FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir Fixed Dose Combination Administered for Four Weeks in Patients Infected with Chronic HCV in the Peri-Operative Liver Transplantation Setting
Name of Test Drug:	Sofosbuvir (SOF)/Velpatasvir (VEL) Fixed-Dose Combination (FDC)
Dose and Formulation:	SOF/VEL FDC (400/100 mg) tablet
Indication:	Hepatitis C virus infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Dr. Foster City, CA 94404 USA
Study No.:	GS-US-342-2083
Phase of Development:	Phase 2
IND No.:	This is a non-IND study
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02728206
Study Start Date:	12 June 2016 (First Subject Screened)
Study End Date:	16 January 2018 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Edward Gane, MBChB, MD, FRACP Affiliation: PPD
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Report Date:	01 June 2018

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-342-2083
Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404
USA

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

Investigator: Edward Gane, MBChB, MD, FRACP

Study Centers: 1 site in New Zealand

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

Study Period:

12 June 2016 (First Subject Screened)
16 January 2018 (Last Subject Last Observation for the Primary Endpoint)

Phase of Development: Phase 2

Objectives:

The primary objectives of this study were as follows:

- To explore the antiviral efficacy of treatment with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) therapy administered for four weeks following liver transplantation as measured by sustained virologic response (SVR) 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of SOF/VEL in HCV-infected subjects in the peri-operative and post-transplant period

The secondary objectives of this study were as follows:

- To determine the percentage of subjects who attain SVR at 4 weeks after cessation of treatment (SVR4)
- To evaluate the proportion of subjects with virologic failure
- To assess rates of graft survival, graft function, acute rejection and immunosuppressive therapy during treatment with SOF/VEL
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To characterize pharmacokinetics (PK) of SOF/VEL

Methodology: This Phase 2, open-label study evaluated the safety, tolerability, and antiviral efficacy of SOF/VEL for 4 weeks in subjects with chronic HCV infection who were undergoing 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. If the screening visit occurred more than 48 hours before liver transplant surgery started, the subject was reassessed within 48 hours of transplantation to determine their continued eligibility at the presurgery visit.

Subjects received their first dose of SOF/VEL the day of the subject's liver transplant if the transplant was completed before noon, or the following day if it was completed after noon and continued treatment once daily for 4 weeks. The planned first dose may have been delayed for up to 1 day if, in the investigator's opinion, delay was in the subject's medical interest.

All subjects completed the following study visits: screening, presurgery (if needed), on-treatment visits on Days 1, 3, 5, 7, 14, 21, and 28, and posttreatment visits at Weeks 1, 2, 4, and 12 following the last dose of study drug.

All subjects participated in a PK substudy in which intensive serial PK sample collection was performed on Day 1 to determine the PK of SOF (as well as SOF metabolites GS-566500 and GS-331007) and VEL.

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: 10 subjects
Analyzed: 9 subjects were enrolled and included in the Full Analysis Set, PK Analysis Set, and Safety Analysis Set

Diagnosis and Main Criteria for Inclusion: Males or females ≥ 18 years of age who had chronic 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, and were not hepatitis B surface antigen or HIV-positive. Treatment-experienced subjects could not have received treatment with a HCV nonstructural protein 5B (NS5B) nucleotide/side inhibitor (including SOF) or with a HCV NS5A inhibitor. Subjects or legally-authorized representatives were willing and able to sign an informed consent form.

Duration of Treatment: Treatment duration was 4 weeks, with 12 weeks of posttreatment follow-up.

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

SOF/VEL (1 × 400/100 mg tablet) was administered once daily with or without food for 4 weeks. If the subject were unable to swallow the tablet, it was crushed and delivered by nasogastric tube.

The lot number of SOF/VEL administered in this study was DU1506B1.

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, presurgery (if needed), on-treatment Days 1, 3, 5, 7, 14, 21, and 28, and at posttreatment Weeks 1, 2, 4, and 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 this assay is 15 IU/mL.

Pharmacokinetics: A single PK blood sample was collected from all subjects at each on-treatment visit except on Days 1, 3, and 5. On Day 1, all subjects participated in an intensive serial PK substudy to determine the plasma concentrations of SOF, GS-566500, GS-331007, and VEL. Serial PK samples were collected at predose, 0.5, 1, 2, 4, 8, 12, and 24 hours postdose.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications (including immunosuppressant medications administered to prevent rejection of the transplanted liver), clinical laboratory analyses, vital signs measurements, and physical examinations. Model for End-Stage Liver Disease (MELD) and Child-Pugh-Turcotte (CPT) scores were performed at the screening and presurgery (if applicable) visits.

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 study is provided in Appendix 16.1.9.

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 SOF/VEL on study Day 1 (eg, first study drug dose posttransplant), and for whom PK parameters of the analytes of interest (SOF, its metabolites GS-566500 and GS-331007, and VEL) were calculated based on intensive PK samples collected on study Day 1.

Efficacy: The primary efficacy endpoint for this study 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 1934}. No statistical hypothesis testing was performed.

The secondary efficacy endpoints included the proportion of subjects who achieved SVR4, the proportion of subjects with HCV RNA < LLOQ by study visit while on-treatment, 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; the denominator for end of treatment response was the number of subjects who completed 28 ± 3 days if treatment; otherwise, the denominator was the number of subjects in the FAS. SVR12 was presented by age group (< and ≥ 60 years), sex, race (white, asian, native hawaiian or pacific islander), body mass index (BMI) group (< and ≥ 30 kg/m^2), HCV genotype, IL28B genotype, prior HCV treatment, and study completion. 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.

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 VEL were estimated for all subjects with evaluable PK profiles. For each subject, the following plasma PK parameters were estimated, as appropriate: AUC_{0-24}, AUC_{last}, C_{last}, C_{max}, C_{24}, $t_{1/2}$, T_{last}, T_{max}, and λ_z.

For the PK substudy on Day 1, individual subject concentration data at each time point, and individual subject PK parameters for SOF, GS-566500, GS-331007, and VEL 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 SOF/VEL administration (oral or nasogastric tube) 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 SOF/VEL administration (oral or nasogastric tube) and overall on study Day 1 (individual subject concentration data and individual subject plasma PK parameters including summary statistics for both tables). For each analyte, 2 figures (on linear and semilogarithmic scales) were provided by route of SOF/VEL 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: All subjects who were randomized or enrolled and received at least 1 dose of study drug were included in the Safety Analysis Set. Adverse events were coded using the Medical Dictionary for Regulatory Affairs (MedDRA), Version 20.1.

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). No summary tables for graded lab abnormalities were produced due to the effects of liver transplantation on laboratory values in the immediate postoperative period, resulting in abnormal graded lab abnormalities at baseline.

Safety data were summarized and included all data collected on or after the first dose of study drug through the date of last dose of study drug plus 30 days.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 9 subjects were enrolled and treated with SOF/VEL after receiving a transplant, and were included in the Full Analysis Set and Safety Analysis Set (Section 15.1, Table 3). Of these 9 subjects, 7 completed study treatment. One subject discontinued study treatment due to an AE of multiple organ dysfunction syndrome that required dialysis which was a predefined protocol discontinuation criterion and 1 subject died as a result of an intra-abdominal hemorrhage.

The majority of subjects were male (7 of 9, 77.8%), and white (5 of 9, 55.6%), with a mean age of 61 years (range: 56–65 years), and all were not Hispanic or Latino (Section 15.1, Table 4). The mean (range) baseline BMI was 28.5 (22.1–34.5) kg/m^2, and the majority of subjects (5 of 9, 55.6%) had BMI ≥ 30 kg/m^2.

Three subjects had genotype 1 and 6 subjects had genotype 3 HCV infection. The majority of subjects were treatment-experienced (5 of 9, 55.6%). All subjects had HCV RNA > LLOQ and < 800,000 IU/mL at baseline (postliver transplant and before the first dose of SOF/VEL), including 6 subjects with HCV RNA ≥ 800,000 IU/mL before the transplant. Mean (range) HCV RNA before and after transplant was 6.4 (5.5–7.4) and 4.3 (3.0–5.4) $\log_{10}$ IU/mL, respectively. All subjects had baseline ALT > 1.5 × ULN, with a mean (range) value of 745 (132-1800) U/L.

The mean (SD) baseline estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation was 109.1 (35.60) mL/min {Cockcroft 1976}.

The majority of subjects had a pretransplant CPT score from 5 to 6 (7 of 9, 77.8%) and had pretransplant native MELD scores > 6 (6 of 9, 66.7%), with a mean (SD) native MELD score of 8 (2.4) (Section 15.1, Table 4). All subjects were transplanted due to hepatocellular carcinoma and 8 of them met local criteria for additional MELD score points, with a pretransplant mean (SD) exceptional MELD score of 23 (1.5). Most subjects (88.9%) received a transplanted liver from a cadaveric donor (7 from a donor who had experienced brain death and 1 from a donor who had experienced cardiac death) and 11.1% of subjects (1 subject) received a transplanted liver from a living donor.

Summaries related to subject disposition, demographics, baseline characteristic, and duration and exposure to study drug are presented in Section 15.1, Tables 1 to 5, 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.

Efficacy Results: Table 1 presents the primary efficacy endpoint, the proportion of subjects who achieved SVR12 following 4 weeks of treatment with SOF/VEL. Overall, 77.8% (95% CI: 40.0% to 97.2%) of subjects (7 of 9) achieved SVR12. Of the 2 subjects who did not achieve SVR12, 1 subject discontinued the study due to an AE (multiple organ dysfunction including renal failure that required dialysis which was a predefined protocol discontinuation criterion) and 1 subject died (intra-abdominal hemorrhage) (Section 15.1, Tables 9 and 10; Appendix 16.2, Listings 10, 13.1, and 22.2). Neither subject had HCV RNA < LLOQ at the time of treatment discontinuation; therefore, their virologic outcomes are classified as ‘other’ (Appendix 16.2, Listing 22.2).

Table 1. GS-US-342-2083: SVR12 and Virologic Outcome (Full Analysis Set)

	SOF/VEL 4 Weeks (N = 9)
SVR12	7/9 (77.8%)
95% CI	40.0% to 97.2%
Overall Virologic Failure	0/9
Relapse	0/6
Completed Study Treatment	0/5
Discontinued Study Treatment	0/1
End of Treatment Virologic Failure	0/7
Other	2/9 (22.2%)

HCV RNA analyzed by LabPlus using Roche COBAS AmpliPrep/COBAS Taqman HCV Test, v2.0 with lower limit of quantitation 15 IU/mL.
The exact 95% CI for proportion of subjects with SVR12 is based on the Clopper-Pearson method.
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 HCV RNA measurement. VF = virologic failure.
End of Treatment VF = Completed SOF/VEL treatment and HCV RNA ≥ LLOQ at last HCV RNA on/prior to last dose date + 3 days.
Other = subject who did not achieve SVR12 and did not meet virologic failure criteria.
Source: Section 15.1, Tables 9 and 10

The SVR4 rate was 88.9% (95% CI: 51.8% to 99.7%); 1 subject achieved SVR4 but did not achieve SVR12; this subject prematurely discontinued SOF/VEL on Day 14 as a result of an AE (multiple organ dysfunction syndrome) (Section 15.1, Table 12; Appendix 16.2, Listing 22.2).

Following treatment with SOF/VEL, HCV RNA levels declined rapidly. At Days 14, 21, and 28, 33.3%, 85.7%, and 85.7% of subjects had HCV RNA < LLOQ, respectively, and 11.1%, 42.9%, and 71.4% of subjects had HCV RNA not detected, respectively (Section 15.1, Table 14).

The small sample size precludes meaningful subgroup analysis. SVR12 in all subgroups is provided in Section 15.1, Table 13. Of note, all 7 subjects who completed study drug achieved SVR12.

All efficacy analyses are provided in Section 15.1, Tables 9 to 14, and in Appendix 16.2, Listings 21 to 22.2.

Virologic Resistance

Pretreatment NS5A and NS5B deep sequencing data were obtained for 5 of 7 subjects in the resistance analysis population who completed the study (Appendix 16.2, Virology Listings 1 and 2). Amplification of NS5A and NS5B failed for 2 subjects.

Basic local alignment search tool (BLAST) analyses of NS5A and NS5B sequences provided a refinement of HCV genotype or subtype for 4 subjects that were initially determined by LiPA assay.

Table 2. GS-US-342-2083: Summary of BLAST Sequencing-Based Subtype Refinements

Subject ID	HCV Genotype at Screening by LiPA	BLAST Sequencing-Based HCV Genotype
PPD	3	3a
PPD	3	3a
PPD	3	3a
PPD	3	3a

BLAST = basic local alignment search tool
Source: Appendix 16.2, Virology Listing 3

Deep sequencing for baseline resistance analysis was successful for all 5 tested subjects. For the purposes of this report, NS5A resistance-associated substitutions (RASs) were defined for genotype 1a: K24A/E/G/N/R, M28A/G/T/V, Q30any, L31F/I/M/V, P32L, S38F, H58D/L/N, A92K/P/T, Y93any; and for genotype 3: M28A/G/T/V, A30E/G/H/K/S/V, L31F/I/M/V, P58D/G, Y93any. NS5A RASs were not detected in any subjects using a 15% assay cutoff.

For the purposes of this report, NS5B nucleoside inhibitor (NI) RASs were defined as follows: S96T, N142T, L159F, E237G, S282T, any S282 variant other than T, C/M289L/I, L320F/I/V, and V321A/I for genotype 1a and genotype 3. NS5B NI RASs were not detected in any subjects using a 15% assay cutoff.

No posttreatment resistance testing was performed since no subject experienced virologic failure.

Pharmacokinetics Results: The PK parameters AUC_{last}, AUC_{0-24}, C_{max}, C_{24} and T_{max} of SOF, GS-566500, and GS-331007, and VEL, from study Day 1 are summarized by route of SOF/VEL administration, either as a crushed tablet through the nasogastric tube or as an orally administered tablet (Table 3). The SOF, GS-566500, GS-331007 and VEL sparse plasma concentrations measured on Day 7 through Day 21 are presented in Appendix 16.2, PK Listing 1.

Only 1 subject was administered SOF/VEL orally as a tablet while the remaining 8 subjects were administered SOF/VEL as a crushed tablet through a nasogastric tube, precluding comparison of the 2 groups.

The study Day 1 plasma concentration-time profiles for all study subjects were irregular with generally prolonged T_{max} for each analyte, and measurable SOF concentrations 24 hours postdose in 6 out of 9 subjects on the study.

Overall, in the nasogastric administration group, the SOF, GS-566500 and GS-331007 study Day 1 exposures were lower compared with exposures in a population of HCV-infected subjects receiving LDV/SOF 90/400-mg crushed tablet through nasogastric tube following liver transplantation (Study GS-US-337-1428). The VEL study Day 1 plasma exposures were notably lower than typically observed following the first dose in HCV-infected non-transplant subjects (Study GS-US-281-0102).

In the single subject administered SOF/VEL tablet orally on study Day 1, the SOF exposures were higher, and the GS-566500 and GS-331007 exposures were lower compared with exposures in a population of HCV-infected subjects receiving LDV/SOF orally following liver transplantation (Study GS-US-337-1428). The VEL exposures observed in this subject on study Day 1 were lower than typically observed following the first dose in HCV-infected non-transplant subjects (Study GS-US-281-0102).

Table 3. GS-US-342-2083: SOF, GS-566500, GS-331007, and VEL PK Parameters on Study Day 1

PK Parameter, mean (%CV)	Nasogastric Administration (N = 8)	Oral Administration (N = 1)
SOF		
AUC_{last} (ng•h/mL)	1001.9 (64.9)	4469.3
AUC_{0-24} (ng•h/mL)	1101.7 (57.5)[b]	4469.3
C_{max} (ng/mL)	340.4 (104.7)	354.0
C_{24} (ng/mL)	17.5 (98.0)[c]	33.5
T_{max} (h) [a]	1.50 (0.50, 4.00)	8.00 (8.00, 8.00)
GS-566500		
AUC_{last} (ng•h/mL)	1890.1 (99.5)	2581.3
AUC_{0-24} (ng•h/mL)	2199.7 (86.5)[b]	2581.3
C_{max} (ng/mL)	236.0 (115.4)	225.0
C_{24} (ng/mL)	22.7 (36.7)[c]	22.4
T_{max} (h) [a]	4.00 (2.04, 6.08)	12.12 (12.12, 12.12)
GS-331007		
AUC_{last} (ng•h/mL)	9338.4 (171.0)	6830.0
AUC_{0-24} (ng•h/mL)	11174.5 (150.1)[b]	6830.0
C_{max} (ng/mL)	641.6 (142.5)	524.0
C_{24} (ng/mL)	348.8 (155.5)[d]	181.0
T_{max} (h) [a]	8.00 (6.00, 12.00)	12.12 (12.12, 12.12)
VEL		
AUC_{last} (ng•h/mL)	482.9 (122.4)	1481.9
AUC_{0-24} (ng•h/mL)	606.8 (110.2)[c]	1481.9
C_{max} (ng/mL)	35.5 (116.1)	107.0
C_{24} (ng/mL)	21.7 (110.6)[c]	61.8
T_{max} (h)[a]	10.00 (8.00, 12.00)	12.12 (12.12, 12.12)

a Median (Q1, Q3)
b N = 7
c N = 5
d N = 6
Source: Section 15.1, PK Tables 6 to 9

SOF, GS-566500, GS-331007, and VEL plasma concentrations measured on study Day 7 through study Day 21 (Section 15.1, PK Listing 1) were generally within the range of Phase 3 PK plasma concentrations in the noncirrhotic subjects in the SOF/VEL program, but these data should be interpreted with caution given the limited number of samples collected through this period.

Overall, SOF, GS-566500, GS-331007, and VEL plasma exposures on study Day 1 of SOF/VEL administration in HCV-infected subjects under liver transplant conditions exhibited irregular profiles and were lower than those observed in HCV-infected subjects in other studies, suggesting potential effect of gastroparesis following liver transplantation or issues with administration. However, based on the established pharmacokinetic-pharmacodynamic (PK-PD) relationships for SOF, GS-331007 and VEL, the exposures observed in this study even on study Day 1 reside in the near-maximal portion of their respective exposure-response curves. Moreover, limited sparse PK data on study Day 7 through study Day 21 may indicate that SOF and VEL exposures were within the typically observed range at steady state. The effect of nasogastric administration of crushed SOF/VEL 400/100-mg tablet on the respective analytes PK cannot be fully established due to the limited number of subjects in the comparator oral administration arm.

All PK results are provided in Section 15.1, PK Tables 1 to 9 and PK Figures 1 to 8, and Appendix 16.2, PK Listing 1.

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.

Extent of Exposure

The mean (SD) duration of exposure to SOF/VEL was 25 (5.98) days, and 77.8% of subjects (7 of 9) completed study treatment (Section 15.1, Table 5). The median adherence rate to SOF/VEL, as measured by tablet counts, was 100.0% (Section 15.1, Table 6).

Adverse Events and Serious Adverse Events

All subjects (100.0%) experienced at least 1 AE and 1 subject experienced a treatment-related AE (Grade 2 gastroesophageal reflux disease) (Section 15.1, Table 17; Appendix 16.2, Listing 8). The 3 most frequently reported AEs were liver transplant rejection (55.6%, 5 of 9 subjects), constipation (44.4%, 4 of 9 subjects), and gastroesophageal reflux disease (33.3%, 3 of 9 subjects) (Section 15.1, Table 25). Most AEs were either Grade 1 or Grade 2 in severity (Appendix 16.2, Listings 8 and 9). Three subjects experienced Grade 3 AEs and 2 subjects experienced Grade 4 AEs. Grade 3 AEs included supraventricular tachycardia (2 subjects), acute kidney injury, immune thrombocytopenic purpura, tachyarrhythmia, back pain, and intensive care unit acquired weakness (1 subject each). Grade 4 events included multiple organ dysfunction syndrome, including renal failure requiring dialysis, and posttreatment bile leak (1 subject) and intra-abdominal hemorrhage (1 subject). None of these Grade 3 or 4 events were assessed as related to SOF/VEL (Section 15.1, Table 19; Appendix 16.2, Listing 9). A total of 5 subjects (55.6%) experienced serious adverse events (SAEs). Serious AEs occurring in more than 1 subject were liver transplant rejection (3 subjects) and post procedural bile duct leak (2 subjects) (Section 15.1, Tables 27). None of the SAEs were

assessed as related to study drug (Section 15.1, Tables 28). One subject experienced an AE of multiple organ dysfunction syndrome that required dialysis which was a predefined protocol discontinuation criterion; as such the subject was prematurely discontinued from study treatment on study Day 14. One death occurred during the study; the subject died on Day 15 as a result of an intra-abdominal hemorrhage (Appendix 16.2, Listing 13.1). No pregnancies were reported (Appendix 16.2, Listings 12).

Narratives for all SAEs, deaths, and AEs leading to discontinuation of study drug from the first dose of study drug through the end of the study are provided in Section 15.2. All AE results are provided in Section 15.1, Tables 15 to 28, and Appendix 16.2, Listings 8 to 13.1.

Clinical Laboratory Results

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 29.1, 29.2, 29.4, and 29.12). By posttreatment Week 4, platelets were within normal limits (Section 15.1, Table 29.11; Appendix 16.2, Listing 16.1).

Postbaseline, all subjects had at least 1 hemoglobin value < 10 g/dL and 88.9% of subjects had at least 1 hemoglobin value < 8.5 g/dL (Section 15.1, Table 30).

Abnormal laboratory results were consistent with hospitalized subjects in the immediate postliver transplant period (Appendix 16.2, Listings 15 to 20). No adverse trends attributable to study drug were identified.

All laboratory results are provided in Section 15.1, Tables 29.1 to 30, and Appendix 16.2, Listings 15 to 20.

Vital Signs Measurements

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) or ECG were reported during the study (Section 15.1, Tables 31.1-31.3, and Appendix 16.2, Listings 23 and 24).

All vital sign measurements are provided in Section 15.1, Tables 31.1 to 31.3, and Appendix 16.2, Listings 23 and 24.

Other Safety Measurements

No subjects experienced an episode of graft loss during the study. Five subjects had transplant rejection episodes which were managed with changes to their immunosuppressant regimen (Appendix 16.2, Listings 7, 8 and 13.2).

All subjects received at least 1 concomitant immunosuppressant medication; the most common immunosuppressant medications were prednisone (100.0%, 9 subjects), tacrolimus (100.0%, 9 subjects), and methylprednisone (55.6%, 5 subjects) (Section 15.1, Table 8).

CONCLUSIONS:

The conclusions from Study GS-US-342-2083 are as follows:

- In subjects with chronic HCV infection, treatment with SOF/VEL for 4 weeks initiated immediately following liver transplantation resulted in an SVR12 rate of 77.8% (7 of 9 subjects). Of the 7 subjects who completed treatment, none experienced virologic failure.
- Treatment with SOF/VEL was generally safe and well tolerated. The safety profile was consistent with this population of hospitalized subject in the immediate postliver transplant period.