STATISTICAL ANALYSIS PLAN

Study Title:	A Multicenter, Randomized, Phase 3, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir ± Ribavirin for 12 Weeks in Subjects with Chronic HCV Infection and Decompensated Cirrhosis
Name of Test Drug:	SOF/VEL Fixed Dose Combination (FDC)
Study Number:	GS-US-342-4019
Protocol Version (Date):	Amendment 1: 17 November 2016
Analysis Type:	SVR12 and Final Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	27 February 2018
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BMI	body mass index
CI	confidence interval
CPT	Child-Pugh-Turcotte
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FAS	full analysis set
FDC	fixed dose combination
FU	follow-up
HCV	hepatitis C virus
HLGT	high level group term
HLT	high level term
ID	Identification
INR	International normalized ratio
IWRS	Interactive Web Response System
LLT	lower level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
PT%	Prothrombin Activation %
Q1	first quartile
Q3	third quartile
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
SOF	sofosbuvir (Sovaldi®)
SVR	sustained virologic response

SVRx	sustained virologic response x weeks after stopping study drug
TE	treatment-emergent
TFLs	tables, figures, and listings
TND	target not detected
ULN	upper limit of the normal range
VEL	velpatasvir
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) in the clinical study report (CSR) for Study GS-US-342-4019. This SAP is based on the study protocol amendment 1 dated 17 November 2016 and the electronic case report form (eCRF). The SAP will be finalized before database 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 evaluate the antiviral efficacy of therapy with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) with or without ribavirin for 12 weeks as measured by the proportion of subjects with sustained virologic response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of each treatment regimen

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate therapeutic efficacy as measured by the change of Child-Pugh-Turcotte (CPT) score and Model for End Stage Liver Disease (MELD) score
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

The exploratory objectives of this study are as follows:

- PPD
- PPD

1.2. Study Design

This multicenter, randomized, open-label study evaluates the efficacy and safety of SOF/VEL ± RBV for 12 weeks in subjects with chronic HCV infection with decompensated cirrhosis.

Initially only subjects with CPT B cirrhosis at screening (score 7-9) will be enrolled. Enrollment of subjects with CPT C cirrhosis at screening (score 10-12) will begin after the data monitoring committee (DMC) has reviewed accumulated safety data when the first 20 subjects enrolled have completed 4 weeks of treatment (or early treatment discontinuation) and concluded that these data support enrollment of subjects with CPT C cirrhosis.

Approximately 100 subjects will be randomized (1:1) to 1 of the following 2 treatment groups:

- SOF/VEL (400/100 mg) for 12 weeks (n=50)
- SOF/VEL (400/100 mg) with RBV for 12 weeks (n=50)

Randomization will be stratified by CPT class at screening (CPT B/CPT C) and HCV genotype (genotype 1/nongenotype 1). CPT class for randomization will be based on the site's calculation of CPT score. For the purposes of randomization, a subject with nondefinitive or mixed HCV genotype results by central laboratory analysis will be considered nongenotype 1. At least 15 subjects will have nongenotype 1 HCV infection. Approximately 10% of subjects will have CPT C (score 10-12) decompensated cirrhosis.

Subjects will be treated with SOF/VEL or SOF/VEL+RBV for 12 weeks. The total time to complete all study visits is approximately 40 weeks (42 weeks for those requiring an extension of the screening period):

- 28-day (4-week) screening period
- 12-week study treatment period
- 24-week posttreatment period

1.3. Sample Size and Power

A sample size of 50 subjects in each treatment group will provide over 99% power to detect at least 40% improvement in SVR12 rate from the assumed spontaneous rate of 1% or less using a 2-sided exact 1-sample binomial test at significance level of 0.025.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee

An external multidisciplinary DMC will perform a review of accumulated safety data when the first 20 subjects with CPT B cirrhosis at screening enrolled have completed 4 weeks of treatment (or treatment discontinuation) and provide a recommendation to Gilead on whether these data support enrollment of subjects with CPT C cirrhosis. The DMC may also provide recommendations as needed regarding study design, conduct, and the need for additional meetings.

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. Interim Analysis

2.2.1. Posttreatment Week 4 Analysis

A posttreatment Week 4 analysis will be conducted for administrative purposes after all subjects complete the posttreatment Week 4 visit or prematurely discontinue from study. All safety and efficacy data through the posttreatment Week 4 visit will be included. The results will be restricted to a limited group of individuals within Gilead. There will be no changes to the study design, study conduct, or the sample size as a result of this administrative analysis.

2.2.2. Posttreatment Week 12 Analysis

The analysis for the primary endpoint SVR12 will occur after all subjects complete the posttreatment Week 12 visit or prematurely discontinue from study. All safety and efficacy data through the posttreatment Week 12 visit will be cleaned, finalized, and included for the analysis.

2.3. Final Analysis

After all subjects have completed the study, outstanding data queries 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] or standard error [SE], median, first quartile [Q1], third quartile [Q3], minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level, unless otherwise specified.

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 in ascending order, unless otherwise specified.

For screening, CPT scores can be assessed using prothrombin activation % (PT%) or international normalized ratio (INR) for the coagulation parameter. In the clinical database, all CPT scores will be assessed using PT% 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 Randomized Analysis Set

The All Randomized Analysis Set includes all subjects randomized in the study after screening. All analyses based on the All Randomized Analysis Set will be performed according to the treatment subjects randomized.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized into the study and received at least 1 dose of study drug. The study drugs in this study are SOF/VEL and RBV. Subjects are grouped within the FAS by the treatment group to which they were randomized.

This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

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

This is the primary analysis set for safety analyses.

3.1.4. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes all subjects who were randomized into the study, received at least 1 dose of the study drugs and had at least 1 nonmissing concentration value for the corresponding analyte in plasma. The analyte of interest may include SOF, GS-566500, GS-331007, or VEL. The PK Analysis Set will be used for analyses of general PK.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set or FAS, subjects will be grouped according to the treatment to which they were randomized. For analyses based on other analysis sets, such as the Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received is defined as the randomized treatment except for subjects who received treatment that differs from the randomized treatment for the entire treatment duration. In this case, the actual treatment received is defined as the treatment received for the entire treatment duration.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive web response system (IWRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- CPT class at screening (CPT B/CPT C) calculated by sites
- HCV genotype (genotype 1/nongenotype 1). For the purposes of randomization, a subject with nondefinitive or mixed HCV genotype results by central laboratory analysis will be considered nongenotype 1

If there are discrepancies in stratification factor values between the IWRS and the clinical database, the values recorded in the clinical database will be used for analyses unless otherwise specified.

3.4. Examination of Subject Subsets

Subgroup analyses will be explored by HCV genotype (genotype 1/nongenotype 1) and/or by CPT class at baseline in clinical database.

Other subject subsets will also be explored for the primary efficacy endpoint (SVR12), including the following:

- age (< 65 years, ≥ 65 years)
- sex (male, female)
- baseline BMI (< 25 kg/m^2 , ≥ 25 kg/m^2)

- HCV genotype and subtype (if applicable)
- IL28B genotype (CC, non-CC; with non-CC further broken down to CT, TT)
- baseline HCV RNA (< 800,000 IU/mL, ≥ 800,000 IU/mL and < 5 $\log_{10}$ IU/mL, ≥ 5 $\log_{10}$ IU/mL)
- baseline CPT class (CPT A [5-6], CPT B [7-9], or CPT C [10-15])
- baseline MELD score category (<10, 10-15, 16-20, 21-25, >25)
- baseline alanine aminotransferase (ALT) (≤ 1.5 × upper limit of normal [ULN], > 1.5 × ULN)
- prior HCV treatment experience (treatment naive, treatment experienced)
- study treatment status (completed study treatment, discontinued study treatment)
- adherence to study regimen (<80%, ≥ 80%)
- adherence to SOF/VEL (<80%, ≥ 80%)
- adherence to RBV (Group 2 only) (< 80%, ≥ 80%)

3.5. Multiple Comparisons

In the primary efficacy analysis, the SVR12 rate in each of the 2 treatment groups will be compared with the spontaneous clearance rate of 1% using 2-sided exact 1-sample binomial test with Bonferroni alpha adjustment (each at significance level 0.025).

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 the missing data imputed up to the time of the last dose (for on-treatment displays). If the study day associated with the last dosing date is greater than or equal to the lower bound of a visit window and the value at the visit

is missing, 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, 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 "< lower limit of quantitation (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) except for SVR24, which will be imputed according to SVR12 status. Success for SVR12 who have no further HCV RNA measurements collected will be counted as a success for SVR24 due to the high correlation between these 2 endpoints.

For the analyses of continuous HCV RNA efficacy data, when and only when a missing HCV RNA value is imputed as < LLOQ TND or < LLOQ detected according to the imputation rule described above, the corresponding continuous value will be imputed to LLOQ - 1 IU/mL. No other imputation will be performed for continuous HCV RNA data.

For health-related quality of life (HRQoL) data including 36-Item Short Form Health Survey (SF-36), Chronic Liver Disease Questionnaire (CLDQ-HCV), Fatigue Index (FACIT-F), and Work Productivity and Activity Impairment Questionnaire: Hepatitis C, v2.0 (WPAI: Hepatitis C), missing data will not be imputed.

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 and 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 for each 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 instead of first dose date of study drug.

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 1 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 < 1. For the values reported as < 1 or < 0.1, value of 0.9 or 0.09 will be used for calculation of summary statistics.

- A value that is 1 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 same 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).

The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to determine HCV RNA results in this study. The LLOQ of the assay is 15 IU/mL.

When the calculated HCV RNA value is within the linear range of the assay, 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 result.

When HCV RNA is not detected, the result is reported as "No HCV RNA 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 HCV RNA detected". 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 14 IU/mL.

For selected analyses, HCV RNA data (IU/mL) will be transformed to the logarithmic (base 10) scale ($\log_{10}$ IU/mL).

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 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 for an individual study drug will be the end date on study drug administration eCRF for the record where the "subject permanently withdrawn" flag is 'Yes'. The last dose date will be defined as the maximum of the last dose dates of individual study drugs in a treatment group.

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, 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 the purpose of analysis, observations will be assigned to analysis windows.

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

HCV RNA, CPT, MELD, vital signs, and safety laboratory data collected up to the last dose date + 3 days are considered to be on-treatment data and HCV RNA, CPT, MELD, 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 and safety laboratory data; MELD and CPT data; and vital signs and weight data are provided in Table 3-1 , Table 3-2, and Table 3-3.

Table 3-1. Analysis Windows for On-Treatment HCV RNA and Safety Laboratory Data

	HCV RNA and Safety Laboratory Data		
Nominal Visit	**Nominal Day**	**Lower Limit**	**Upper Limit**
Baseline	1	(none)	1
Week 2	14	2	21
Week 4	28	22	42
Week 8	56	43	70
Week 12	84	71	≥ 85

Table 3-2. Analysis Windows for On-Treatment MELD and CPT Data

	MELD and CPT Data		
Nominal Visit	**Nominal Day**	**Lower Limit**	**Upper Limit**
Baseline	1	(none)	1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	≥ 85

Table 3-3. Analysis Windows for On-Treatment Vital Signs[a] and Weight Data

	Vital Signs and Weight Data		
Nominal Visit	**Nominal Day**	**Lower Limit**	**Upper Limit**
Baseline	1	(none)	1
Week 1	7	2	11
Week 2	14	12	18
Week 3	21	19	25
Week 4	28	26	32
Week 5	35	33	39
Week 6	42	40	46
Week 7	49	47	53
Week 8	56	54	60
Week 9	63	61	67
Week 10	70	68	74
Week 11	77	75	81
Week 12	84	82	≥ 85

a Vital signs include resting blood pressure, pulse, respiratory rate, and temperature.

HCV RNA, CPT, MELD, vital signs, and safety laboratory data collected after the last dose date + 3 days will be assigned to the posttreatment follow-up (FU) visits. Visit windows will be calculated from the last dose date (ie, FU Day = collection date minus the last dose date) as shown in Table 3-4.

Table 3-4. Analysis Windows for Posttreatment HCV RNA, CPT, MELD, Vital Signs, and Safety Laboratory Data

	HCV RNA, CPT and MELD data			Vital Signs and Safety Laboratory Data [b]		
Nominal FU [a] Visit	Nominal FU Day	Lower Limit	Upper Limit	Nominal FU Day	Lower Limit	Upper Limit
FU-4	28	21	69	28	4	30
FU-12	84	70	146	NA	NA	NA
FU-24	168	147	210	NA	NA	NA

a FU-x visit = posttreatment Week-x follow-up visit.
b Vital signs and safety labs will only be summarized for the posttreatment Week 4 (FU-4) visit (up to 30 days after last dose).

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis 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 1 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 recorded on the same day, average (arithmetic mean) will be used for the baseline value. If multiple ECG measurements occur on the same day prior to first dose of any study drug, the average will be used as baseline value for continuous data, regardless of the timing of these multiple ECG measurements.

- For postbaseline visits:

  — The record closest to the nominal day for that visit will be selected except for HCV RNA posttreatment follow-up visits, for which the latest record in the analysis window will be selected.

  — If there are 2 records that are equidistant from the nominal day, the later record will be selected.

  — 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 the 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 value with the lowest severity will be selected (eg, normal will be selected over abnormal). If multiple ECG measurements occur on the same day prior to the first dose of any study drug, the value with the lowest severity will be selected regardless of the timing of these multiple ECG measurements.

  — 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 and Disposition

A summary of subject enrollment will be provided for each investigator within Japan by treatment group and overall. The summary will present the number and percentage of subjects in the Safety Analysis Set. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A similar enrollment table will be provided by CPT class at baseline and HCV genotype for each treatment group and overall. The denominator for the percentage of subjects in the category will be the total number of subjects in the Safety Analysis Set within that category for each treatment group and overall. A listing of discrepancies between IWRS and database values in CPT class and HCV genotype at screening will also be provided. A summary of reasons for screen failure will be provided. A by-subject listing will be provided for subjects randomized and treated who did not meet eligibility criteria.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group and overall. Two additional summaries will be provided, one by CPT class at baseline (CPT B, CPT C, total) and one by HCV genotype (genotype 1, nongenotype 1, total) within each treatment group and overall. The summaries will present the number of subjects screened, the number of subjects not randomized, the number of subjects randomized, the number of subjects randomized but never treated, and the number of subjects in each of the categories listed below:

- In Safety Analysis Set
- In FAS
- In PK Analysis Set
- Completed study treatment
- Did not complete study treatment with reasons for premature discontinuation of study treatment
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the percentage of subjects who completed or did not complete study treatment or study, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set. Among subjects who completed study treatment and who discontinued study treatment, the number of subjects will be summarized for:

- Subjects who had no HCV posttreatment Week 4 assessment and thereafter (No HCV FU-4 and thereafter)
- Subjects who had HCV posttreatment Week 4 assessment, but no HCV posttreatment Week 12 assessment and thereafter (With HCV FU-4 but No FU-12 and thereafter)

If a subject did not have any HCV RNA assessment ≥ 21 days after the last dose of any study drug (ie, lower bound of FU-4 visit for HCV RNA data), the subject is categorized as having "No HCV FU-4 and thereafter". If a subject had the HCV FU-4 assessment but did not have any HCV RNA assessment ≥ 70 days after the last dose of any study drug (ie, lower bound of FU-12 visit for HCV RNA data), the subject is categorized as having "With HCV FU-4 but No FU-12 and thereafter".

In addition, the total number of subjects who were randomized and the number of subjects in each of the disposition categories listed above will be depicted by a flowchart.

The following by-subject listings will be provided by subject ID number in ascending order to support the above summary tables:

- Disposition for subjects who completed study treatment and study
- Disposition for subjects who did not complete study treatment and/or study with reasons for premature discontinuation of study treatment and/or study
- Lot number and kit ID (if applicable)

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

Total duration of exposure to study drug will be defined as last dose date minus first dose date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

The total duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: baseline (Day 1), Week1 (Day 7), Week 2 (Day 14), Week 3 (Day 21), Week 4 (Day 28), Week 5 (Day 35), Week 6 (Day 42), Week 7 (Day 49), Week 8 (Day 56), Week 9 (Day 63), Week 10 (Day 70), Week 11 (Day 77), and Week 12 (Day 84). A 3-day window will be applied to the last planned on-treatment visit to match with the protocol-specified visit window (ie, the number of subjects exposed through Week 12 will be calculated as the number of subjects who were exposed to study drug for at least 81 days). Summaries will be provided by treatment group for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

The presumed total number of tablets administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Number of Doses Administered} = \left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets returned}\right)$$

The level of adherence to the study drug regimen will be assessed based on the total amount of study drug administered relative to the total amount of study drug prescribed at baseline.

The level of adherence will be expressed in percentage using the following formula:

$$\text{Level of Adherence}(\%) = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Total Amount of Study Drug Prescribed at baseline}}\right) \times 100$$

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

In the SOF/VEL 12 Week group, the total amount of SOF/VEL (400 mg/100 mg) prescribed for 12 weeks would require 84 tablets.

In the SOF/VEL+RBV 12 Week group, the total amount of SOF/VEL (400 mg/100 mg) prescribed for 12 weeks would require 84 tablets. For subjects with CPT B cirrhosis at screening as recorded in IWRS, weight-based RBV (200 mg) prescribed for 12 weeks would require 252 tablets (3 tablets/day) for baseline weight ≤ 60 kg, 336 tablets (4 tablets/day) for baseline weight > 60 kg to ≤ 80 kg, or 420 tablets (5 tablets/day) for baseline weight > 80 kg. For subjects with CPT C cirrhosis at screening as recorded in IWRS, 252 tablets (3 tablets/day) of RBV would be required. Subjects who prematurely discontinued study drug for lack of efficacy (ie, virologic failure) will have the total amount of study drug prescribed calculated up to the first date when virologic failure criteria were met. For virologic failure confirmed by 2 consecutive measurements the date of the first measurement will be used. If there were study drug bottles dispensed on or after the subject first met virologic failure criteria, these bottles will not be included in the calculation of adherence. If a bottle was dispensed and the bottle was returned empty, then the number of tablets returned will be entered as zero. If a bottle was dispensed but not returned (missing), the number of tablets taken from that bottle will be counted as zero.

Descriptive statistics for the level of adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80 to < 90%, ≥ 90%) will be provided by treatment group for the Safety Analysis Set. Categorical displays will be provided for the number of subjects who are at least 80% adherent to their study drug regimen (ie, adherence is ≥ 80% for each of the study drugs).

No inferential statistics will be provided for duration of exposure and adherence to study drug.

A separate by-subject listing of study drug administration and drug accountability will be provided by subject ID number (in ascending order) and visit (in chronological order).

4.2.3. Ribavirin Dosing Summary

This analysis will only be performed on subjects in Group 2 and by CPT class at baseline (CPT B, CPT C, total).Average RBV daily dose and average weight-based RBV daily dose will be calculated for each subject as follows (and then summarized for the treatment group):

Average RBV Daily Dose = (RBV [mg] taken during the study) ÷ (Days on any RBV)

Average Weight-based RBV dose = (Average RBV Daily Dose) ÷ (Weight [kg] at baseline)

where,

Days on RBV = Sum of number of days that the subject took a non-zero dose of RBV from the log form study drug administration page.

RBV (mg) taken during the study= Sum of all RBV entries on EX eCRF for: (RBV last dose date – RBV first dose date + 1) x (# RBV tablets per day x 200 mg).

The number and percentage of subjects who prematurely discontinued RBV dosing will be presented. Premature discontinuation will be defined by:

subjects will be considered prematurely d/c from RBV if total days on RBV (ie, last dose date of RBV – first dose date of RBV +1) is < 81 days.

The number and percentage of subjects who interrupted (ie, zero dose, or a gap of ≥ 3 days between RBV stop date of one entry and start date of the next entry) or decreased their RBV dose (ie, for at least 3 consecutive days) while on study drug will be presented. Subjects will be counted once for each category.

4.3. Protocol Deviations

A summary of important protocol deviations will be provided by the Clinical Operations group for subjects in the Safety Analysis Set.

Subjects who received study drug other than their randomized treatment assignment will be listed with the start and stop dates that they received incorrect study drug.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group and overall. Two additional summaries will be provided, one by CPT class at baseline (CPT B, CPT C, total) and one by HCV genotype (genotype 1, nongenotype 1, total) within each treatment group using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for age and using the numbers and percentages of subjects for age categories (< 65 years, ≥ 65 years), sex, race, and ethnicity. Age is calculated in years at the date of initial study drug administration. If a subject did not receive study drug after randomization/enrollment, the subject's age will be calculated from the date that the subject signed the informed consent form. The summary of demographic data will be provided for the Safety Analysis Set.

A by-subject demographic listing, which includes the date the informed consent was signed, will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include the following:

- body mass index (BMI; in kg/m^2) as a continuous variable and as categories (< 25 kg/m^2, ≥ 25 kg/m^2)
- HCV genotype and subtype (if applicable)
- IL28B genotype (CC, non-CC; with non-CC further broken down to CT, TT)
- baseline HCV RNA (log10 IU/mL) as a continuous variable and as categories (< 800,000 IU/mL, ≥ 800,000 IU/mL and < 5 $\log_{10}$ IU/mL, ≥ 5 $\log_{10}$ IU/mL)
- baseline ALT (U/L) as a continuous variable and as categories (≤1.5 × ULN, > 1.5 × ULN)
- baseline CPT score and category (CPT A [5-6], CPT B [7-9], CPT C [10-15])
- baseline MELD score and category (<10, 10-15, 16-20, 21-25, >25)
- baseline ascites (none, mild/moderate, severe)
- baseline hepatic encephalopathy (none, medication-controlled, medication-refractory)
- prior HCV treatment experience (treatment-naive, treatment-experienced)
- estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation

eGFR will be calculated by the Cockcroft-Gault method: $eGFR_{CG}$ (mL/min) = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] / (serum creatinine (mg/dL) × 72), where weight is total body mass in kilograms.

These baseline characteristics will be summarized by treatment group and overall. Two additional summaries will be provided, one by CPT class at baseline (CPT B, CPTC, total) and one by HCV genotype (genotype 1, nongenotype 1, total) within each treatment group using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using the numbers and percentages of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

A separate by-subject data listing for cirrhosis determination and prior HCV treatment and response will be provided for all subjects at screening.

5.3. Medical History

A by-subject listing of disease-specific medical history will be provided by subject ID number (in ascending order) and medical history (in chronological order).

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with SVR12, defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after cessation of treatment. The primary analysis will be performed after all randomized subjects have been followed through 12 weeks posttreatment or discontinued from study. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 will be used to measure HCV RNA.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

In the primary efficacy analysis, the SVR12 rate in each of the 2 treatment groups will be compared with the spontaneous clearance rate of 1% using 2-sided exact 1-sample binomial test with Bonferroni alpha adjustment (each at significance level 0.025) and, for each treatment group, the hypothesis for superiority is as follows:

H0: SVR12 rate = 1%,
H1: SVR12 rate ≠ 1%

This 1% spontaneous rate was assumed in the statistical test of treatment benefit because there are no currently available treatment options for these subjects and nontreatment rarely results in spontaneous cure.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The 2-sided exact 1-sample binomial test will be used to test the statistical hypotheses described above for each treatment group.

A point estimate with a 2-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate by treatment group (Clopper and Pearson 1934).

6.1.4. Subgroup Analysis of the Primary Efficacy Endpoint

Point estimates and 95% exact CIs of the SVR12 rates will be displayed by treatment group and HCV genotype (genotype 1, nongenotype 1, total) for each subgroup outlined in Section 3.4.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- The proportion of subjects with HCV RNA < LLOQ at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- Proportion of subjects who have HCV RNA < LLOQ by visit while on treatment
- HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through end of treatment (EOT)
- MELD and CPT score changes from baseline
- The proportion of subjects with virologic failure as the following:

  On-treatment virologic failure

  — HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ, while on treatment, confirmed with 2 consecutive values (note, second confirmation value can be posttreatment), or last available on-treatment measurement with no subsequent follow-up values (ie, breakthrough)

  — 1 log_{10}IU/mL increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values (note, second confirmation value can be posttreatment), or last available on-treatment measurement with no subsequent follow-up values (ie, rebound)

  — HCV RNA persistently ≥ LLOQ through 8 weeks of treatment (ie, nonresponse)

  Relapse

  — HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available posttreatment measurement

- Characterization of HCV drug resistance substitutions at baseline, during, and after therapy with SOF/VEL and SOF/VEL+RBV

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

6.2.2.1. Analysis Methods for Efficacy Endpoints – Viral Kinetics

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. The 2-sided 95% exact confidence interval based on Clopper-Pearson method will be provided by HCV genotype (genotype 1, nongenotype 1, total) for the percentage of subjects with HCV RNA < LLOQ at each visit in each treatment group. The overall category for "HCV RNA < LLOQ" will be split into the following 2 subcategories: "< LLOQ TND" for subjects with target not detected and "< LLOQ detected" for subjects with < LLOQ detected in tabular displays.

Graphs for the percentage of subjects with HCV RNA < LLOQ over time during treatment will be displayed by HCV genotype (genotype 1, nongenotype 1, total).

Summary statistics will be presented for absolute values and change from baseline in HCV RNA (log_{10} IU/mL) by HCV genotype (genotype 1, nongenotype 1, total) and by visit through EOT. Imputation rules described in Section 3.6.1 will be used to assign HCV RNA values for missing values at a visit that are bracketed by "< LLOQ TND" and/or "< LLOQ detected". Otherwise, a missing = excluded analysis will be performed. Plots of the mean ± SD and median (Q1, Q3) of absolute values and changes from baseline in HCV RNA through EOT will be presented by HCV genotype (genotype 1, nongenotype 1, total).

For the SVR12 endpoint analysis, a summary table of the number and percentage of subjects with SVR12, virologic failure (VF), and Other will be created by HCV genotype (genotype 1, nongenotype 1, total) for each treatment group. All subjects who achieve SVR12 will be categorized as SVR12. Virologic failure will be descriptively summarized as "on-treatment virologic failure" and relapse (which will be broken down by study drug completed yes/no). Subjects who do not achieve SVR12 and do not meet criteria for 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; otherwise, the denominator will be the number of subjects in the FAS. This summary table will also be provided by CPT class at baseline (CPT B, CPT C) and by HCV genotype (genotype 1, nongenotype 1, total) for each treatment group.

For subjects with virologic failure, a summary table of the point estimates and 95% exact CIs based on Clopper-Pearson method of the rate of virologic failure within each treatment group will be displayed by HCV genotype (genotype 1, nongenotype 1, total).

A concordance table between SVR12 and SVR24 will be provided for each treatment group and HCV genotype (genotype 1, nongenotype 1, total). Subjects with both observed SVR12 and observed SVR24 data will be included for this analysis.

In addition, a summary table of the number and percentage of subjects with HCV RNA < LLOQ and ≥ LLOQ at the posttreatment follow-up visit (observed and imputed, with reasons for imputed) will be provided by HCV genotype (genotype 1, nongenotype 1, total) for each

posttreatment follow-up visit. 95% Clopper-Pearson exact CIs will be presented for the overall proportion of subjects with HCV RNA < LLOQ.

Drug resistant substitutions will be analyzed as part of the Virology Study Report.

6.2.2.2. Analysis Methods for Other Efficacy Endpoints – CPT and MELD Scores

Analyses of CPT and MELD scores will be presented separately for the subset of subjects in the FAS who achieved SVR12 for the SVR12 analysis or SVR24 for the final analysis.

6.2.2.2.1. Child-Pugh-Turcotte Score

In the clinical database, CPT score will be assessed using prothrombin activation % for the coagulation parameter as described in Table 6-1. CPT score calculated by sites at screening/randomization can be assessed using either INR or PT% for coagulation parameter.

CPT scores will be 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 will not be calculated):

Table 6-1. Child-Pugh-Turcotte Scoring of the Severity of Cirrhosis

Measure		1 point	2 points	3 points
Total bilirubin, mg/dL, (µmol/L)		<2, (<34)	2-3, (34-50)	>3, (>50)
Serum albumin, g/dL		>3.5	2.8-3.5	<2.8
Coagulation[a]	INR	<1.7	1.7-2.3	> 2.3
	Prothrombin Activation %	>70%	40-70%	<40%
Ascites		**None** No ascites and not on treatment for ascites	**Mild/Moderate** Cross sectional imaging showing ascites Abdominal distension Medication for ascites	**Severe (diuretic-refractory)** Visible clinically
Hepatic encephalopathy		**None** No encephalopathy and not on any treatment for hepatic encephalopathy	**Medication-Controlled** Subject is lethargic, may have moderate confusion Subject is receiving medical therapy for hepatic encephalopathy	**Medication-Refractory** Marked confusion/incoherent, rousable but sleeping unless aroused or comatosed

a For coagulation, either INR or prothrombin activation % will be used

CPT class will be assigned as:

CPT class: A = 5-6 points
B = 7-9 points
C = 10-15 points

CPT class will be analyzed for subjects who achieve SVR12 and SVR24 respectively by treatment group and overall:

- Shift table of baseline CPT class vs. posttreatment week 12 CPT classes
- Shift table of baseline CPT class vs. posttreatment week 24 CPT classes (for final analysis)

A by-subject listing of CPT score based on INR and %PT and change from baseline will be provided for all subjects in Safety Analysis Set.

6.2.2.2.2. MELD Score

MELD score will be assessed as follows:

MELD = 0.957 x Loge (serum creatinine mg/dL)

+ 0.378 x Loge (Total bilirubin mg/dL)

+1.120 x Loge (INR)

+0.643

Multiple the score by 10 and round to the nearest whole number. Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD score calculation.

If subject has had dialysis twice within a week prior to the serum creatinine measurement or has received 24 hours of continuous venovenous hemodiafiltration within the prior week, then serum creatinine will be set to 4.0 mg/dL in the above formula.

The following analyses of MELD scores will be performed by treatment group and overall for subjects who achieved SVR12 at the posttreatment Week 12 analysis and those who achieved SVR24 at the final analysis:

- The number and percentage of subjects with “no change”, “increase”, and “decrease” between baseline and posttreatment Week 12 and 24 visits will be presented. “No change” will be assigned for differences (posttreatment visits MELD score minus baseline MELD score) of -1, 0 or 1; “decrease” will be assigned for differences that are ≤ -2; and “increase” will be assigned for values that are ≥ 2.

A by-subject listing of MELD score and change from baseline will be provided for all subjects in Safety Analysis Set.

6.3. Exploratory Efficacy Endpoints

PPD

PPD

PPD

6.4. Changes From Protocol-Specified Efficacy Analyses

There are no planned changes from protocol-specified efficacy analyses.

7. SAFETY ANALYSES

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 eCRF to the question of "Related to Study Treatment." Events for which the investigator did not record relationships to study drug will be considered 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 AEs met the definitions 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 Gilead Drug Safety and Public Health 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 one 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 dates are the same as or after the month and year (or year) of the first dose date of study drug.
- The AE onset date is the same as or before the month and year (or year) of the 30th day 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 by treatment group and by the number and percentage of subjects who had the following: any AE, any AE of Grade 3 or above, any AE of Grade 2 or above, any treatment-related AE, any treatment-related AE of Grade 3 or above, any treatment-related AE of Grade 2 or above, any SAE, any treatment-related SAE, any AE leading to premature discontinuation of any study drug, any AE leading to premature discontinuation of SOF/VEL, any AE leading to premature discontinuation of RBV, any AE leading to premature discontinuation of all study drugs, any AE leading to modification or interruption of any study drug, any AE leading to interruption of SOF/VEL, any AE leading to modification or interruption of RBV, any AE leading to modification or interruption of all study drugs. 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.

A brief summary of TEAEs by age group (ie, <65 years, ≥65 years, total) and by CPT class at baseline (CPT B, CPT C, total) will also be explored. Each brief summary will be presented by treatment group.

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT, by treatment group, by CPT class at baseline (CPT B, CPT C, total) within each treatment group based on the Safety Analysis Set as follows:

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs

- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- All treatment-related SAEs
- AEs leading to premature discontinuation of any study drug
- AEs leading to premature discontinuation of SOF/VEL
- AEs leading to premature discontinuation of RBV
- AEs leading to premature discontinuation of all study drugs
- AEs leading to modification or interruption of any study drug
- AEs leading to interruption of SOF/VEL
- AEs leading to modification or interruption of RBV
- AEs leading to modification or interruption of all study drugs

Multiple events will be counted once only per subject in each summary. Adverse events will be summarized and listed for each treatment first in alphabetic order of SOC and then by PT in order of descending incidence of the pooled treatment groups within each 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 be summarized by PT only, in order of descending incidence within pooled treatment groups for:

- AEs that occurred in at least 5% of subjects within any treatment group
- AEs of Grade 3 or above
- All treatment-related AEs
- All SAEs
- AEs leading to premature discontinuation of any study drug
- AEs leading to premature discontinuation of SOF/VEL
- AEs leading to premature discontinuation of RBV

- AEs leading to premature discontinuation of all study drugs
- AEs leading to modification or interruption of any study drug
- AEs leading to interruption of SOF/VEL
- AEs leading to modification or interruption of RBV
- AEs leading to modification or interruption of all study drugs

In addition to the by-treatment summaries described above, data listings will be provided for the following:

- All AEs
- AEs of Grade 3 or above
- SAEs
- Deaths
- AEs leading to premature discontinuation of any study drug
- AEs leading to modification or interruption of any study drug
- AE with changes other than resolution dates between the SVR12 and SVR24 analyses (provided only at the final analysis)

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. 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 study drug or all available data at the time of the database snapshot for subjects those who were ongoing at the time of an interim analysis. The analysis will be based on values reported in conventional units. When values are below the limit of quantitation, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics. For example, if "< 0.2" was recorded, a value of 0.1 will be used for the purpose of calculating summary statistics; if "< 0.1" was recorded, a value of 0.09 will be used for the purpose of calculating summary statistics. Hemolyzed test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for 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.

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 by treatment group for ALT, aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, hemoglobin, reticulocytes, red blood cell (RBC), white blood cell (WBC), neutrophils, lymphocytes, platelets, albumin, INR, prothrombin activation %, creatinine, eGFR, and creatine kinase as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline laboratory value will be defined as the final assessment performed on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum will be displayed to the reported number of digits; SD to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values for ALT, AST, total bilirubin, alkaline phosphatase, hemoglobin, reticulocytes, RBC, WBC, lymphocytes, platelets, and albumin will be plotted using a line plot by treatment group and visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3 (Selection of Data in the Event of Multiple Records in a Window).

The number of subjects with hemoglobin < 10 g/dL and < 8.5 g/dL at any postbaseline visit (up to 30 days after the last dose of any study drug) will be summarized by treatment group and by CPT class at baseline (CPT B, CPT C, total) within each treatment group. A by-subject listing will be provided for subjects with postbaseline hemoglobin < 10 g/dL and < 8.5 g/dL.

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 to laboratory results for analysis as Grade 0, Grade 1 (mild) , Grade 2 (moderate), Grade 3 (severe), or Grade 4 (potentially life threatening). Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. Some laboratory tests have laboratory toxicity criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug.

If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline visit.

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by analyte and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for a given analyte:

- Graded laboratory abnormalities
- Grade 3 or above laboratory abnormalities

For all summaries of treatment-emergent laboratory abnormalities, the denominator will be the number of subjects with nonmissing postbaseline values up to 30 days after last dose of study drug for the laboratory parameter of interest.

A by-subject listing of treatment-emergent Grade 3 or above laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the analyte of interest, with all applicable severity grades or abnormal flags displayed.

7.3. Body Weight, Height, and Vital Signs

Vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min]) at each visit, and change from baseline at each visit will be summarized for the Safety Analysis Set using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group. The baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No inferential statistics will be generated.

A by-subject listing of vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min], respiration [breaths/min], and body temperature [^{o}C]) will be provided by subject ID number and visit in chronological order. In the same manner, a by-subject listing of body weight, height, and BMI will be provided separately.

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, concomitant, or both 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 initially taken on or after the initial study drug dosing date and within the study drug treatment period (including the study drug therapeutic reach)

Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2, and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary of concomitant medications will be ordered by descending active treatment group frequency of ATC drug classes and then preferred names within an ATC medical class. For drugs 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 a 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 dosing 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. Medications with completely missing dates will be included in the concomitant medication summary.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

In addition, use of concomitant blood products and epoetin medication while the subject is taking study drug will be summarized (number and percentage of subjects) by treatment group, WHO drug class, and WHO generic name. Multiple drug use (by generic name) will be counted once only per subject. The summary will be sorted alphabetically by drug class and then by decreasing total frequency of generic name within a class. This subset analysis will be performed by selecting for the following generic terms: HUMAN RED BLOOD CELLS; BLOOD CELLS, PACKED HUMAN; RED BLOOD CELLS, CONCENTRATED; PLATELETS, HUMAN BLOOD; PLASMA; EPOETIN ALFA, ERYTHROPOIETIN, DARBEPOETIN ALFA. A listing of subjects with use of prior and concomitant blood products and epoetin medication while taking study drug will be provided.

Similarly, use of concomitant ascites and hepatic encephalopathy medication will be summarized. A listing of subjects with use of prior and concomitant medications for ascites and hepatic encephalopathy will be provided.

A listing of subjects with treatment for most recent prior hepatocellular carcinoma will also be provided.

7.5. Electrocardiogram Results

A by-subject listing for ECG assessment results will be provided by subject ID number and visit in chronological order. A by-subject listing for subjects with clinically significant abnormalities from ECG assessment results will also be provided by subject ID number and visit in chronological order.

7.6. Other Safety Measures

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

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

For the PK analysis set, plasma concentrations of SOF (and its metabolites GS-566500 and GS-331007) and VEL in plasma will be determined using validated bioanalytical assays. Population PK models for SOF, GS-331007 and VEL, previously developed for the Phase 2/3 SOF/VEL US NDA population analyses, will be applied to the data from all PK samples collected in this study. Details of the population PK analysis will be provided in a separate population PK analysis plan. Plasma PK sampling details and PK concentrations will be provided in a listing.

9. REFERENCES

Clopper, C. J. and E. S. Pearson (1934). "The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Dec." Biometrika **26**(4): pp. 404-413.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

11. APPENDICES

Appendix 1. Study Procedures Table

			Treatment Week (±3 days)												Posttreatment Week (±5 days)		
	Screening	Day 1[a]	1	2	3	4	5	6	7	8	9	10	11	12/ET[b]	4	12	24
Clinical Assessments																	
Informed Consent	X																
Determine Eligibility	X	X															
Verification of CPT score[c]		X															
Medical History	X																
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[e]	X	X															
Adverse Events and Concomitant Medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling		X				X				X				X	X	X	
Health Related Quality of Life[g]		X												X		X	
Assessment of ascites and hepatic encephalopathy	X	X				X				X				X	X	X	X
Imaging for HCC[h]	X																
Review of Study Drug Adherence and Drug Accountability[i]			X	X	X	X	X	X	X	X	X	X	X	X			
Study Drug Dispensing[j]		X				X				X							

	Screening	Day 1[a]	Treatment Week (±3 days) 1	2	3	4	5	6	7	8	9	10	11	12/ET[b]	Posttreatment Week (±5 days) 4	12	24
Close Monitoring of Subjects with CPT C Cirrhosis[k]		X															
Laboratory Assessments																	
Hematology, Chemistry	X	X		X		X				X				X	X	X	X
Coagulation (Prothrombin activation %, PT, aPTT and INR)	X	X		X		X				X				X	X	X	X
Urinalysis	X																
HCV RNA	X	X		X		X				X				X	X	X	X
Viral RNA Sequencing / Phenotyping		X		X		X				X				X	X	X	X
HBV DNA sample[l]				X		X				X				X	X	X	X
Single PK				X		X				X				X			
Serum or Urine Pregnancy Test[m]	X	X				X				X				X	X	X	X
HCV Genotyping	X																
IL28B Genotype		X															
HCV Ab, HIV Ab, HBsAg, HBsAb, HBcAb	X																
FibroTest®	X																
Archive Plasma sample[n]		X												X			
Single Genomic sample[o]		X															

a Day 1 assessments must be performed prior to dosing.
b ET = early termination.
c Prior to randomization on Day 1, CPT score should be calculated using laboratory values from the local lab to verify that it is between 7-12; however, randomization will be based on CPT score at Screening.
d Vital signs include resting blood pressure, pulse, respiratory rate and temperature.
e Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording. The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities.

f Adverse events and Concomitant Medications will be collected up to 30 days after the last dose of all study drugs. In addition, records of Concomitant Medications for ascites and hepatic encephalopathy taken through posttreatment Week 24 will be collected in the eCRF.

g Health Related Quality of Life (HRQoL) Surveys (eg, SF-36, CLDQ-HCV, FACIT-F and WPAI) will be conducted for all subjects where the surveys are available at Day 1.

h Liver imaging (eg, ultrasound or CT scan, at the discretion of the investigator) should be performed to exclude the presence of hepatocellular carcinoma (HCC) in all subjects within 4 months of Day 1.

i Study drugs will be reconciled at every post- Day 1 visit by the investigator in order to monitor the subject's adherence with the study drugs. Subjects must be instructed to bring back all bottles of study drugs in the original container at every post- Day 1 visit through the end of treatment.

j The IWRS will provide direction on the specifics of each subject's study drug dispensing.

k Subjects with CPT C cirrhosis at Screening should be monitored closely during treatment with SOF/VEL ± RBV. The extent and duration of monitoring is at the discretion of the Investigator, based on assessment of each individual subject, but may include daily contact with subject (or subject's family) or in-patient hospitalization. Proximity of subject's residence to the investigator's institution should be taken into consideration. The objective of this close monitoring is to facilitate prompt communication and response to adverse events that may occur.

l Reflex testing done only when ALT > 2x Day 1 value in subjects who are HBsAb or HBcAb positive at Screening.

m All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks through posttreatment Week 4. In addition, females of childbearing potential in the treatment group receiving RBV will have additional urine pregnancy testing every 4 weeks for a minimum of 6 months following last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. In the event of a positive urine pregnancy result, subjects will be instructed to return to the clinic as soon as possible for a serum pregnancy test. The subject will be contacted by telephone monthly to confirm that urine pregnancy testing has been performed posttreatment and to record the outcome. Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine pregnancy tests.

n Only for subjects who have provided separate consent for this sample and testing

o Only for subjects who have provided separate consent for this sample and testing. This sample can be obtained at a subsequent visit if not obtained at Day 1.

Appendix 2. QOL Score Calculation Algorithm

CLDQ – HCV

CLDQ-HCV scores are calculated using subject responses to 29 questions in the questionnaire. If Ri is the score for the patient's response to the item i, for i=1, 2, …., 29 then the 4 domain scores are calculated as follows:

- Activity/Energy (AE) = Mean of {R1, R3, R4, R5, R7, R18}
- Emotion (EM) = Mean of {R6, R8, R9, R11, R16, R23, R24, R27, R28}
- Worry (WO) = Mean of {R14, R15, R17, R19, R20, R21, R22, R29}
- Systemic (SY) = Mean of {R2, R10, R12, R13, R25, R26}

Here "Mean" is the average of nonmissing items (SAS mean function). Each score is calculated only if at least half of corresponding items are not missing. Otherwise, the score will be missing.

Over all CLDQ-HCV score is calculated by taking the mean of 4 domain scores {AE, EM, WO, SY}.

FACIT-F

Patient responses to 40 questions in FACIT-F questionnaire are rated in 0-4 score.

If less than 50% of responses in the corresponding domain are missing, the subscales for five domains are calculated as follows:

- Physical Well-Being (PWB) = 7 × Mean of {of GP1-GP7}
- Social/Family Well-Being (SWB) = 7 × Mean of {GS1-GS7}
- Emotional Well-Being (EWB) = 6 × Mean of {GE1-GE6}
- Functional Well-Being (FWB) = 7 × Mean of {GF1-GF7}
- Fatigue Subscale (FS) = 13 × Mean of {HI7, HI12, An1-An5, An7, An8 An12, An14-An16}

and

- FACIT-F Trial Outcome Index (TOI) = PWB+FWB+FS

If less than 20% of all items included are not missing,

- TACIT-F Total Score = PWB+SWB+EWB+FWB+FS

WAPI: Hepatitis C

The response to Question 1 of this questionnaire provides the binary endpoint whether or not the subject had been in a paid employment during the week prior to assessment.

If the subject had been in a paid employment (Response to Q1 is "Yes") at the visit when questionnaire was given, then following three scores are derived:

- Percent work time missed due to hepatitis C = 100×Q2/(Q2+Q4)
- Percent impairment while working due to hepatitis C = 100×Q5/10
- Percent overall work impairment due to hepatitis C =

$$100 \times \left[\frac{Q2}{(Q2+Q4)} + \left(1 - \frac{Q2}{Q2+Q4)} \right) \times \frac{Q5}{10} \right]$$

Question 6 is applicable to all subjects:

- Percent activity impairment due to hepatitis C = 100×Q6/10.