STATISTICAL ANALYSIS PLAN

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/Velpatasvir Fixed Dose Combination
Study Number:	GS-US-342-2083
Protocol Version/Date:	Original/26 February 2016
Analysis Type:	SVR12 (Primary Endpoint and Final CSR)
Analysis Plan Version:	Version 1
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Analysis Plan Author:	PPD

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemistry
BLQ	below limit of quantitation
BMI	body mass index
CI	confidence interval
CPT	Child-Pugh-Turcotte
CrCl	creatinine clearance
CSR	clinical study report
DAA	direct-acting antiviral
eCRF	electronic case report form
DMC	Data Monitoring Committee
ECG	electrocardiogram
FAS	full analysis set
FDC	fixed-dose combination
FU	posttreatment follow-up
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HLT	high level term
HLGT	high level group term
INR	international normalized ratio of prothrombin time
LLOQ	lower limit of quantitation
LLT	lower level term
LOQ	limit of quantitation (PK samples)
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
NAT	nucleic acid amplification test
NG	nasogastric
PCR	polymerase chain reaction
PEG	pegylated interferon
PG	pharmacogenetics
PK	pharmacokinetics
PO	oral
PT	preferred term
Q1	first quartile
Q3	third quartile
RBV	Ribavirin
RNA	ribonucleic acid

SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	study days or standard deviation
SOC	system organ class
SOF	Sofosbuvir
SVR	sustained virologic response
SVRx	sustained virologic response x weeks after stopping all study drugs
TE	treatment-emergent
TFLs	tables, figures, and listings
TND	target not detected
ULN	upper limit of the normal range
VEL	Velpatasvir
VF	virologic failure
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the clinical study report (CSR) for Study GS-US-342-2083. This SAP is based on the original protocol dated 26 February 2016 and the electronic case report form (eCRF). The SAP will be finalized before data finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To explore the antiviral efficacy of treatment with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) therapy administered for 4 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 hepatitis C virus (HCV)-infected subjects in the perioperative and posttransplant period

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 weeks after cessation of therapy (SVR4)
- To evaluate the proportion of subjects with virologic failure (VF)
- 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 of SOF/VEL

The exploratory objectives of this study are as follows:

PPD

1.2. Study Design

This is an open-label study that will evaluate the safety, tolerability and antiviral efficacy of SOF/VEL administered for 4 weeks in HCV–infected adult male and non-pregnant/non-lactating female subjects 18 years of age or older who are undergoing liver transplantation. A detailed list of inclusion and exclusion criteria can be found in Sections 4.2 and 4.3 of the study protocol.

Screening assessments will be completed at the time the subject is identified as a potential participant for the study in order to allow the subject time to provide informed consent and to perform screening procedures. Subject's screening data will be confirmed in the pre-operative period (within 48 hours of the planned transplant) if the screening visit was conducted more than 48 hours prior to the start of the transplant. If a separate consent is signed for the liver explant substudy, samples of the explanted liver will be taken during surgery.

For all subjects, SOF/VEL tablet (400/100 mg) once daily given orally or via nasogastric tube will be started the day of the subject's liver transplant if the procedure is completed by noon and the following day if the transplant is completed after noon. Study personnel will observe the subject taking their first dose of study drug and record the date and time the first dose was taken.

The subject will receive treatment for 4 weeks. Treatment initiation may be delayed for up to 1 day if warranted by the subject's medical condition post-surgery.

All subjects will complete the following study visits: screening, pre-surgery (if screening was conducted more than 48 hours prior to start of liver transplant), on-treatment Days 1, 3, 5, 7, 14, 21, and 28, and posttreatment Weeks 1, 2, 4, and 12 following last dose of study drug.

Pharmacokinetic (PK) Sub-study (Required)

All subjects will participate in a PK substudy in which intensive serial PK sample collection (samples obtained over 24 hours) will be performed on Day 1 to determine pharmacokinetics of SOF, its metabolites GS-566500 and GS-331007, and VEL.

The schedule of assessments can be found in Appendix 2 of the study protocol.

Subjects will be initially screened to determine their eligibility for participation in the study. Subjects will have an additional pre-surgery visit if the screening visit was conducted more than 48 hours prior to the start of liver transplant (ie, duration of screening period is variable depending on availability of a donor organ).

Subjects will be treated for 4 weeks and followed off-treatment for 12 weeks. All subjects will be eligible to participate in the PG substudy if consent is obtained. A blood sample should be drawn at the Day 1 visit. If not obtained at the Day 1 visit, the sample may be drawn at any time during the study.

Subjects with VF (either at end of treatment or during follow-up) will have a confirmation sample collected. If VF is confirmed, the subject will be discontinued from study.

Subjects who prematurely discontinue from study drug but complete all posttreatment visits will be considered to have completed study.

1.3. Sample Size

A total of 10 subjects are expected to be enrolled, receive a transplant, and be dosed with SOF/VEL. With a sample size of 10 subjects, a 2-sided 95% exact confidence interval (CI) will extend at most 63% in length.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Meetings

A data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data. The initial meeting will occur after the first 5 subjects have completed the treatment period; a second meeting will occur after all subjects complete the treatment period. The DMC will provide recommendations, and determine whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The investigator, medical monitor/study director, study biostatistician, and a sponsor representative who is not involved with the conduct of the study will be members of the DMC.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

2.2. Final Analysis

After all subjects have completed the study (posttreatment Week 12 or prematurely discontinued from study), all outstanding data queries for the study have been resolved, and the database has been cleaned and finalized, the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects [n], mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum will be presented.

Data collected in the study will be presented in by-subject listings for all subjects in the Safety Analysis Set, unless otherwise specified. All by-subject listings will be presented by subject identification (ID) number is ascending order, unless otherwise specified.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The number of subjects eligible for each analysis set will be provided. Subjects who were excluded from each analysis set will be summarized or provided in a by-subject listing with reasons for exclusion by treatment group.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes subjects who were enrolled into the study (ie, subjects assigned a 5-digit subject ID). Subjects will be grouped by assigned treatment at enrollment (SOF/VEL 4 Weeks).

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled subjects who received a liver transplant, and took at least 1 dose of study drug. Since all subjects enrolled in this study received a liver transplant and took at least 1 dose of study drug, the FAS will be the same as the Safety Analysis Set.

This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. Subjects are grouped within the Safety Analysis Set according to the treatment they actually received.

This is the primary analysis set for safety analyses.

3.1.4. Pharmacokinetic Substudy Analysis Set

The Pharmacokinetic (PK) Substudy Analysis Set includes all subjects who took a dose of SOF/VEL on Study Day 1, and for whom PK parameters of the analytes of interest (SOF, its metabolites GS-566500 and GS-331007, and VEL) could be calculated based on intensive PK samples collected on Study Day 1 after the first posttransplant dose of SOF/VEL.

The PK Substudy Analysis Set will be used for analyses of the intensive PK data collected on study Day 1.

3.2. Subject Grouping

The treatment group for all efficacy and safety analyses will be "SOF/VEL 4 Weeks."

PK substudy analyses will be presented by SOF/VEL route of administration ("oral" or "nasogastric") on Study Day 1; and overall (ie, "all subjects").

3.3. Strata and Covariates

There are no strata or covariates for this study.

3.4. Examination of Subject Subsets

SVR12 will be presented for the SOF/VEL 4 Weeks group by:

- age (< 60 and ≥ 60 years)
- sex at birth (male, female)
- race (White, Asian, Native Hawaiian or Pacific Islander)
- BMI (< 30 or ≥ 30 kg/m^2)
- HCV genotype
- IL28B genotype (CC, CT, or TT)
- prior HCV treatment (yes, no)
- completed study drug (yes, no)

3.5. Multiple Comparisons

No multiplicity adjustment will be made since SVR12 is the primary efficacy parameter.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

For missing last dosing date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for adverse event (AE) onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

For analyses of categorical HCV RNA data, missing posttreatment HCV RNA data will have the missing data imputed. Missing on-treatment HCV RNA will have missing data imputed up to the

date of the last dose (for on-treatment displays). If the study day associated with the last dosing date of study drug is greater than or equal to the lower bound of a visit window, and the value at the visit is missing, then the value will be imputed. If the study day associated with the last dosing date is less than the lower bound of a visit window then the on-treatment value at that visit will remain missing.

If an HCV RNA data point is missing and is preceded and followed in time by values that are "<LLOQ target not detected (TND)," then the missing data point will be set to "< LLOQ TND." If a data point is missing and preceded and followed by values that are "< LLOQ detected," or preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected," then the missing value will be set to "< LLOQ detected." In these situations the data point will be termed a bracketed success; otherwise, the data point will be termed a bracketed failure (ie, ≥ LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (ie, ≥ LLOQ detected).

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

By subject listings will be presented for all subjects in the Safety Analysis Set sorted by subject ID number, visit date, and time (if applicable) unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within subject.

Age (in years) on the date of the first dose of study drug and sex at birth will be used for analyses and presentation in listings.

If a subject was not dosed with study drug, then the date the informed consent was signed will be used in place of the first dose date of study drug for calculation of age.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed as follows:

- A value that is one unit less than the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (where x is considered the limit of quantitation). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception for this rule is any value reported as < 1. For the values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively will be used for calculation of summary statistics.

- A value that is one unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the limit of quantitation). Values with decimal points will follow the logic as above.

- The limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the limit of quantitation).

LabPlus laboratories used COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0 to determine HCV RNA results in this study. The LLOQ of the assay is 15 IU/mL.

When the calculated HCV RNA IU/mL is within the linear range of the assay, then the result will be reported as the "<< numeric value>> IU/mL." This result will be referred to in this document as the numeric result or as "≥ LLOQ detected" for categorical results.

When HCV RNA is not detected, the result is reported as "Not Detected" or "target not detected." This result will be referred to in this document as "< LLOQ target not detected" or "< LLOQ TND."

When the HCV RNA IU/mL is less than LLOQ of the assay, the result is reported as "< 15 IU/mL." This result will be referred to in this document as "< LLOQ detected."

The overall category of HCV RNA < LLOQ includes "< LLOQ TND" and "< LLOQ detected."

For numerical HCV RNA data, values below LLOQ will be set to the LLOQ – 1 IU/mL (ie, 14 HCV RNA IU/mL). HCV RNA values returned as "target not detected" will also be set to LLOQ – 1 IU/mL. For selected analyses, HCV RNA data (IU/mL) will be transformed to the logarithmic (base 10) scale ($\log_{10}$ IU/mL).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (eg, $\log_{10}$ scale) or nonparametric analysis methods may be used, as appropriate.

Natural logarithm transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postbaseline time points, where LOQ is corrected for the dilution factor (ie, reported LOQ/dilution factor) for determination of summary and order statistics.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

Pharmacokinetic parameters that are BLQ will be imputed as one-half LOQ before log transformation.

3.8. Visit Windows

3.8.1. Definition of Study Day

Study day is the day relative to the date of the first dose of study drug. Study Day 1 will be defined as the day of the first dose of study drug administration.

Study day will be calculated from the date of first dose of study drug administration and derived as follows:

- For postdose study days: Assessment Date – First Dose Date + 1
- For days prior to the first dose: Assessment Date – First Dose Date

The last dose date of study drug will be the end date for SOF/VEL on the study drug administration eCRF for the record where the "subject permanently discontinued" flag is 'Yes'.

If there are subjects for whom the date of last study drug is unknown due to the reason that the subject was lost to follow-up and not able to be contacted, the date of last dose will be estimated using the maximum of nonmissing study drug start or stop dates, and on-treatment visit dates and laboratory collection dates (posttreatment visits and unscheduled visits are not included).

3.8.2. Analysis Windows

Subject visits might not occur on protocol-specified days. Therefore, for purposes of analysis, visit windows will be utilized when a single value at a visit is required for analysis.

In general, the baseline value will be the last nonmissing value on or prior to the first dose date of study drug.

HCV RNA, vital signs, and safety laboratory data collected up to last study drug dose date + 3 days will be considered to be on-treatment data; and HCV RNA, vital signs, and safety laboratory data collected after the last dose date + 3 days are considered posttreatment data. The analysis windows for on-treatment HCV RNA, vital signs and safety laboratory data are provided in Table 1.

Table 1. Analysis Windows for On-Treatment HCV RNA, Safety Laboratory Data, and Vital Signs

Visit ID	SOF/VEL 4 Weeks On-Treatment Visit Windows for HCV RNA, Safety Laboratory Values and Vital Signs
Baseline/Day 1[a]	Date/time of lab sample (date for other) ≤ date/time (date for non-lab) of first dose SOF/VEL
Day 3	2 ≤ Study Day ≤ 4
Day 5	5 ≤ Study Day ≤ 6
Day 7 (Week 1)	7 ≤ Study Day ≤ 11
Day 14 (Week 2)[a]	12 ≤ Study Day ≤ 17
Day 21 (Week 3)	18 ≤ Study Day ≤ 24
Day 28 (Week 4)[a]	25 ≤ Study Day ≤ 41

a Pregnancy testing required at Day 1, Day 14, and Day 28 for SOF/VEL 4 Weeks.
Safety Labs include hematology, chemistry, urinalysis, and coagulation.
Only the date of assessment is collected for vital signs data.

Pre-transplant CPT and MELD scores and ECGs are to be collected at screening, and pre-surgery (if more than 48 hours between screening visit and start of transplant), and will be listed with their nominal visit with study days assigned.

HCV RNA, vital signs, and safety laboratory data collected after the last dose date + 3 days will be assigned to posttreatment visits. Visit windows will be calculated from the last dose date (ie, FU Day = Collection Date – Last Dose Date) as shown in Table 2.

Table 2. Analysis Windows for Posttreatment HCV RNA, Safety Laboratory Data and Vital Signs

Post-Trt FU Visit ID	Posttreatment Visit Windows for HCV RNA[a] (Days from Date of Last SOF/VEL)	Safety Labs[b] (Days from Date of Last SOF/VEL)	Vital Signs[c] (Days from Date of Last SOF/VEL)
FU-1	4 ≤ FU Day ≤ 10	4 ≤ FU Day ≤ 10	N/A
FU-2	11 ≤ FU Day ≤ 20	11 ≤ FU Day ≤ 20	N/A
FU-4	21 ≤ FU Day ≤ 69	21 ≤ FU Day ≤ 30	4 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	N/A	N/A

a SVR follow-up visit window (lower bound) must occur within 7 (SVR4) and 14 (SVR12) days of target, respectively.
b Safety labs will only be summarized up to posttreatment Week 4 (up to 30 days post last dose).
c Vital Signs are only collected at posttreatment Week 4 (summarized up to 30 days post last dose).

3.8.3. Selection of Data in the Event of Multiple Records in a Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require one value per analysis window.

If multiple valid nonmissing numeric observations exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time is recorded for the same day, the average (arithmetic mean) will be used for the baseline value.

- For postbaseline visits:

1) Select the record closest to the nominal day (ie, visit weeks × 7 days) for that visit; except for posttreatment HCV RNA follow-up visits, for which the latest record in the analysis window will be selected)

2) If there are 2 visits equidistant from the nominal day, the later record will be selected

3) If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified

If multiple valid nonmissing categorical observations exist in a window, records will be selected as follows:

- For baseline, the last available record on or prior to the date of first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the values with the lowest severity will be selected (eg, normal will be selected over abnormal)

- For postbaseline visits, follow the same rules described above for postbaseline numeric observations, except that if there are multiple records on the same day, the most conservative value will be selected (eg, abnormal will be selected over normal)

4. SUBJECT DISPOSITION

4.1. Subject Enrollment, Screen Fails, and Disposition

4.1.1. Subject Enrollment

A summary of subjects enrolled and treated will be provided for each country and investigator within country for the "SOF/VEL 4 Weeks" group for subjects in the safety analysis set.

4.1.2. Reasons for Screen Failure

Reasons for screen failure will be summarized for each screen that was performed for the study. The total number of screens and number of screen failures will be provided. Screen failures will be split into the following 2 groups:

- screen failures that did not meet eligibility criteria (with inclusion/exclusion criteria not met summarized)
- screen failures that met eligibility criteria (with reasons for non-enrollment summarized)

Percentages will be calculated for the screen failure rate (denominator is number of screens), each inclusion/exclusion criteria not met (denominator is screen fails that did not meet criteria), and reasons for non-enrollment (denominator is screen fails that met eligibility criteria). A listing of inclusion/exclusion criteria that were not met for screen failure subjects will be provided, sorted by screening ID for subjects who were screened but not treated.

4.1.3. Subject Disposition

A summary of subject disposition will be provided for "SOF/VEL 4 Weeks." The summary will present the number of subjects enrolled, and evaluated for each analysis set (ie, safety analysis set and/or FAS analysis set).

In addition, the number and percentage of subjects in the safety analysis set who met the following criteria will be summarized:

- Completed the study treatment period
- Did not complete the study treatment period (with reasons for not completing the study treatment period)
- Completed the study
- Did not complete the study (with reasons for not completing the study)

Among subjects who completed study treatment and those who prematurely discontinued study treatment, the number and percentage of subjects will be summarized for subjects with:

- No HCV RNA at the posttreatment Week 4 assessment (ie, *No FU-4 HCV RNA Assessment*)
- HCV posttreatment Week 4 assessment but no HCV posttreatment Week 12 assessment (ie, *With FU-4 but No FU-12 HCV RNA Assessment*)

If a subject has no HCV RNA assessments beyond 21 days after the last dose of any study drug (ie, lower bound of FU-4 visit for HCV), the subject is categorized as having "*No FU-4 HCV RNA Assessment.*" If a subject has an HCV RNA value for the FU-4 assessment but does not have any observed HCV RNA assessment beyond 70 days after the last dose of any study drug (ie, lower bound of FU-12 visit for HCV), the subject is categorized as having "*With FU-4 but No FU-12 HCV RNA Assessment.*"

A summary of the number of subjects in the PK Substudy analysis set will be provided by route of administration of SOF/VEL on Study Day 1 (PO or NG) and overall as part of the PK substudy analysis.

A data listing of date of informed consent, date/time transplant ended, first posttransplant dose date/time, last dose date (study day), completed study treatment (yes/no), completed study (yes/no) and reasons for premature study treatment/study discontinuation will be provided. The last observed non-missing HCV RNA value on/prior to the date the subject stopped SOF/VEL plus 3 days will be included in this listing.

A listing of subjects who were excluded from the safety and/or FAS analysis set will be provided.

4.2. Extent of Exposure

Extent of exposure to study drug will be examined by assessing the total duration of study drug exposure and the level of adherence to the study drug regimen specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Duration of exposure to SOF/VEL will be defined as (last dose date of SOF/VEL – first dose date of SOF/VEL + 1) regardless of temporary interruptions in study drug administration. All duration of exposure will be expressed in days.

Duration of exposure to SOF/VEL will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum) and using the number (ie, cumulative counts) and percentage of subjects exposed through the timepoints: Baseline (≥ 1 Day); Week 1 (≥ 7 Days); Week 2 (≥ 14 Days); Week 3 (≥ 21 Days) and Week 4 (≥ 28 Days). A ± 3 day window for the last assessment will be applied to match with the protocol-specified visit window. Summaries will be provided by treatment group for subjects in the safety analysis set.

A by-subject listing of study drug administration will be provided for subjects in the safety analysis set.

4.2.2. Adherence to Study Drug

Adherence will be calculated for SOF/VEL as:

[(Number of tablets taken) ÷ (Number of study drug tablets prescribed)] x 100

Note: If calculated adherence is greater than 100%, the result will be set to 100%.

A descriptive summary (n, mean, SD, median, Q1, Q3, minimum and maximum) and the number and percentage of subjects with < 80% , ≥ 80 to < 90%, and ≥ 90% adherence will be presented for the safety analysis set for subjects assigned to receive SOF/VEL for 4 Weeks.

A by-subject listing of adherence will be provided for subjects in the safety analysis set.

4.2.2.1. Calculation of Number of Tablets Prescribed for Study Drug

Subjects assigned to receive 4 weeks of SOF/VEL will require 1 tablet/day for 28 days.

4.2.2.2. Calculation of Number of Tablets Taken

The number of tablets taken for SOF/VEL during the treatment period will be calculated as the sum of (number of tablets dispensed – number of tablets returned) at each distinct dispensing period across all bottles dispensed. If a bottle is dispensed, and the bottle is returned empty, then the number of tablets returned will be entered as zero. If a bottle is dispensed but not returned (missing), the number of tablets taken from that bottle will be counted as zero.

4.3. Protocol Deviations

A listing of important protocol violations will be provided by the Clinical Operations group for subjects in the Safety Analysis set. The listing will include the criteria not met and related comments.

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized for the SOF/VEL 4 Week group for subjects in the Safety Analysis Set using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percentage of subjects for categorical data. Variables to be summarized include the following:

- Age (on date of first dose of study medication) as a continuous variable and for categories (< 60 and ≥ 60 years)
- Sex at birth (male, female)
- Race (White, Black or African American, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline body mass index (BMI) as a continuous variable and for categories (< 30 kg/m^2, ≥ 30 kg/m^2)
- Pretransplant HCV genotype
- Pretransplant IL28B (CC, CT, TT)
- Pretransplant HCV RNA as a continuous variable and for categories (< 800,000 IU/mL and ≥ 800,000 IU/mL)
- Pretransplant Child-Pugh-Turcotte (CPT) class
- Pretransplant CPT score (eg. 5, 6, 8) as a categorical variable
- Pretransplant native model for end stage liver disease (MELD) score as a continuous variable and as a categorical variable for individual MELD scores
- Pretransplant hepatocellular carcinoma (HCC) (yes, no)
- Pretransplant Exception MELD (from liver transplant eCRF) as a continuous variable
- Donor Type (living, cadaveric brain death, cadaveric cardiac death)
- Cadaveric Donor Type (split, whole)
- Prior HCV treatment (yes, no)

- Response to last HCV treatment regimen (non–responder, relapse/breakthrough, early discontinuation)
- Last HCV treatment regimen (pegylated interferon [PEG], PEG+RBV)
- Baseline HCV RNA as a continuous variable and for categories (< 800,000 IU/mL and ≥ 800,000 IU/mL)
- Baseline alanine aminotransferase (ALT) as a continuous variable (absolute value) and for categories (≤1.5 × upper limit of normal [ULN] and > 1.5 × ULN)
- Baseline creatinine clearance (CrCL) using the Cockcroft-Gault formula (using for weight the lesser of ideal body weight and actual body weight)

Age of the patient will be calculated as the integer of age in years on the date of first dose of study medication.

Pretransplant CPT and native MELD scores will be listed by nominal visit (eg, screening and pre-surgery) and will be calculated using the following formulas:

CPT score is calculated as: the sum of the scores related to the 5 items in the table below (if any of the components are missing, the score is not calculated):

MEASURE	1 point	2 points	3 points
Total Bilirubin (mg/dL)	< 2	2-3	> 3
Serum Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
International normalized ratio for prothrombin time (INR)	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Slight/Moderate (medically controlled)	Severe (medically uncontrolled)
Hepatic Encephalopathy	None	Slight/Moderate (medically controlled)	Severe (medically uncontrolled)

Native MELD score is calculated as:

$10 \times \{[0.957 \times \text{Ln}(\text{Scr})] + [0.378 \times \text{Ln}(\text{Tbil})] + [1.12 \times \text{Ln}(\text{INR})] + 0.643)\}$

Where Scr = serum creatinine (in mg/dL), Tbil = Total Bilirubin (in mg/dL), INR = international normalized ratio, and Ln = natural log. If any lab value is less than 1.0, then set to 1.0 in the calculation. If the subject received dialysis at least twice in the past week, or if the serum creatinine value is > 4.0, then Scr is set to 4.0 mg/dL in the above formula. The result will be rounded to the nearest whole number.

MELD Exception score

At this site in New Zealand, subjects with HCC eligible for liver transplantation may be awarded additional MELD score points if they meet exception point criteria. Subjects will have an exception score of 22 assigned if they have a single HCC lesion greater than 2 centimeters or more than 1 lesion of any size. Two additional points are awarded every 3 months that the subject is on the liver transplant waitlist.

The laboratory collection date for each laboratory test used to calculate the pretransplant MELD and CPT scores are collected on the MELD/CPT eCRF form and are to be merged, individually for each laboratory test with the laboratory collection date on the COVLAB dataset to obtain the numeric result for the test.

By-subject listings of demographic and baseline characteristics will be provided for subjects in the safety analysis set.

A separate by-subject listing for prior HCV treatment and response will be provided.

A by-subject listing of transplant information and donor organ characteristics will be provided for subjects in the FAS and will include: transplant start and end date/time, hours and minutes (HH:MM) of cold/ischemia time, pretransplant HCC (yes/no), pretransplant MELD native score, pretransplant MELD exception score (when applicable), donor type, cadaveric donor type, cause of donor death, donor age/sex/race/ethnicity [when available], donor hepatitis C nucleic acid amplification test (NAT) status, and location of organ (local, regional, national).

5.2. Medical History

Clinically relevant medical history (ie, conditions not specific to the disease being studied that are clinically relevant) will be listed only. General medical history will not be coded.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is SVR12, defined as HCV RNA < LLOQ (ie, 15 IU/mL) 12 weeks after cessation of treatment in the FAS. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0 will be used to measure and report HCV RNA results.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

No hypothesis testing will be performed.

6.1.3. Analysis of the Primary Efficacy Endpoint

The estimate of SVR12 and a 2-sided 95% CI calculated using the Clopper-Pearson method {Clopper et al 1934} will be provided for the "SOF/VEL 4 Week" treatment group.

6.1.4. Subgroup Analysis of the Primary Efficacy Endpoint

Point estimates and the 2-sided exact 95% CI calculated using the Clopper-Pearson method will be presented for each subgroup presented in Section 3.4.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints to be summarized for the "SOF/VEL 4 Week" treatment group for subjects in the FAS include:

- The proportion of subjects with SVR at 4 weeks after cessation of treatment (SVR4)
- The proportion of subjects with HCV RNA < LLOQ by visit while on treatment
- The proportion of subjects with VF. End of treatment VF and relapse will be defined by:

End of Treatment Virologic Failure: HCV RNA ≥ 15 IU/mL at last observed HCV RNA measurement on or prior to last dose date of SOF/VEL + 3 days after completion of 28 ± 3 days of SOF/VEL treatment.

Relapse: HCV RNA ≥ 15 IU/mL during the posttreatment follow-up period having achieved HCV RNA < 15 IU/mL at the end of treatment, confirmed with 2 consecutive values or last available posttreatment measurement.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

All secondary efficacy endpoints will be evaluated for the "SOF/VEL 4 Week" treatment group for subjects included in the FAS. For analyses of HCV RNA < LLOQ by visit while on treatment and during the posttreatment (SVR) follow-up period, subjects will be assigned a value at each visit based on the analysis visit windows specified in Section 3.8.2. Missing values will be imputed based on the categorical imputation rules described in Section 3.6.1. Estimates of the proportion of subjects < LLOQ by visit and the 95% exact CI using the Clopper-Pearson method will be calculated. The overall category for "HCV RNA < LLOQ" will be split into the subcategories "< LLOQ TND" for subjects with target not detected and "< LLOQ detected" for subjects with < LLOQ in tabular displays.

A summary table of the number and proportion of subjects with SVR12, VF, and Other will be presented for the "SOF/VEL 4 Week" treatment group. All subjects who achieve SVR12 will be categorized as SVR12. VF will be summarized for "end of treatment failure" and "relapse" (relapse will be broken down by study drug completed yes/no). Subjects who do not achieve SVR12 or VF will be categorized as Other.

The denominator for relapse will be the number of subjects who had HCV RNA < LLOQ on their last observed on-treatment HCV RNA measurement; the denominator for end of treatment response will be the number of subjects who completed 28 ± 3 days of treatment; otherwise, the denominator will be the number of subjects in the FAS.

For analyses of HCV RNA < LLOQ by visit while on treatment, subjects will be assigned a value at each visit based on the categorical imputation rules described in Section 3.7 of this SAP. Subjects with HCV RNA < LLOQ will be displayed into 2 subcategories: < LLOQ TND and < LLOQ detected. Point estimates and 2-sided exact 95% CIs using the Clopper-Pearson method will be displayed for the proportion of subjects < LLOQ at each visit.

A listing of HCV RNA ($\log_{10}$ IU/mL) will be provided for FAS subjects, FAS subjects with VF, and FAS subjects with Other Virologic Outcome.

Drug resistant substitutions will be discussed as part of the clinical study report.

6.3. Exploratory Efficacy Analysis

None

6.4. Changes From Protocol-Specified Efficacy Analyses

None

7. SAFETY ANALYSES

Safety data will be summarized for the SOF/VEL 4 Week group for the Safety Analysis Set.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, or 4 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and the most severe will be considered (for sorting purpose only) in data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Events for which the investigator did not record relationship to study drug will be considered to be related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing from that captured on the eCRF.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definition of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Pharmacovigilance and Epidemiology Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent, as long as the AE stop date is

not prior to the first dose date of study drug. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset and end date is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dose date of study drug will be considered to be treatment-emergent.

7.1.6. Summaries of Adverse Events and Deaths

A brief high-level summary of TEAEs will be provided for the SOF/VEL 4 Week group. The number and percentage of subjects who had the following: any AE; any treatment-related AE; any AE of Grade 3 or above; any treatment-related AE of Grade 3 or above; any AE of Grade 2 or above; any treatment-related AE of Grade 2 or above; any SAE; any treatment-related SAE; any AE leading to premature discontinuation of SOF/VEL; and any AE leading to interruption of SOF/VEL. All deaths (including those that are treatment-emergent and those that are not treatment-emergent) observed during the study will also be summarized and included in this table.

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT for the SOF/VEL 4 Week group based on the the Safety Analysis Set as follows:

- All AEs
- All treatment-related AEs
- AEs of Grade 3 or above
- Treatment-related AEs of Grade 3 or above
- AEs of Grade 2 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- Treatment-Emergent Non-Serious Adverse Events Occurring in At Least 5% of Subjects

Multiple events will be counted once only per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in order of descending incidence within an SOC. In summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, TEAEs will also be summarized for the SOF/VEL 4 Week treatment group by PT only, in order of descending incidence for:

- AEs that occurred in > 1 subject
- AEs leading to interruption of SOF/VEL
- AEs leading to premature discontinuation of SOF/VEL
- All SAEs
- All treatment-related SAEs

In addition to the by-treatment summaries described above, by-subject data listings, with a variable indicating whether the event is treatment-emergent, will be provided for the following:

- All AEs
- AEs leading to premature discontinuation of SOF/VEL
- All AEs of Grade 3 or above
- SAEs
- All Deaths
- Graft Loss

7.1.7. Additional Analysis of Adverse Events

None

7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued the study drug. The analysis will be based on values reported in conventional units. When values are below the lower limit of quantitation, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as described in Section 3.7 of this SAP.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for screening lab tests, hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

A listing of the LabPlus laboratory normal ranges will be provided. Ranges are based on the sex and age of the patient on the date of collection of the laboratory sample.

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum) will be provided for the SOF/VEL 4 Week group by analysis visit for: ALT, aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, direct bilirubin, white blood cell (WBC), neutrophils (absolute), lymphocytes (absolute), reticulocyte count, hemoglobin, platelets, albumin, international normalized ratio of prothrombin time (INR), serum creatinine, and creatinine clearance (CrCl).

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. The mean, median, Q1, Q3, minimum and maximum will be displayed to reported number of digits, and SD to reported number of digits +1 for each on-treatment visit. The posttreatment Week 1, 2, and 4 visits will be presented as additional separate visits. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3 of this SAP.

The number and percentage of subjects with at least 1 postbaseline (up to 30 days post last dose) hemoglobin value < 10 g/dL and < 8.5 g/dL will be summarized. The denominator will be the number of subjects with at least 1 postbaseline hemoglobin value.

A listing of subjects meeting the criteria for postbaseline hemoglobin < 10 g/dL and < 8.5 g/dL will be provided.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning toxicity grades (0 to 4) to laboratory results. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels.

Toxicity grading will be presented in listings of laboratory data. No summary tables for toxicity grading will be produced due to the effects of liver transplantation on laboratory values in the immediate post-operative period.

7.3. Body Weight, Height, BMI, and Vital Signs

Vital signs (systolic and diastolic blood pressure [mmHg] and pulse [bpm]) at each visit will be summarized for the Safety Analysis Set using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for the SOF/VEL 4 Week group. The baseline value will be defined as the last available value collected on or prior to the date of first dose of study drug. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3 of this SAP. No inferential statistics will be generated.

A by-subject listing of height (cm), body weight (kg), BMI (kg/m2) and vital signs (systolic and diastolic blood pressure [mmHg], pulse [bpm], respiration [breaths/min], and body temperature [°C]) will be provided. Data will be sorted for each subject and visit in chronologic order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary. The medications will be categorized as prior or concomitant using the following definitions:

- Prior medications: any medications taken and stopped prior to or on the date of first study drug administration
- Concomitant medications: any medications taken after the date of first study drug administration and up to the last dosing date of study drug

Concomitant medications (other than study drug and drugs administered to prevent rejection of the transplanted organ) will be summarized by preferred drug name using the number and percentage of subjects for the SOF/VEL 4 Week group. A subject reporting the same medication for a preferred drug name more than once will be counted once only per subject. The summary of concomitant medications will be ordered by descending frequency of preferred drug name. For preferred drug names with the same frequency, sorting will be done alphabetically.

Summaries will be based on the Safety Analysis Set. No inferential statistics will be generated.

For purposes of analysis, any medication with a stop date that is on or prior to the initial study drug dosing date or start date that is after the last study drug dosing date will be excluded from a concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the initial study drug start date will be excluded from the concomitant medication summary. If a partial start date is entered, then any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary.

All prior and concomitant medications (other than per-protocol study drugs and drugs administered to prevent rejection of the transplanted organ) will be provided in a by-subject listing sorted by subject ID number and administration date in chronologic order.

7.5. Concomitant Immunosuppressant Medications

Immunosuppressant medications administered to prevent rejection of the transplanted organ collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary. Concomitant (as described in Section 7.4) immunosuppressant medications will be summarized by preferred drug name for the SOF/VEL 4 Week group for subjects in the Safety Analysis Set.

All prior and concomitant immunosuppressant medications administered to prevent rejection of the transplanted organ will be presented in a by-subject listing sorted by subject ID number and start date of administration for subjects in the safety analysis set.

7.6. Investigator Electrocardiogram Assessment

A by-subject listing for ECG assessment results collected at screening and at the pre-surgery visit including comments regarding clinically significant abnormalities will be provided for subjects in the safety analysis set. ECGs will be listed by the nominal visit and will be presented in chronological order.

7.7. Other Safety Measures

A data listing will be provided for subjects who become pregnant during the study.

7.8. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC ANALYSIS

The plasma concentrations of SOF (and its metabolites GS-566500 and GS-331007) and VEL will be determined using validated bioanalytical assays.

8.1. PK Sample Collection

A single PK blood sample will be collected at Study Days 7, 14, 21, and 28 (or end of treatment).

A PK Substudy will be performed on Study Day 1 for all subjects. PK samples will be collected predose, and at 0.5, 1, 2, 4, 8, 12, and 24 hours postdose to determine the PK of SOF, SOF metabolites GS-566500 and GS-331007, and VEL.

8.2. PK Analyses Related to Intensive PK Sampling

PK over a 24-hour dosing interval will be determined in subjects in the PK Substudy analysis set. Concentrations of SOF, GS-566500, GS-331007, and VEL in plasma collected on Study Day 1 will be determined using validated bioanalytical assays.

8.2.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic (PK) parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear up/log down trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0.

For area under the curve (AUC), samples BLQ of the bioanalytical assay occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile by profile basis.

Pharmacokinetic parameters such as AUC_{tau}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.2.2. Pharmacokinetic Parameters

Pharmacokinetic parameters will be generated for all subjects in the PK substudy analysis set based on intensive PK samples collected on Study Day 1.

The pharmacokinetic parameters for VEL, SOF, GS-566500 and GS-331007 will be computed for all subjects with evaluable PK profiles. For each subject, the following PK parameters will be calculated, as appropriate:

Table 3. Pharmacokinetic Parameters for Each Analyte

Parameter	Description
AUC_{0-24}	area under the concentration versus time curve over the dosing interval
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
C_{last}	last observed quantifiable concentration of the drug in plasma
C_{max}	maximum observed concentration of drug in plasma
C_{24}	observed drug concentration at the end of the dosing interval
$t_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate estimated by linear regression of the terminal elimination phase of the plasma concentration of drug versus time curve

Individual subject concentration data at each timepoint, and individual subject PK parameters for VEL, SOF, and SOF metabolites GS-566500 and GS-331007 in plasma will be listed and summarized using descriptive statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) by route of SOF/VEL administration (PO or NG) 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 will be presented.

Individual concentration data listings and summaries (intensive PK) will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower limit of quantitation (LLOQ) for the analyte being summarized at postdose time points, where LLOQ is corrected for the dilution factor (ie, reported dilution/dilution factor).

Individual PK parameter data listings and summaries will include all subjects for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of subjects with nonmissing data for that PK parameter.

The following tables will be provided for each analyte by route of SOF/VEL administration (PO or NG) and overall on study Day 1:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics

The following figures may be provided for each analyte by SOF/VEL route of administration (PO or NG) on Study Day 1:

- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Mean and median postdose concentration values that are ≤ LLOQ will not be displayed in the figures and remaining points connected.

The following listing will be provided:

- PK sampling details (and PK concentrations) by subject that includes both intensive and sparse PK samples

9. REFERENCES

Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Dec. Biometrika 1934;26 (4):pp. 404-13.

10. SOFTWARE

SAS® Software Version 9.1. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 7.0. Statistical Solutions, Cork, Ireland.

11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Table Number	Title	Analysis Set
1	Subjects Enrolled and Treated by Investigator	Safety Analysis Set
2.1	Reasons for Screen Failure	Screened Subjects
2.2	Subjects Enrolled and Treated Who Did Not Meet Eligibility Criteria	Safety Analysis Set
3*	Subject Disposition	Enrolled Subjects
4*	Demographics and Baseline Characteristics	Safety Analysis Set
5*	Duration of Exposure to Study Drug	Safety Analysis Set
6	Adherence to Study Drug	Safety Analysis Set
7	Concomitant Medications	Safety Analysis Set
8	Concomitant Immunosuppressant Medications	Safety Analysis Set
9	SVR12	Full Analysis Set
10	Virologic Outcome	Full Analysis Set
11	SVR by Visit During Posttreatment Follow Up	Full Analysis Set
12	Virologic Outcome at Posttreatment Weeks 4 and 12	Full Analysis Set
13	SVR12 by Subgroup	Full Analysis Set
14*	Proportion of Subjects with HCV RNA Less Than LLOQ (15 IU/mL) While on Treatment by Visit	Full Analysis Set
15*	Adverse Events: Brief Summary	Safety Analysis Set
16*	All Treatment-Emergent Adverse Events	Safety Analysis Set
17	Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set
18*	Treatment-Emergent Adverse Events of Grade 3 or Above	Safety Analysis Set
19*	Treatment-Emergent Treatment-Related Adverse Events of Grade 3 or Above	Safety Analysis Set
20	Treatment-Emergent Adverse Events of Grade 2 or Above	Safety Analysis Set
21	Treatment-Emergent Treatment-Related Adverse Events of Grade 2 or Above	Safety Analysis Set
22	Treatment-Emergent Serious Adverse Events	Safety Analysis Set
23	Treatment-Emergent Non-Serious Adverse Events Occurring in At Least 5% of Subjects	Safety Analysis Set
24*	Adverse Events That Led to Premature Discontinuation of SOF/VEL by Preferred Term	Safety Analysis Set
25	Treatment-Emergent Adverse Events Occurring in > 1 Subject by Preferred Term	Safety Analysis Set

Table Number	Title	Analysis Set
26	Adverse Events Leading to Interruption of SOF/VEL by Preferred Term	Safety Analysis Set
27*	Treatment-Emergent Serious Adverse Events by Preferred Term	Safety Analysis Set
28*	Treatment-Emergent Treatment-Related Serious Adverse Events by Preferred Term	Safety Analysis Set
29.1*	ALT (U/L) by Visit	Safety Analysis Set
29.2*	AST (U/L) by Visit	Safety Analysis Set
29.3*	Alkaline Phosphatase (U/L) by Visit	Safety Analysis Set
29.4*	Total Bilirubin (mg/dL) by Visit	Safety Analysis Set
29.5*	Direct Bilirubin (mg/dL) by Visit	Safety Analysis Set
29.6*	WBC (x 10^3/μL) by Visit	Safety Analysis Set
29.7*	Neutrophils (x 10^3/μL) by Visit	Safety Analysis Set
29.8*	Lymphocytes (x 10^3/μL) by Visit	Safety Analysis Set
29.9*	Reticulocyte Count (x 10^3/μL) by Visit	Safety Analysis Set
29.10*	Hemoglobin (g/dL) by Visit	Safety Analysis Set
29.11*	Platelets (x 10^3/μL) by Visit	Safety Analysis Set
29.12*	Albumin (g/dL) by Visit	Safety Analysis Set
29.13*	INR by Visit	Safety Analysis Set
29.14*	Serum Creatinine (mg/dL) by Visit	Safety Analysis Set
29.15*	Creatinine Clearance (mL/min)	Safety Analysis Set
30	Postbaseline Hemoglobin < 10 g/dL and < 8.5 g/dL	Safety Analysis Set
31.1	Pulse (bpm) by Visit	Safety Analysis Set
31.2	Diastolic Blood Pressure (mmHg) by Visit	Safety Analysis Set
31.3	Systolic Blood Pressure (mmHg) by Visit	Safety Analysis Set

* Included in DMC analysis.

PK Table or Figure Number	Title	Analysis Set
PK Table 1	Subjects Evaluable by Study Day 1 SOF/VEL Route of Administration	PK Substudy Analysis Set
PK Table 2	Plasma SOF Concentrations (ng/mL) by Subject with Summary Statistics for Each Substudy Timepoint (by Route of SOF/VEL Administration on Day 1)	PK Substudy Analysis Set
PK Table 3	Plasma GS-331007 Concentrations (ng/mL) by Subject with Summary Statistics for Each Substudy Timepoint (by Route of SOF/VEL Administration on Day 1)	PK Substudy Analysis Set
PK Table 4	Plasma GS-566500 Concentrations (ng/mL) by Subject with Summary Statistics for Each Substudy Timepoint (by Route of SOF/VEL Administration on Day 1)	PK Substudy Analysis Set
PK Table 5	Plasma VEL Concentrations (ng/mL) by Subject with Summary Statistics for Each Substudy Timepoint (by Route of SOF/VEL Administration on Day 1)	PK Substudy Analysis Set
PK Table 6	Plasma SOF Pharmacokinetic Parameters by Subject with Summary Statistics for Each Parameter (by Route of SOF/VEL Administration on Day 1)	PK Substudy Analysis Set
PK Table 7	Plasma GS-331007 Pharmacokinetic Parameters by Subject with Summary Statistics for Each Parameter (by Route of SOF/VEL Administration on Day 1)	PK Substudy Analysis Set
PK Table 8	Plasma GS-566500 Pharmacokinetic Parameters by Subject with Summary Statistics for Each Parameter (by Route of SOF/VEL Administration on Day 1)	PK Substudy Analysis Set
PK Table 9	Plasma VEL Pharmacokinetic Parameters by Subject with Summary Statistics for Each Parameter (by Route of SOF/VEL Administration on Day 1)	PK Substudy Analysis Set
PK Figure 1	Mean (SD) Plasma Concentration – Time Profile (Analyte=SOF)	PK Substudy Analysis Set
PK Figure 2	Mean (SD) Plasma Concentration –Time Profile (Analyte=GS-331007)	PK Substudy Analysis Set
PK Figure 3	Mean (SD) Plasma Concentration –Time Profile (Analyte=GS-566500)	PK Substudy Analysis Set
PK Figure 4	Mean (SD) Plasma Concentration –Time Profile (Analyte=VEL)	PK Substudy Analysis Set
PK Figure 5	Median (Q1, Q3) Plasma Concentration –Time Profile (Analyte=SOF)	PK Substudy Analysis Set
PK Figure 6	Median (Q1, Q3) Plasma Concentration –Time Profile (Analyte=GS-331007)	PK Substudy Analysis Set
PK Figure 7	Median (Q1, Q3) Plasma Concentration –Time Profile (Analyte=GS-566500)	PK Substudy Analysis Set
PK Figure 8	Median (Q1, Q3) Plasma Concentration–Time Profile (Analyte=VEL)	PK Substudy Analysis Set

Listing Number	Title	Analysis Set
1#	Subject Disposition	Safety Analysis Set
2.1	Subjects Who Were Excluded from Safety and Full Analysis Sets	Enrolled Subjects
2.2	Inclusion and Exclusion Criteria Not Met	Subjects Not Treated
3.1	Subject Demographics and Baseline Characteristics	Safety Analysis Set
3.2*	Transplant Information and Donor Characteristics	Safety Analysis Set
4	Medical History	Safety Analysis Set
5.1	Study Drug Administration	Safety Analysis Set
5.2	Study Drug Accountability and Adherence	Safety Analysis Set
6.1	Prior and Concomitant Medications	Safety Analysis Set
6.2	Prior HCV Medications	Safety Analysis Set
7	Immunosuppressant Medications	Safety Analysis Set
8*	All Adverse Events	Safety Analysis Set
9*	Adverse Events of Grade 3 or Above	Safety Analysis Set
10*	Adverse Events Leading to Premature Discontinuation of SOF/VEL	Safety Analysis Set
11*	Serious Adverse Events	Safety Analysis Set
12*	Pregnancy	Safety Analysis Set
13.1*	Deaths	Safety Analysis Set
13.2*	Graft Loss	Safety Analysis Set
14*	LabPlus Laboratory Normal Ranges	
15	Screen Labs: HBsAg, HIV-1,2 Ab, and Hepatitis C Ab	Safety Analysis Set
16.1*	Hematology: Hematocrit, Hemoglobin, Reticulocyte Count, MCV, RBC, WBC, and Platelets	Safety Analysis Set
16.2*	Hematology: WBC, Neutrophils, and Lymphocytes	Safety Analysis Set
16.3*	Hematology: Eosinophils, Basophils, and Monocytes	Safety Analysis Set
17.1*	Chemistry: Sodium, Potassium, Serum Creatinine, Creatinine Clearance (Cockcroft-Gault), and Glucose	Safety Analysis Set
17.2*	Chemistry: AST, ALT, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, GGT, Albumin, and Lipase	Safety Analysis Set
18*	Coagulation Tests: INR and APTT	Safety Analysis Set
19.1	Urinalysis: Urine Blood, Glucose, pH, Protein, Urobilinogen, and Leukocyte Esterase	Safety Analysis Set
19.2	Urinalysis: RBC/HPF, WBC/HPF, Epithelial Cells, and Bacteria	Safety Analysis Set

Listing Number	Title	Analysis Set
20	Subjects with Postbaseline Hemoglobin < 10 g/dL and <8.5 g/dL	Safety Analysis Set
21	HCV RNA (log_{10} IU/mL) by Visit	Full Analysis Set
22.1	Subjects with Virologic Failure	Full Analysis Set
22.2	Subjects with Other Virologic Outcome	Full Analysis Set
23	Height, Weight, BMI, and Vital Signs	Safety Analysis Set
24	12–Lead Electrocardiogram (ECG) Results	Safety Analysis Set
25	Pretransplant Native Model for End Stage Liver Disease (MELD) Scores	Safety Analysis Set
26	Pretransplant Child-Pugh-Turcotte (CPT) Scores	Safety Analysis Set
PK Listing 1	Plasma PK Sampling Details and PK Concentrations	PK Analysis Set

* Included in DMC analysis.
#=Premature discontinuations from study drug will be produced for DMC Meeting.