported (Section 15.1, Tables 30, 30-C4, 31, and 31-C4).

These changes did not impact the overall interpretation or conclusions of the clinical laboratory data. No other notable changes to clinical laboratory results were observed.

All laboratory results are provided in Section 15.1, Tables 29.1 to 31.1 and 29.1-C4 to 31.1-C4 and Figures 5.1 to 5.10 and 5.1-C4 to 5.10-C4, and Appendix 16.2, Listings 15 to 21.2 and 15-C4 to 21.2-C4.

Vital Signs Measurements and ECGs

Vital signs measurements (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) and weight were collected through the posttreatment Week 24 visit. No notable changes were observed (Section 15.1, Tables 33.1 to 33.4 and 33.1-C4 to 33.4-C4, and Appendix 16.2, Listings 23.1 to 23.2 and 23.1-C4 to 23.2-C4).

All vital signs measurement and ECG results are provided in Section 15.1, Tables 32 to 33.4 and 32-C4 to 33.4-C4, and Appendix 16.2, Listings 22 to 23.2 and 22-C4 to 23.2-C4.

CONCLUSIONS:

The overall conclusions from this study are as follows:

Cohort 1, Groups 1 and 2

- Treatment with LDV/SOF+RBV for 12 weeks in subjects with genotype 1 HCV infection who had been previously treated in Study P7977-0523 (ELECTRON) and did not achieve SVR, resulted in high SVR12 rates of 100.0% in subjects who received LDV/SOF+RBV.
- Treatment with SOF+Peg-IFN+RBV for 12 weeks in subjects with genotype 3 HCV infection, who had been previously treated in Study P7977-0523 (ELECTRON) and did not achieve SVR, resulted in high SVR12 rates of 90.0% (9 of 10) in subjects who received SOF+Peg-IFN+RBV.
- No resistance was detected in the 1 subject with genotype 3a HCV infection who relapsed following treatment with SOF+Peg-IFN+RBV.
- High SVR rates following retreatment of subjects who have previously failed SOF-containing regimens, together with the lack of detection NS5B resistance-associated variants (RAVs) or treatment-emergent variants (TEVs), supports the lack of selection of clinically meaningful SOF resistance during prior therapy.
- Treatment with LDV/SOF+RBV for 12 weeks in treatment-experienced subjects with genotype 1 HCV infection who had been previously treated in Study P7977-0523 (ELECTRON) and did not achieve SVR was safe and well tolerated. There were no new safety signals.

Cohort 2, Groups 1 and 2

- Treatment with LDV/SOF+RBV or LDV/SOF+GS-9669 for 12 weeks in treatment-experienced subjects with genotype 1 HCV infection and advanced liver fibrosis or compensated cirrhosis resulted in a high SVR12 rate of 100.0%. Treatment-experienced patients with advanced liver disease or cirrhosis may benefit from the use of additional agents.
- The PK of SOF, GS-566500, GS-331007, and LDV were within the range of Phase 2 and 3 studies and GS-9669 PK was similar to historical data.
- Treatment with LDV/SOF+RBV or LDV/SOF+GS-9669 for 12 weeks in treatment-experienced subjects with genotype 1 HCV infection and advanced liver fibrosis or compensated cirrhosis was safe and well tolerated. There were no new safety signals.

Cohort 2, Groups 3 to 6

- Treatment with LDV/SOF+RBV for 12 weeks resulted in a 100.0% SVR12, whereas treatment with LDV/SOF resulted in a 64.0% SVR12, suggesting an advantage to the inclusion of RBV when treating subjects with genotype 3 HCV infection with LDV/SOF.
- Treatment with LDV/SOF+RBV for 12 weeks in treatment-experienced subjects with genotype 3 HCV infection resulted in an SVR12 rate of 82.0%. One subject experienced on-treatment breakthrough. Though limited by small numbers, this result suggests comparable efficacy between LDV/SOF+RBV for 12 weeks and SOF+RBV for 24 weeks.
- Treatment with LDV/SOF for 12 weeks in subjects with genotype 6 HCV infection resulted in a high SVR12 rate of 96.0%; all subjects who completed study drug achieved SVR12. This is the first reported highly-effective, all-oral therapy for subjects with genotype 6 HCV infection.
- Of all the subjects with genotype 3 HCV infection who experienced virologic failure, NS5A resistance-associated polymorphisms (RAPs) and NS5B S282T were emerged in 4 of 17 and 1 of 17 subjects, respectively. The on-treatment breakthrough in 1 subject was associated with the emergence of low levels of NS5B L159F only.
- The emergence of NS5B S282T was observed in the 1 subject with genotype 6 HCV infection who completed 8 weeks of treatment and relapsed.
- The PK of SOF, GS-566500, GS-331007, and LDV were similar to historical data observed in LDV/SOF Phase 2 or 3 studies.
- Treatment with LDV/SOF±RBV in subjects with genotype 3 or 6 HCV infection was safe and well tolerated. There were no new safety signals.

Cohort 3, Group 1

- Treatment with LDV/SOF for 12 weeks in treatment treatment-naive or treatment-experienced subjects with genotype 1 HCV infection and decompensated CPT B cirrhosis resulted in an SVR12 rate of 65.0%.
- Pretreatment NS5A RAPs had no apparent effect on treatment outcome in subjects with genotype 1 HCV infection with CPT B cirrhosis who received LDV/SOF for 12 weeks.
- Viral relapse was associated with the detection of a single class of NS5A RAVs.
- The PK of SOF, GS-566500, GS-331007, and LDV were similar to historical data observed in subjects with decompensated cirrhosis receiving LDV/SOF.
- Treatment with LDV/SOF for 12 weeks in treatment treatment-naive or treatment-experienced subjects with genotype 1 HCV infection and decompensated CPT B cirrhosis was safe and well tolerated. There were no new safety signals.

Cohort 4, Groups 1 to 4

- Treatment with SOF + VEL 25 or 100 mg ± RBV for 8 weeks in treatment-naive subjects with genotype 3 HCV infection without cirrhosis resulted in a high SVR12 rate in all treatment groups. There was no trend in SVR12 with respect to VEL dose or contribution of RBV.

- Pretreatment NS5A RAPs did not have a negative effect on treatment outcome in treatment-naive subjects with genotype 3 HCV infection who received SOF + VEL 25 or 100 mg ± RBV. Single class of NS5A RAP (Y93H) was detected in 1 of 2 subjects who relapsed following 8 weeks of treatment with SOF + VEL 25 mg + RBV.
- Administration of SOF + VEL 100 mg ± RBV resulted in an approximately 65% higher SOF and GS-566500 exposures compared with administration of SOF + VEL 25 mg ± RBV. GS-331007 exposure was similar regardless of VEL dose. Velpatasvir exposure was not dose-proportional between VEL 25 mg and VEL 100 mg.
- Treatment with SOF + VEL 25 or 100 mg ± RBV for 8 weeks in treatment-naive subjects with genotype 3 HCV infection was safe and well tolerated.

Cohort 5, Group 1

- Treatment with LDV/SOF+RBV for 24 weeks in treatment-experienced subjects with genotype 1 or 3 HCV infection who had received a SOF-containing regimen in Study P7977-0523 (ELECTRON) or Study GS-US-337-0122 resulted in an SVR12 rate of 75.0%.
- Treatment with LDV/SOF+RBV for 24 weeks in treatment-experienced subjects with genotype 1 or 3 HCV infection who had received a SOF-containing regimen in Study P7977-0523 or Study GS-US-337-0122 was safe and well tolerated. There were no new safety signals.

Cohort 6, Group 1

- Treatment with LDV/SOF for 12 weeks in subjects with HCV and HBV coinfection resulted in a high SVR12 rate of 100.0%.
- The PK of SOF, GS-566500, GS-331007, and LDV for the subjects with coinfection were within the range observed in LDV/SOF Phase 2 and 3 studies in monoinfected subjects with HCV.
- Treatment of subjects with HBV and HCV coinfection was safe and well tolerated. There were no new safety signals. Some subjects with HBV and HCV coinfection experienced increases in HBV DNA and HBsAg; however, there were no clinical hepatitis flares. No treatment for HBV infection was required.