FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination Administered in Patients Infected with Chronic HCV for Use in the Peri-Operative Liver Transplantation Setting
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-337-1428 (CRUSH-C)
Phase of Development:	Phase 2
IND No.:	115268
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02350569
Study Start Date:	22 May 2015 (First Subject Screened)
Study End Date:	22 April 2016 (Last Subject Observation for the Retreatment Period)
Principal or Coordinating Investigator:	Name: Josh Levitsky, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Theo Brandt-Sarif, MD Telephone: PPD Fax: PPD
Report Date:	03 August 2016

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-337-1428
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination Administered in Patients Infected with Chronic HCV for Use in the Peri-Operative Liver Transplantation Setting

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled at a total of 6 sites in the United States.

Publications: There are no publications at the time of this CSR.

Study Period:

22 May 2015 (First Subject Screened)
28 March 2016 (Last Subject Observation in Main Study)
22 April 2016 (Last Subject Observation for the Retreatment Period)

Phase of Development: Phase 2

Objectives:

The primary objective of this study was as follows:

- To explore the antiviral efficacy of treatment with ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) therapy for 4 weeks at the time of liver transplantation and through 4 weeks posttransplantation, as measured by sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12 defined as HCV RNA < lower limit of quantification [LLOQ] 12 weeks after stopping study drug).

The secondary objectives of this study were as follows:

- To evaluate safety and tolerability of LDV/SOF in HCV-infected subjects in the peri-operative and posttransplant period
- To determine the percentage of subjects who attained SVR at 4 weeks after discontinuation of therapy (SVR4)
- To assess rates of graft survival, graft function, acute rejection, and immunosuppressive therapy during treatment with LDV/SOF
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation
- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation

- To characterize pharmacokinetics (PK) of LDV/SOF

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 provided their separate and specific consent

Methodology: This Phase 2, open-label, multicenter study evaluated the safety, tolerability, and antiviral efficacy of LDV/SOF treatment in subjects with genotype 1 or 4 HCV infection who were undergoing primary liver transplantation.

Subjects were initially screened to determine eligibility for participation in the study, which included the requirement to be on the waitlist for liver transplantation. Following the initial confirmation of eligibility, subjects were rescreened and reconsented every 6 months. Eligibility was reconfirmed on Day −1, the day the subject was called to the hospital to receive their liver transplant.

After confirmation of eligibility on Day −1, subjects received a dose of LDV/SOF. The first morning after transplant, subjects received the next dose of LDV/SOF and continued treatment once daily for 4 weeks. If subjects were unable to swallow the LDV/SOF tablet, the tablet was crushed and administered by nasogastric tube. Following the last dose of study drug, subjects completed posttreatment visits at Weeks 1, 2, 4, 8, and 12. For this report, this part of the study is referred to as the Main Study.

If a subject received LDV/SOF on Day −1 and the transplant was not performed, the subject was discontinued from LDV/SOF treatment. Study eligibility was reconfirmed if the subject was brought back again for transplant.

Subjects who completed 28 days of treatment and experienced virologic failure in the Main Study were able to be retreated with an additional 12 weeks of LDV/SOF treatment within 1 month of follow-up Week 4 of the original treatment. Subjects attended study visits at restart/Day 1, retreatment Weeks 1, 2, 4, 8, and 12 and post-retreatment Weeks 1, 2, 4, 8, and 12.

All subjects participated in a PK substudy in which intensive serial PK sample collection was performed on Day 1 to determine the PK of LDV and SOF (as well as SOF metabolites GS-566500 and GS-331007). The purpose of the intensive PK collection was to determine if administration of crushed LDV/SOF through a nasogastric tube had similar PK to oral administration of LDV/SOF tablets.

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 25 subjects undergoing transplantation

Analyzed: In the Main Study, 16 transplanted subjects were included in the Full Analysis Set and the Safety Analysis Set (LDV/SOF 4 Week group). Three subjects were called to transplant, took 1 pretransplant LDV/SOF dose, and their transplant was subsequently cancelled. These 3 subjects are included in the Safety Analysis Set (LDV/SOF 1 Day group) and their data is included in listings. For the PK Substudy Analysis Set, 16 subjects were included. One subject who experienced relapse after completing 28 days of LDV/SOF in the Main Study was retreated for an additional 12 weeks with LDV/SOF.

Diagnosis and Main Criteria for Inclusion: Males or females ≥ 18 years of age who had chronic genotype 1 or 4 HCV infection, who had quantifiable HCV RNA infection at screening, and who had been listed for liver transplantation were eligible for this study. Subjects did not have any serious or active medical or psychiatric illnesses. In addition, no history of prior organ transplantation was allowed. Treatment-experienced subjects could not have received treatment with interferon, ribavirin (RBV), telaprevir, boceprevir, or any other approved or experimental medication with known anti-HCV activity within 1 month prior to screening nor have had any prior exposure to an HCV nonstructural protein 5A (NS5A) specific inhibitor (with the exception of LDV/SOF as part of this study if LDV/SOF was restarted). Subjects or legally-authorized representatives were willing and able to sign an informed consent form.

Duration of Treatment: In the Main Study, treatment duration was 4 weeks for subjects who received a transplant and 1 day for subjects whose transplant was canceled. Subjects who completed study treatment and experienced virologic failure were retreated for an additional 12 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 DK1208B1R, DK1209B1R-C, and DK1303B1.

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

Criteria for Evaluation:

Efficacy: 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.

In the Main Study, blood samples to determine HCV RNA levels were collected from subjects at screening, rescreening, baseline/Day −1 (predose), pretransplant, Days 1, 3, 5, 7, 14, 21, and 28 during treatment (or upon early termination), and posttreatment Weeks 1, 2, 4, 8, and 12.

For subjects who completed treatment and experienced virologic failure and restarted LDV/SOF treatment, blood samples to determine HCV RNA levels were collected at restart/Day 1, retreatment Weeks 1, 2, 4, 8, and 12 (or upon early termination), and post-retreatment Weeks 1, 2, 4, 8, and 12.

Pharmacokinetics: A single, sparse PK blood sample was collected from all subjects at each posttransplant, on-treatment visit except on Day 1. On Day 1, all subjects participated in an intensive serial PK substudy to determine the plasma concentrations of SOF, GS-566500, GS-331007, and LDV. Serial PK samples were collected at the following time points:

- Day 1: 0 (pre-dose), 0.5, 1, 2, 4, 8, 12 and 24 hours postdose.

Safety: For the Main Study, safety assessments included monitoring of adverse events (AEs), concomitant medications, concomitant immunosuppressant medications administered to prevent rejection of the transplanted liver, and clinical laboratory analyses at prespecified intervals through the posttreatment Week 12 visit. Vital sign measurements, electrocardiograms (ECG), and physical examinations also were collected during treatment at prespecified intervals. Model for End-Stage Liver Disease (MELD) and Child-Pugh-Turcotte (CPT) scores were performed at the screening and Day −1 visits.

For subjects who completed treatment and experienced virologic failure and restarted LDV/SOF treatment, safety assessments included monitoring of AEs, concomitant medications, and clinical laboratory analyses at prespecified intervals through the post-retreatment Week 12 visit. Vital sign measurements, ECG, and physical examination also were collected during retreatment.

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 for the Main Study is provided in Appendix 16.1.9; an addendum to the statistical analysis plan also is provided in Appendix 16.1.9 for Subject PPD who completed 28 days of LDV/SOF treatment, relapsed at the posttreatment Week 4 visit, and received LDV/SOF retreatment for 12 weeks.

The Enrolled Analysis Set included subjects who were enrolled into the study. The Full Analysis Set included subjects who were enrolled into the study, received a liver transplant, and received at least 1 dose of study drug. The Safety Analysis Set included subjects who were enrolled into the study and received at least 1 dose of study drug. The PK Substudy analysis set included subjects who were enrolled, received study drug on study Day 1 (eg, first study drug dose posttransplant), and for whom PK parameters of the analytes of interest (SOF, GS-566500, and GS-331007, and LDV) were calculated based on intensive PK samples collected on study Day 1.

Efficacy: In the Main Study, 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 was calculated; exact 2-sided 95% CIs were constructed using the Clopper-Pearson method {Clopper et al 1934}. No statistical hypothesis testing was performed.

In the Main Study, secondary efficacy endpoints included the proportion of subjects with HCV RNA < LLOQ by study visit, the proportion of subjects who achieved SVR 4 weeks after discontinuation of therapy (SVR4), and the proportion of subjects with virologic failure. For the proportion of subjects with end-of-treatment virologic failure or relapse, a summary table of the number and percentage of subjects with SVR12, overall virologic failure (with subgroups for end-of-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.

SVR12 was presented by age group (< and ≥ 65 years), sex, black/non-black, HCV genotype (1a, 1b, or 4), IL28B genotype, BMI group (< and ≥ 30 kg/m^2), and prior HCV treatment. In addition, a summary table of the number and percentage of subjects with SVR by posttreatment week was provided; 95% Clopper-Pearson exact CIs were presented for the proportion of subjects with SVR.

In the Main Study, to determine the $\log_{10}$ reduction achieved after a single, perioperative LDV/SOF dose prior to transplant, a descriptive, exploratory analysis summarized the HCV RNA values on Day −1, the HCV RNA values immediately prior to transplant, and the change in HCV RNA values from Day −1 to pretransplant for subjects with measurements at both time points.

For Subject PPD who completed 28 days of treatment, experienced virologic failure, and restarted LDV/SOF for 12 weeks, a listing was provided for HCV RNA data from the first dose of retreatment study drug to the last observation of post-retreatment follow-up.

Pharmacokinetics: Pharmacokinetic parameters were generated for all subjects in the PK Substudy Analysis Set based on intensive PK samples collected on study Day 1 (ie, the first posttransplant dose). The PK parameters for SOF, GS-566500, GS-331007, and LDV were estimated for all subjects with evaluable PK profiles. For each subject, the following plasma PK parameters were estimated, as appropriate: $AUC_{0\text{-}24}$, AUC_{last}, C_{last}, C_{max}, C_{24}, $t_{1/2}$, T_{last}, T_{max}, and λ_z.

Individual subject concentration data at each time point, and individual subject PK parameters for SOF, GS-566500, GS-331007, and LDV in plasma were listed and summarized using descriptive statistics (n, mean, SD, coefficient of variation [%CV], median, minimum, maximum, first quartile [Q1], and third quartile [Q3]) by route of LDV/SOF administration (oral or nasogastric tube) and overall on study Day 1. In addition, for individual subject PK parameter data, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values were presented.

For each analyte, 2 tables were provided by route of LDV/SOF administration (oral or nasogastric tube) and overall on study Day 1: individual subject concentration data and individual subject plasma PK parameters. For each analyte, 2 figures (on linear and semilogarithmic scales) were provided by route of LDV/SOF administration (oral or nasogastric tube) and overall on study Day 1: mean (± SD) concentration data versus time and median (Q1, Q3) concentration data versus time. A by-subject listing was provided of PK sampling details (and PK concentrations), including both intensive and sparse PK samples.

Safety: 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 Affairs (MedDRA), Version 18.1. Laboratory results were assigned toxicity grades of Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4. No summary tables for toxicity grading were produced due to the effects of liver transplantation on laboratory values in the immediate postoperative period.

In the Main Study, all enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety data for the LDV/SOF 4 Week group were summarized and included all data collected on or after the first dose of study drug (ie, Day −1) through the date of last dose of study drug plus 30 days. In addition, screening and Day −1 CPT and MELD scores

were listed for the Safety Analysis Set; baseline values for the LDV/SOF 4 Week group were summarized in the demographics table.

For Subject PPD who completed treatment, relapsed at posttreatment Week 4, and restarted LDV/SOF for 12 weeks, retreatment listings were provided for AE and safety laboratory data from the first dose of retreatment study drug to the last observation of post-retreatment follow-up.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Due to limited availability of the target population, fewer than the planned 25 subjects were enrolled. In the Main Study, 16 subjects were enrolled, transplanted, received LDV/SOF treatment, and were included in the Full Analysis Set and Safety Analysis Set (LDV/SOF 4 Weeks) (Section 15.1, Table 3). Of these 16 subjects, 15 completed study drug. Subject PPD discontinued study drug on Day 5 after meeting the protocol-defined study drug discontinuation criterion, confirmed creatinine clearance < 30 mL/min on study Day 5 (Appendix 16.2, Listing 1).

Three subjects were excluded from the Full Analysis Set; these subjects were called for transplant, received LDV/SOF on Day −1, but did not receive a liver transplant. Two of the 3 subjects (Subjects PPD and PPD were re-enrolled into the study and received LDV/SOF posttransplant as Subjects PPD and PPD The third subject (Subject PPD was rescreened but did not undergo a liver transplant (Section 15.1, Table 3; Appendix 16.2, Listings 1, 2.1, and 5.1).

In the Main Study, half of the LDV/SOF 4 Week subjects were male (50.0% male, 8 subjects), most were white (81.3% white, 13 subjects), and not of Hispanic or Latino ethnicity (75.0% not Hispanic or Latino, 12 subjects). Subjects had a mean age of 59 years (range: 52-72 years). The mean baseline BMI was 27.3 kg/m^2 (range: 19.1, 40.0), and most subjects (75.0%, 12 subjects) had a baseline BMI < 30 kg/m^2 (Section 15.1, Table 4).

All LDV/SOF 4 Week subjects had genotype 1 HCV infection (68.8%, genotype 1a and 31.3%, genotype 1b). Most subjects had a baseline HCV RNA < 800,000 IU/mL (62.5%), baseline ALT ≤ 1.5 × ULN (56.3%), and no prior HCV treatment experience (56.3%). Most subjects (68.8%) had non-CC (CT or TT) IL28B alleles, while 31.3% of subjects had the IL28B CC allele. The mean (SD) baseline estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation was 81.2 (25.17) mL/min {Cockcroft et al 1976}.

More subjects had a baseline CPT score from 10 to 15 (40.0%) than CPT scores from 5 to 6 (26.7%) or 7 to 9 (33.3%), respectively. Most subjects had baseline native MELD scores from 10 to 15 (57.1%), with 21.4% each having native MELD scores that were < 10 or 16 to 20, respectively (Section 15.1, Table 4). The mean (SD) baseline native MELD score was 13 (3.8). A total of 10 subjects (62.5%) met the HCC criteria and Milan criteria; for these subjects, an exception MELD score was calculated that added additional MELD score points based on the subject's time on the liver transplantation waitlist. The mean (SD) baseline exception MELD score was 24 (4.8). Most subjects (75.0%) received a transplanted liver from cadaveric donor (11 from a donor who had experienced brain death and 1 from a donor who had experienced cardiac death) and 25.0% of subjects (4 subjects) received a transplanted liver from a living donor.

Analyses related to disposition, demographics, and exposure for the Main Study are presented in Section 15.1, Tables 1 to 6, and Appendix 16.2, Listings 1 to 5.2. In addition, an Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

One subject (Subject PPD who completed 4 weeks of LDV/SOF in the Main Study and relapsed at posttreatment Week 4, was retreated with 12 weeks of LDV/SOF (Appendix 16.2, Listings 21 and 27-29).

Efficacy Results: Table 1 presents the primary efficacy endpoint in the Main Study, the proportion of subjects with SVR12 (HCV RNA < LLOQ 12 weeks after LDV/SOF discontinuation). The SVR12 rate was 87.5% (95% CI: 61.7%-98.4%). Of the 2 subjects who did not achieve SVR12, 1 subject (Subject PPD discontinued study drug after meeting a protocol-defined study drug discontinuation criterion (creatinine clearance < 30 mL/min at Day 5) without having HCV RNA < LLOQ while on treatment and 1 subject relapsed (Subject PPD relapsed at posttreatment Week 4) (Section 15.1, Tables 10 and 11; Appendix 16.2, Listings 1, 21, and 22).

Table 1. GS-US-337-1428: SVR12 and Virologic Outcome (Full Analysis Set)

	LDV/SOF 4 Weeks (N = 16)
SVR12	14/16 (87.5%)
95% CI	61.7% to 98.4%
Overall Virologic Failure	1/16 (6.3%)
Relapse	1/15 (6.7%)
Completed Study Treatment	1/15 (6.7%)
End of Treatment Virologic Failure	0/16
Other	1/16 (6.3%)

HCV RNA was analyzed using the Roche COBAS AmpliPrep/COBAS Taqman HCV Test, v2.0 with lower limit of quantitation 15 IU/mL.
Relapse to posttreatment Week 12 = confirmed HCV RNA ≥ LLOQ during the posttreatment period up to posttreatment Day 146 having achieved HCV RNA < LLOQ at last on-treatment visit.
End of Treatment Virologic Failure = Completed LDV/SOF for 28 Days and HCV RNA ≥ LLOQ at last on-treatment measurement.
Other = subject who did not achieve SVR12 and did not meet virologic failure criteria.
Source: Section 15.1, Tables 10 and 11

The SVR4 rate was 87.5% (95% CI: 61.7%-98.4%); no subjects achieved SVR4 who did not achieve SVR12 (Section 15.1, Table 12).

After liver transplantation, HCV RNA levels declined rapidly. At Days 14, 21, and 28, 93.3%, 100.0%, and 100.0% of subjects had HCV RNA < LLOQ, respectively, and 33.3%, 80.0%, and 100.0% of subjects had HCV RNA not detected, respectively (Section 15.1, Table 16). In an exploratory analysis, the mean (SD) change in HCV RNA (log_{10} IU/L) from Day −1 to pretransplant was −0.24 (0.613) (Section 15.1, Table 15).

Subgroup analyses of SVR12 rates should be interpreted with caution due to the small sample size in the subgroups. However, the point estimates for most subgroups were similar to the

overall SVR12 estimate and the subgroup confidence intervals overlapped the overall SVR12 estimate in all subgroups (Section 15.1, Table 14).

Subject PPD completed LDV/SOF treatment in the Main Study, relapsed at posttreatment Week 4, received 12 weeks of LDV/SOF retreatment, and achieved SVR12 after retreatment (Appendix 16.2, Listing 29).

Virologic Resistance: The full-length nonstructural protein 5A (NS5A) and NS5B coding regions were successfully deep sequenced at pretreatment (baseline) for all 16 subjects including 1 relapsed subject and 1 subject who discontinued study drug on Day 5. Baseline and posttreatment analyses were conducted with a 1% cutoff. Subject PPD who discontinued study drug on Day 5 was excluded from the baseline resistance and treatment outcome analysis.

Overall, 3 of 15 subjects (20.0%) had NS5A resistance-associated variants (RAVs) at baseline and 2 of the 3 subjects (66.7%) achieved SVR12 compared with 12 of 12 subjects (100%) without NS5A RAVs who achieved SVR12 (Appendix 16.2, Virology Listing 1). Two of the 15 subjects (13.3%) had NS5B nucleotide-inhibitor RAVs at baseline (1 with S282G 1.3% and another with N142T 85.0%) and both achieved SVR12 (Appendix 16.2, Virology Listing 2).

One of the 15 subjects was treatment-experienced with HCV genotype 1a infection and experienced virologic relapse at posttreatment Week 4 (Table 2). The subject had NS5A RAVs Q30H (96.4%), Q30R (1.8%), and H58D (1.5%) at baseline. At the time of relapse, Q30R enriched to > 99% and Q30H and H58D were no longer detected. The subject did not have any NS5B RAVs at baseline or at the time of relapse. This subject achieved SVR12 following retreatment with 12 weeks of LDV/SOF.

Subject PPD who discontinued study drug on Day 5 had no NS5A RAVs at baseline, however, NS5A RAVs emerged at 3 positions (M28T, Q30H/R, and Y93C/N) at posttreatment Week 4 (Table 2). The subject did not have any NS5B RAVs at baseline or at posttreatment Week 4 visit.

Table 2. GS-US-337-1428: Baseline and Postbaseline NS5A and NS5B RAVs in Subjects with Virologic Failure

Subject	Genotype	Treatment	NS5A RAVs		NS5B RAVs	
			Baseline	Posttreatment	Baseline	Posttreatment
PPD	1a	LDV/SOF FDC 4 weeks	Q30H (96.4%) Q30R (1.8%) H58D (1.5%)	Q30R (> 99%)	None	None
PPD	1a	LDV/SOF FDC 4 weeks	None	M28T (91.3%) Q30H (22.4%) Q30R (69.0%) Y93C (6.0%) Y93N (1.9%)	None	None

a Subject PPD discontinued study drug on Day 5
Source: Appendix 16.2, Virology Listings 3 and 4

Pharmacokinetic Results: The PK parameters AUC_{last}, AUC_{0-24}, C_{max}, and C_{24} of SOF, its metabolites GS-566500 and GS-331007, and LDV, from study Day 1 are summarized by method of LDV/SOF administration, either as a crushed tablet through the nasogastric tube or as an orally administered tablet (Table 3).

The study Day 1 plasma concentration-time profile for Subject PPD (nasogastric administration) was irregular and low compared to the rest of the subjects with intensive data and relative to sparse samples throughout the remainder of the study for that subject, suggesting potential administration-related issues. Thus, this subject was excluded from the intensive PK summary presented in Table 3. A summary of PK data including this subject is presented in Section 15.1, PK Tables 6 to 9.

Sofosbuvir AUC was similar following nasogastric or oral administration. Sofosbuvir C_{max} was higher following nasogastric administration, which could have been related to preparation of the tablet slurry yielding a portion of the SOF dose in the solubilized state. Sofosbuvir C_{24} was not detectable in the nasogastric administration group but was detectable in 9 of 12 subjects in the oral administration group. Detectable SOF concentrations at 24 hours are typically unexpected, though T_{max} of all analytes was highly variable and could be attributable to gastroparesis following solid organ transplantation (Section 15.1, PK Tables 6 to 9). GS-566500 AUC was higher for the nasogastric administration group, while GS-566500 C_{max} and C_{24} were similar between both groups. GS-331007 exposure parameters (AUC, C_{max}, and C_{tau}) were higher following nasogastric administration compared with oral administration and is likely linked to the renal function of the subjects in the respective administration groups. Ledipasvir AUC, C_{max}, and C_{24} were modestly lower following nasogastric administration. While some differences in the PK of SOF, GS-566500, GS-331007, and LDV were observed following nasogastric administration compared with oral administration, these data should be interpreted with caution given the limited number of subjects being compared.

Table 3. GS-US-337-1428: SOF, GS-566500, GS-331007, and LDV Pharmacokinetic Parameters

PK Parameter, mean (%CV)	Nasogastric (NG) Administration (N=3)[a]	Oral Administration (N=12)
SOF		
AUC_{last} (ng•h/mL)	3321.0 (72.1)	3027.9 (124.7)
AUC_{0-24} (ng•h/mL)	3402.8 (68.3)	2889.2 (135.9)[b]
C_{max} (ng/mL)	1601.0 (57.3)	563.5 (87.8)
C_{24} (ng/mL)	-	90.1 (114.6)[c]
GS-566500		
AUC_{last} (ng•h/mL)	8398.3 (48.3)	4636.7 (78.9)
AUC_{0-24} (ng•h/mL)	8500.4 (45.9)	4659.4 (78.1)
C_{max} (ng/mL)	785.7 (35.2)	531.8 (95.2)
C_{24} (ng/mL)	138.8 (44.1)[d]	139.4 (99.0)[e]
GS-331007		
AUC_{last} (ng•h/mL)	45,842.2 (47.1)	29,580.9 (66.8)
C_{max} (ng/mL)	2333.3 (42.2)	1566.8 (56.6)
C_{24} (ng/mL)	1910.3 (62.3)	1129.9 (67.1)
LDV		
AUC_{last} (ng•h/mL)	2283.2 (24.4)	3686.7 (52.1)
AUC_{0-24} (ng•h/mL)	2283.2 (24.4)	3686.7 (52.1)
C_{max} (ng/mL)	117.9 (16.7)	203.1 (56.9)
C_{24} (ng/mL)	97.2 (43.3)	160.7 (45.4)

a Subject PPD excluded
b n = 11
c n = 9
d n = 2
e n = 10
Source: Section 15.1, PK Tables 6 to 9 and Ad hoc Analysis Tables 8213.1 to Tables 8213.4

Overall, the exposures of SOF and GS-566500 in this study were similar to exposures in a reference population of HCV-infected subjects following liver transplantation (Studies GS-US-337-0123 and GS-US-337-0124). Study Day 1 exposures of GS-331007, the renally eliminated SOF metabolite, in this study were higher than the reference population in Studies GS-US-337-0123 and GS-US-337-0124, but were consistent with varying degrees of renal impairment observed in subjects during this study. Ledipasvir PK was similar to the reference population based on the expected accumulation of LDV after multiple dose administration.

Sofosbuvir, GS-566500, GS-331007, and LDV plasma concentrations measured on Day 3 through Day 28 visits were generally within the range of concentrations observed in the reference population (Studies GS-US-337-0123 and GS-US-337-0124).

Subject PPD who experienced virologic relapse at posttreatment Week 4, had SOF, GS-566500, GS-331007, and LDV exposures on study Day 1 within the range of exposures

observed for other subjects. The concentration of sparse plasma samples for these analytes also was within the range of concentrations observed in other subjects in this study. Collectively, the exposures of SOF, GS-566500, GS-331007, and LDV observed in this subject do not explain relapse for this subject.

Safety Results: In the Main Study, the mean (SD) duration of exposure to study regimen was 27.6 (5.78) days, with 15 of 16 subjects (93.8%) receiving ≥ 28 days of study drug (Section 15.1, Table 5). Adherence rates for LDV/SOF ranged from 96.6% to 100.0% as measured by tablet counts (Section 15.1, Table 6).

In the Main Study, most subjects (87.5%, 14 of 16 subjects) experienced at least 1 AE and 1 subject experienced an AE that was considered by the investigator to be related to study drug (Grade 2 dry eye) (Section 15.1, Table 17; Appendix 16.2, Listing 8). The most frequently reported AE was hyperglycemia (43.8%, 7 of 16 subjects), followed by acute kidney injury, anemia, constipation, hypertension, malnutrition, nausea, and edema (31.3% each, 5 of 16 subjects) (Section 15.1, Table 26). Most AEs were either Grade 1 or Grade 2 in severity (Appendix 16.2, Listings 8 and 9). No Grade 4 AEs were reported. Four subjects experienced a Grade 3 AE (malnutrition [3 subjects], incision site cellulitis and hepatic artery flow decreased [1 subject each]); none of these events were considered by the investigator to be related to study drug (Section 15.1, Table 20; Appendix 16.2, Listing 9). A total of 5 subjects (31.3%) reported serious adverse events (SAEs); no SAEs were considered by the investigator to be related to study drug (Section 15.1, Tables 24 and 30). No subjects experienced AEs leading to discontinuation of LDV/SOF (Section 15.1, Table 25). No pregnancies or deaths were reported (Section 15.1, Table 17 and Appendix 16.2, Listings 12 and 13.1).

Between study Day 1 and posttreatment Week 4, decreases in median ALT, AST, and total bilirubin and increases in median albumin were observed, consistent with improvement in liver function following successful transplantation (Section 15.1, Tables 31.1, 31.2, 31.4, and 31.12). By posttreatment Week 4, platelets were within normal limits (Section 15.1, Table 31.11; Appendix 16.2, Listing 14). On Day −1 (prior to transplantation), 31.3% of subjects had a hemoglobin value < 10 g/dL and 1 subject (6.3%) had a hemoglobin value < 8.5 g/dL (Section 15.1, Ad hoc Table 8134). Posttransplantation, most subjects (87.5%, 14 subjects) had at least 1 hemoglobin value < 10 g/dL and 62.5% of subjects had at least 1 hemoglobin value < 8.5 g/dL (Section 15.1, Table 32). Abnormal laboratory results were consistent with the subject's advanced liver disease and postsurgery status (Appendix 16.2, Listings 15−20). No adverse trends attributable to study drug were identified.

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) were reported during the study (Section 15.1, Tables 33-1-33.3). One subject (Subject PPD had a clinically significant ECG change from baseline (ST elevation replaced ST depression in inferior leads); the event was reported as a nonserious, Grade 1 AE on posttreatment Day 1 and was not considered related to study drug (Section 15.1, Table 35; Appendix 16.2, Listing 24). The ECG change occurred in the context of admission for posttransplant complications and was not present when the ECG was repeated 2 days later.

No subjects experienced an episode of graft loss during the study, though 2 subjects had a transplant rejection episode (Appendix 16.2, Listings 8 and 13.2). All subjects received at least 1 concomitant immunosuppressant medication; the most common immunosuppressant medications were tacrolimus (100.0%, 16 subjects), prednisone (81.3%, 13 subjects), and

mycophenolate mofetil (75.0%, 12 subjects) (Section 15.1, Table 9). Three subjects (Subjects PPD PPD and PPD had changes to their immunosuppressant regimen for management of rejection (Appendix 16.2, Listing 7). One subject (6.3%) received a concomitant proton pump inhibitor (omeprazole) between Day −1 and Day 1 (Section 15.1, Table 8).

The AE results for the Main Study are provided in Section 15.1, Tables 19 to 30, and Appendix 16.2, Listings 8 to 13.1. Laboratory results for the Main Study are provided in Section 15.1, Tables 31.1−31.15 and 32; Appendix 16.2, Listings 15−20).

During retreatment, Subject PPD received 12 weeks of LDV/SOF and experienced 4 AEs (Grade 1 acne, Grade 1 abnormal hair growth, Grade 2 abdominal pain, and Grade 2 pruritus), none of these adverse events were serious and none were considered related to study drug by the investigator (Appendix 16.2, Listing 27). There were no treatment-emergent Grade 3 or 4 laboratory abnormalities (Appendix 16.2, Listing 28).

CONCLUSIONS: The conclusions from Study GS-US-337-1428 are as follows:

- In subjects with genotype 1 HCV infection who underwent primary liver transplantation, 4 weeks of LDV/SOF treatment resulted in an SVR12 rate of 87.5%. Of the 2 subjects not achieving SVR12, 1 met early stopping criteria due to low CL_{cr} on study Day 5; the second relapsed at posttreatment Week 4, was retreated with LDV/SOF for 12 weeks, and achieved SVR12.
- No meaningful differences in the PK of SOF, GS-566500, GS-331007, and LDV could be identified following nasogastric or oral administration of LDV/SOF.
- The PK of SOF, GS-566500, and LDV was similar to that observed in the postliver transplant population in Studies GS-US-337-0123 and GS-US-337-0124. Comparatively higher GS-331007 exposures observed in this study were consistent with the reduced renal function of subjects who are immediately posttransplantation.
- NS5A RAVs were observed at the time of virologic failure in a single subject who relapsed following LDV/SOF for 4 weeks posttransplantation. Despite these RAVs, this subject achieved SVR12 after retreatment with LDV/SOF for 12 weeks.
- Treatment with LDV/SOF was generally safe and well tolerated, with no deaths, graft losses, discontinuations of LDV/SOF due to AEs, and few Grade 3 AEs.