FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Open Label Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed Dose Combination (FDC) Tablet for 12 or 24 Weeks in Kidney Transplant Recipients with Chronic HCV Infection
Name of Test Drug:	Ledipasvir/Sofosbuvir fixed-dose combination (FDC)
Dose and Formulation:	Ledipasvir/Sofosbuvir FDC (90/400 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-337-1406
Phase of Development:	Phase 2
IND No.:	This is a non-IND study
EudraCT No.:	2014-002121-35
ClinicalTrials.gov Identifier:	NCT02251717
Study Start Date:	14 October 2014 (First Subject Screened)
Study End Date:	16 June 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Massimo Colombo, Professor of Gastroenterology Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Benedetta Massetto, MD, PhD Telephone: PPD Fax: PPD
Report Date:	10 October 2016

STUDY SYNOPSIS

Study GS-US-337-1406
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Open Label Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed Dose Combination (FDC) Tablet for 12 or 24 Weeks in Kidney Transplant Recipients with Chronic HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled at a total of 5 sites, including 2 sites in France, 1 site in Austria, 1 site in Germany, and 1 site in Italy.

Publications:

Colombo M, Aghemo A, Liu H, Dvory-Sobol H, Hyland RH, Yun C, Brainard DM, McHutchison JG, Bourliere M, Peck-Radosavljevic M, Manns M, Pol S. Ledipasvir/Sofosbuvir (LDV/SOF) for 12 or 24 Weeks Is Safe and Effective in Kidney Transplant Recipients With Chronic Genotype 1 or 4 HCV Infection. Journal of Hepatology. 2016**;**64 pp S183–S212**.** **(**GS 13, oral presentation**)**.

Study Period:

14 October 2014 (First Subject Screened)
16 June 2016 (Last Subject Observation)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To determine the antiviral efficacy of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) as measured by the proportion of subjects who attain sustained virologic response (SVR) at 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of each treatment regimen as assessed by review of the accumulated safety data

The secondary objectives of this study were as follows:

- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

- To characterize steady state pharmacokinetics (PK) of study drug
- To determine the proportion of subjects who attained SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)

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, response to therapy and/or tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics), in subjects who provide their separate and specific consent

Methodology: This Phase 2, open-label, randomized, multicenter study evaluated the safety, tolerability, and antiviral efficacy of LDV/SOF treatment for 12 or 24 weeks in subjects with genotype 1 or 4 HCV infection following kidney transplantation.

Following screening and confirmation of eligibility, subjects were randomized in a 1:1 ratio to receive LDV/SOF for 12 or 24 weeks. Randomization was stratified by HCV genotype (1 or 4), prior treatment (naive or experienced), and the presence or absence of cirrhosis.

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

All subjects were eligible to participate in a pharmacogenomics substudy 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. Subjects provided additional, specific consent prior to participation in this substudy.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 150 subjects (75 in LDV/SOF 12 Week group and 75 in LDV/SOF 24 Week group)

Analyzed: 114 subjects (57 in LDV/SOF 12 Week group and 57 in LDV/SOF 24 Week group)

- Full Analysis Set: 114 subjects
- Safety Analysis Set: 114 subjects

Diagnosis and Main Criteria for Inclusion: Males or females ≥ 18 years of age who had chronic genotype 1 or 4 HCV infection, screening HCV RNA levels ≥ LLOQ, a kidney transplant > 6 months before baseline, and an estimated glomerular filtration rate (eGFR; {Cockcroft et al 1976}) ≥ 40 mL/min were eligible for this study. Subjects did not have any serious or active medical or psychiatric illnesses other than HCV and kidney disease. In addition, no history of prior organ transplantation other than kidney was allowed. Subjects were treatment naive or treatment experienced and had documentation of the presence or absence of cirrhosis. Subjects could not have received any experimental medication or device within 30 days prior to screening. Subjects were willing and able to sign an informed consent form.

Duration of Treatment: LDV/SOF treatment duration was either 12 or 24 weeks

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

LDV/SOF was administered orally at a dose of 90/400 mg (1 tablet once daily). The lot numbers of study drug administered in this study were DK1303B1 and DK1312B3.

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

Criteria for Evaluation:

Efficacy: Blood samples to determine HCV RNA levels were collected from subjects at screening, baseline/Day 1 (predose), Weeks 1, 2, 4, 8, and 12 (both groups), and Weeks 16, 20, and 24 (LDV/SOF 24 Week group) during treatment (or upon early termination), and posttreatment Weeks 4, 12, and 24 (for subjects with HCV RNA < LLOQ at posttreatment Week 12). The COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: A single pharmacokinetic (PK) blood sample was collected from all subjects at each treatment visit (Weeks 1, 2, 4, 8, and 12 [both groups] and 16, 20, and 24 [LDV/SOF 24 Week group]). Samples for PK analysis also were drawn at the early termination visit, as applicable.

Safety: Safety assessments included monitoring of adverse events (AEs), concomitant medications, concomitant immunosuppressant medications administered to prevent rejection of the kidney graft, transient elastography (FibroScan®) of the liver and kidney, and clinical laboratory analyses at prespecified intervals through the posttreatment Week 12 visit (or posttreatment Week 24 visit, if applicable). Vital sign measurements and physical examinations also were collected during treatment at prespecified intervals; electrocardiograms (ECG) were collected at baseline and at early study discontinuation.

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.

The All Randomized Analysis Set included subjects who were randomized into the study. The Full Analysis Set included subjects who were randomized into the study and received at least 1 dose of study drug. The Safety Analysis Set included subjects who received at least 1 dose of study drug.

Efficacy: The primary efficacy endpoint was the proportion of subjects with HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after discontinuation of study treatment (SVR12) for the Full Analysis Set. The proportion of subjects who achieved SVR12 in each treatment group was calculated; exact 2-sided 95% CIs were constructed using the Clopper-Pearson method {Clopper et al 1934}. No statistical hypothesis testing was performed.

Secondary efficacy endpoints included the proportion of subjects who achieved SVR4 and SVR24, the proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through the end of treatment, and the proportion of subjects with virologic failure.

For the proportion of subjects with on-treatment virologic failure or relapse, a summary table of the number and percentage of subjects with SVR12, overall virologic failure (with subgroups for on-treatment virologic failure and relapse), and other (those who did not achieve SVR12 and did not meet virologic failure criteria), was provided. The denominator for relapse was the number of subjects who had HCV RNA < LLOQ at their last observed on-treatment HCV RNA measurement; otherwise, the denominator was the number of subjects in the Full Analysis Set. In addition, a summary table of the number and percentage of subjects with HCV RNA < LLOQ and ≥ LLOQ at each posttreatment follow-up visit (observed and imputed, with method for imputed) was provided; 95% Clopper-Pearson exact CIs were presented for the overall proportion of subjects with HCV RNA< LLOQ. A concordance table between SVR12 and SVR24 was provided by treatment group and overall.

Exploratory efficacy endpoints included the proportion of subjects with alanine aminotransferase (ALT) normalization (defined as ALT > the upper limit of the normal range [ULN] at baseline and ALT ≤ ULN at each visit) summarized by study visit and subgroup analyses of SVR12 by demographic and baseline characteristics and by early viral response.

All continuous endpoints were summarized using descriptive statistics. All categorical endpoints were summarized by the number and percentage of subjects who met the endpoint definition.

Pharmacokinetics: No PK analyses were performed for this study.

Safety: Safety data were analyzed by treatment group and included all data collected on or after the first dose of study drug through the date of the last dose of study drug plus 30 days for subjects in the Safety Analysis Set. All AEs and laboratory abnormalities discussed in this clinical study report were treatment emergent and are referred to as AEs for the purposes of this report. Adverse events and laboratory abnormalities were graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 16.1.1, Appendix 3). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0.

Laboratory results were assigned toxicity grades of Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4. Laboratory abnormalities were defined as values that increased at least 1 toxicity grade from baseline at any postbaseline time point to the date of the last dose of any study drug plus 30 days (ie, treatment emergent). The number and percentage of subjects by treatment group who had any graded laboratory abnormality or any Grade 3 or 4 laboratory abnormality were summarized. Laboratory data were summarized using descriptive statistics by treatment group with corresponding changes from baseline. The number of subjects with hemoglobin values < 10 g/dL and < 8.5 g/dL at any postbaseline visit also was summarized by treatment group. The FibroScan result of liver and kidney and change from baseline in FibroScan result of liver and kidney also was provided.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: All of the 114 subjects who were randomized were included in the Full and Safety Analysis Sets (57 in LDV/SOF 12 Week group and 57 in LDV/SOF 24 Week group) (Section 15.1, Table 3). Of the 114 subjects who were randomized and treated, only 1 subject (Subject PPD LDV/SOF 12 weeks) prematurely discontinued study drug due to a serious AE (SAE) of syncope on Day 30; on the same day, this subject also withdrew consent from the study. A second subject (Subject PPD LDV/SOF 24 weeks) discontinued the study early due to an SAE of osteoarthritis on posttreatment Day 165 following LDV/SOF 24 Week treatment (Appendix 16.2, Listings 3 and 10).

The mean age of subjects was 53 years (range: 25-75 years) and the mean BMI was 24.7 kg/m^2 (range: 18.1-42.6). Most subjects were male (57.9%), white (93.9%), and not of Hispanic or Latino ethnicity (95.6%). The majority of subjects had genotype 1b HCV infection (74.6%) and non-CC IL28B alleles (71.9%). The overall mean (SD) baseline HCV RNA value was 6.30 (0.58) $\log_{10}$ IU/mL and most subjects had baseline HCV RNA ≥ 800,000 IU/mL (76.3%). The overall mean (SD) baseline eGFR was 61.3 (20.41) mL/min and the overall mean (SD) Fibrotest score was 0.49 (0.250). Overall, demographics and disease characteristics were generally similar between the 2 treatment groups; however, subjects in the LDV/SOF 24 Week group had a longer mean time since the most recent kidney transplant to baseline than subjects in the LDV/SOF 12 Week group (14.4 and 12.1 years, respectively) and a numerically higher mean estimated eGFR (63.5 and 59.1 mL/min, respectively). Additionally, a numerically higher percentage of subjects in the LDV/SOF 12 Week group than the LDV/SOF 24 Week group had the IL28B non-CC allele (75.4% and 68.4%, respectively), baseline HCV RNA ≥ 800,000 IU/mL (80.7% and 71.9%, respectively), and baseline ALT ≤ 1.5 × ULN (84.2% and 68.4%, respectively) (Section 15.1, Table 5). Most subjects did not have cirrhosis (85.1%) and were treatment-naive (69.3%). For subjects who received prior HCV treatment, the most common prior regimens were interferon (37.1%), pegylated interferon (Peg-IFN) +RBV (34.3%), and Peg-IFN (22.9%). The most common responses to prior HCV treatment were nonresponse for 19 of 35 subjects (54.3%) and relapse or breakthrough for 11 of 35 subjects (31.1%) (Section 15.1, Table 5).

Analyses related to disposition, demographics, and exposure are presented in Section 15.1, Tables 1 to 8 and Figure 1, and Appendix 16.2, Listings 1 to 8.3. In addition, an Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

Efficacy Results: Table 1 presents the proportion of subjects with SVR12 by treatment group. In both treatment groups, all subjects achieved SVR12. The SVR12 rates were:

- LDV/SOF 12 Week group: 100.0% (95% CI: 93.7% to 100.0%) of subjects (57 of 57) achieved SVR12
- LDV/SOF 24 Week group: 100.0% (95% CI: 93.7% to 100.0%) of subjects (57 of 57) achieved SVR12

Table 1. GS-US-337-1406: SVR12 and Virologic Outcomes (Full Analysis Set)

	LDV/SOF 12 Weeks (N = 57)	LDV/SOF 24 Weeks (N = 57)
SVR12	57/57 (100.0%)	57/57 (100.0%)
95% CI	93.7% to 100.0%	93.7% to 100.0%
Overall Virologic Failure	0/57	0/57
Relapse	0/57	0/57
Completed Study Treatment	0/56	0/57
Discontinued Study Treatment	0/1	0/0
On-Treatment Virologic Failure	0/57	0/57
Other	0/57	0/57

HCV RNA analyzed using COBAS® AmpliPrep/COBAS® TaqMan® HCV Test with limit of quantitation of 15 IU/mL.
SVR12 is sustained virologic response (HCV RNA < LLOQ) 12 weeks after stopping study treatment.
A missing SVR12 value is imputed as a success if it is bracketed by values that are termed successes (i.e., '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR12 value is imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.
Relapse = confirmed HCV RNA ≥ LLOQ during the post-treatment period having achieved HCV RNA < LLOQ at last on-treatment visit.
On-Treatment Virologic Failure = Breakthrough (confirmed HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment),
Rebound (confirmed > 1 $\log_{10}$IU/mL increase in HCV RNA from nadir while on treatment), or Non-response (HCV RNA persistently ≥ LLOQ through 12 weeks of treatment for LDV/SOF 24 weeks arm only). Other = Subject who did not achieve SVR12 and did not meet virologic failure criteria.
Subject PPD (LDV/SOF 12 Week group) who discontinued study drug on Day 30 was imputed as having achieved SVR12 because HCV RNA at posttreatment Week 12 is bracketed by '< LLOQ detected' at early termination visit (20 days posttreatment) and '< LLOQ TND' at unscheduled visit (277 days posttreatment).
Source: Section 15.1, Tables 10 and 11

In both treatment groups, SVR4 results were the same as the SVR12 results (Section 15.1, Table 13). Each of the 109 subjects with both posttreatment Week 12 and posttreatment Week 24 data available achieved SVR12 and SVR24, demonstrating 100% concordance between SVR12 and SVR24 (Section 15.1, Table 12).

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly in both treatment groups. After 1 week of treatment, mean (SD) changes from baseline in HCV RNA were −4.06 (0.553) and −3.98 (0.648) $\log_{10}$ IU/mL in the LDV/SOF 12 Week and 24 Week groups, respectively (Section 15.1, Table 17). By Week 2, 31 of 57 subjects (54.4%) and 33 of 57 subjects (57.9%) had HCV RNA < LLOQ in the LDV/SOF 12 Week and 24 Week groups, respectively. At Week 8, 100.0% of subjects had HCV RNA < LLOQ (Section 15.1, Table 16 and Figure 3.2).

Similar proportions of subjects had ALT > ULN at baseline in the LDV/SOF 12 Week and 24 Week groups (38.6% and 36.8%, respectively). In both treatment groups, normalization of ALT was observed in most subjects during treatment (100.0% and 95.0%, respectively, by end of treatment), coincident with decreases in HCV RNA (Section 15.1, Table 18).

All efficacy analyses are provided in Section 15.1, Tables 10 to 18, Figures 2.1 to 4.4, and Appendix 16.2, Listings 9.1 to 9.4.

Virologic Resistance

The full-length nonstructural protein 5A (NS5A) and NS5B coding regions were successfully deep sequenced at pretreatment (baseline) for all 114 randomized subjects. Resistance analyses were conducted with 1% and 15% cutoffs.

Among the 114 subjects sequenced, a total of 104 subjects had genotype 1 HCV infection and 10 had genotype 4 HCV infection. Of the 104 subjects with genotype 1 infection, 84 were subtype 1b, 19 were subtype 1a, and 1 subject had subtype 1e. Of the 10 subjects with genotype 4 infection, 5 had subtype 4d, 3 had subtype 4a, 1 had subtype 4c, and 1 had subtype 4o (Appendix 16.2, Virology Listings 1-3).

Table 2 presents the SVR12 rates for subjects with genotype 1 HCV infection with and without NS5A resistance-associated variant (RAVs) at baseline. Of the 104 genotype 1 HCV infection subjects, 27.9% and 14.4% had NS5A RAVs using 1% and 15% sequencing cutoffs, respectively. With a 15% cutoff, 13 of 15 subjects (86.7%) with baseline NS5A RAVs had genotype 1b infection, and 7 of 15 subjects (46.7%) had NS5A Y93H, followed by L31M (4 of 15 subjects, 26.7%). All subjects with and without NS5A RAVs achieved SVR12.

Table 2. GS-US-337-1406: Overall SVR12 for Subjects with Genotype 1 HCV Infection, with and without NS5A RAVs Following LDV/SOF for 12 or 24 Weeks

	RAVs (1% cutoff) n/N (%)			RAVs (15% cutoff) n/N (%)		
	LDV/SOF 12 Weeks (N=51)	LDV/SOF 24 Weeks (N = 53)	Total	LDV/SOF 12 Weeks (N=57)	LDV/SOF 24 Weeks (N = 57)	Total
Subjects with NS5A variants	13/51 (25.5%)	16/53 (30.2%)	29/104 (27.9%)	6/51 (11.8%)	9/53 (17.0%)	15/104 (14.4%)
SVR12 rate for subjects with NS5A variants	13/13 (100%)	16/16 (100%)	29/29 (100%)	6/6 (100%)	9/9 (100%)	15/15 (100%)
SVR12 rate for subjects with no NS5A variants	38/38 (100%)	37/37 (100%)	75/75 (100%)	45/45 (100%)	44/44 (100%)	89/89 (100%)

Source: Appendix 16.2, Virology Listing 1

Of the 10 subjects with genotype 4 HCV infection, 7 subjects had NS5A RAVs (L30R n = 6, L28M+L30T n = 1) using either 1% or 15% cutoffs (5 in the LDV/SOF 12 Week group and 2 in the LDV/SOF 24 Week group). All subjects achieved SVR12.

A total of 26 of the 114 subjects (22.8%) had NS5B nucleoside inhibitor (NI) RAVs using either 1% or 15% deep sequencing cutoffs (23 had L159F and 3 had V321I) (Section 16.2, Virology Listing 2). All 26 subjects had genotype 1b HCV infection and all achieved SVR12 (16 in the LDV/SOF 12 Week group and 10 in the LDV/SOF 24 Week group).

Pharmacokinetic Results: Based on the high SVR rates and overall safety findings, PK analyses were not performed for this study.

Safety Results: The mean (SD) duration of exposure to study regimen was 11.9 (1.03) weeks and 24.1 (0.15) weeks in the LDV/SOF 12 Week and 24 Week groups, respectively. In the LDV/SOF 12 Week group, 98.2% (56 of 57 subjects) received 12 weeks of LDV/SOF and in the LDV/SOF 24 Week group, 100.0% (57 of 57 subjects) received 24 weeks of LDV/SOF (Section 15.1, Table 6). For both groups, LDV/SOF adherence rates were 98.7% as measured by tablet counts (Section 15.1, Table 9).

The majority of subjects experienced at least 1 AE (59.6%, 34 of 57 subjects and 77.2%, 44 of 57 subjects in the LDV/SOF for 12 and 24 Week groups, respectively) (Section 15.1, Table 19). Overall, the most commonly reported AEs were (LDV/SOF 12 Week group, LDV/SOF 24 Week group): headache (15.8%, 22.8%), asthenia (14.0%, 14.0%), and fatigue (7.0%, 12.3%) (Section 15.1, Table 31). AEs considered related to study drug by the investigator were experienced by 33.3% (19 of 57 subjects) and 54.4% (31 of 57 subjects) of subjects in the LDV/SOF 12 and 24 Week groups, respectively. (Section 15.1, Table 22). Overall, the most commonly reported treatment related AEs were the same as for all AEs (LDV/SOF 12 Week group, LDV/SOF 24 Week group): headache (12.3%, 22.8%), fatigue (7.0%, 12.3%), and asthenia (7.0%, 8.8%) (Section 15.1, Table 22).

Most AEs were Grade 1 or 2 in severity. No Grade 3 AE was reported in more than 1 subject (Section 15.1, Tables 20 and 32). One subject had a Grade 4 AE (suicide attempt), which was reported as serious and not considered related to study drug by the investigator (Section 15.1, Table 32; Appendix 16.2, Listing 10). There were no deaths or pregnancies during the study (Appendix 16.2, Listings 14 and 15).

Serious AEs were experienced by 8.8% (5 of 57 subjects) and 14.0% (8 of 57 subjects) of subjects in the LDV/SOF 12 and 24 Week groups, respectively. (Section 15.1, Table 35). No SAE was reported in more than 1 subject (Section 15.1, Table 35). Three SAEs were considered by the investigator to be related to study drug (Section 15.1, Table 30). Subject PPD (LDV/SOF 24 Weeks) experienced a treatment-related, Grade 3 SAE of pulmonary embolism on Day 32 that resolved on Day 50; the event required hospitalization (Appendix 16.2, Listing 13). Subject PPD (LDV/SOF 24 Weeks) experienced two Grade 2 SAEs, treatment-related increased blood creatinine and nontreatment-related urinary tract infection; both events began on Day 83, resolved on Day 135, and required hospitalization and interruption of study drug from Days 118 to 127 (Appendix 16.2, Listings 7.1 and 13). Subject PPD (LDV/SOF 12 Weeks) experienced a treatment-related, Grade 2 SAE of syncope on Day 30. This subject reported a history of hypertension and restrictive pulmonary syndrome and had asymptomatic atrial fibrillation 23 days before the first dose of study drug (Day 1) (Appendix 16.2, Listing 6). During Week 2 of study treatment, the subject had atrial fibrillation for which an external cardiologist prescribed amiodarone hydrochloride, a medication prohibited per protocol. Despite the study site's request to stop amiodarone hydrochloride and the cardiologist's new unspecified prescription, the subject continued treatment with amiodarone hydrochloride and on Day 30 she experienced a Grade 2 AE of bradycardia and a Grade 2 SAE of syncope, which was considered related to study drug by the investigator and led to study drug discontinuation on Day 30. Both the events of bradycardia and syncope resolved on Day 30, the day of onset (Section 15.2 provides a narrative describing the SAE and Appendix 16.2, Listings 7.1, 8.1, and 13).

Permanent discontinuation or interruption of study drug due to AEs were rare. No AE leading to discontinuation or interruption of study drug was experienced by more than 1 subject. Subject PPD (LDV/SOF 24 Weeks) had study drug interrupted due to gastroenteritis and Subject PPD (LDV/SOF 24 Weeks) had study drug interrupted due to a treatment-related SAE of increased blood creatinine and a nontreatment-related SAE of urinary tract infection (Section 15.1, Tables 33 and 34; Appendix 16.2, Listings 7.1 and 13). As discussed above, Subject PPD (LDV/SOF 12 Weeks) permanently discontinued study drug due to a treatment-related SAE of syncope on Day 30 (Section 15.1, Table 33; Appendix 16.2, Listings 7.1 and 13).

Median change in eGFR values remained generally stable throughout the study (Section 15.1, Figure 5.14). After 1 week of treatment, median changes from baseline in eGFR were −1.8 and 0.0 mL/min in the LDV/SOF 12 Week and 24 Week groups, respectively. By the end of treatment, median changes from baseline in eGFR were −1.8 and −1.2 mL/min, respectively (Section 15.1, Table 37.16).

Most subjects had at least 1 laboratory abnormality reported. The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity (Section 15.1, Table 38.1). Two subjects had Grade 4 laboratory abnormalities (1.8% of subjects in each group), including transient, increased uric acid (LDV/SOF 12 Week group) and decreased lymphocytes and transient, decreased neutrophils (LDV/SOF 24 Week group). A total of 11 of 57 subjects (19.3%) and 12 of 57 subjects (21.1%) had Grade 3 laboratory abnormalities in the LDV/SOF 12 Week and 24 Week groups, respectively. The most common Grade 3 laboratory abnormalities were (LDV/SOF 12 Week group, LDV/SOF 24 Week group) increased uric acid (8.8%, 7.0%), blood in the urine (1.8%, 3.5%), and increased lipase (3.5%, 1.8%; no subjects with increased lipase reported an AE of pancreatitis [Appendix 16.2, Listing 10]). Subjects with Grade 3 or 4 increased uric acid had either Grade 1 or 2 increased uric acid at baseline or screening (Appendix 16.2, Listing 17). A total of 5 subjects (8.8%) and 6 subjects (10.5%) in the LDV/SOF 12 Week and 24 Week groups, respectively, had postbaseline hemoglobin < 10 g/dL. One subject (LDV/SOF 12 Week group) had an isolated postbaseline hemoglobin < 8.5 g/dL (Section 15.1, Table 37.6).

No clinically significant changes in mean vital signs (systolic blood pressure, diastolic blood pressure, and pulse) or mean BMI were reported during the study (Section 15.1, Tables 39.1−39.4; Appendix 16.2, Listings 25.1−25.2).

Most subjects received at least 1 concomitant immunosuppressant medication (100.0% and 96.5% in the LDV/SOF for 12 and 24 Week groups, respectively) (Section 15.1, Table 7.2); the most common immunosuppressant medications were (LDV/SOF 12 Week group, LDV/SOF 24 Week group):prednisone (52.6%, 57.9%), tacrolimus (42.1%, 52.6%), mycophenolate mofetil (42.1%, 42.1%), and ciclosporin (40.4%, 36.8%) (Section 15.1, Table 7.2). There were no documented episodes of graft rejection reported during the study (Appendix 16.2, Listing 10).

Section 15.2 provides narratives for all SAEs and AEs leading to discontinuation of LDV/SOF from the first dose of study drug through the end of the study (ie, the SVR24 visit). The AE results are provided in Section 15.1, Tables 19 to 36, and Appendix 16.2, Listings 10 to 13. Laboratory results are provided in Section 15.1, Tables 37.1 to 38.2 and Figures 5.1 to 5.14; Appendix 16.2, Listings 16 to 22.2. Electrocardiogram results are provided in Appendix 16.2, Listing 24.

CONCLUSIONS: The conclusions from Study GS-US-337-1406 are as follows:

- In kidney transplant recipients with genotype 1 or 4 HCV infection, 12 or 24 weeks of LDV/SOF treatment resulted in an SVR12 rate of 100.0%.
- Baseline NS5A and NS5B nucleoside inhibitor (NI) RAVs did not affect the SVR12 rate (100%) of the kidney transplant population with genotype 1 or 4 HCV infection.
- Treatment with LDV/SOF for 12 or 24 weeks was generally safe and well tolerated, with no deaths, one permanent discontinuation of LDV/SOF due to AEs, and few Grade 3 or 4 AEs.