STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 or 24 Weeks in Subjects with Chronic Genotype 1 or 2 HCV Infection Who Have Previously Failed a Direct-Acting Antiviral-Containing Regimen
Name of Test Drug:	Sofosbuvir (SOF)/Velpatasvir (VEL) Fixed-Dose Combination
Study Number:	GS-US-342-3921
Protocol Version/Date:	Amendment 3: 13 June 2016
Analysis Type:	SVR12 and Final Analysis
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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
BPM	beats per minute
CI	confidence interval
DAA	direct-acting antiviral
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
GT	Genotype
HCV	hepatitis C virus
HLGT	high level group term
HLT	high level term
ID	Identification
IWRS	Interactive Web Response System
LLT	lower level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
INR	international normalized ratio
PK	Pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
RBC	red blood cell
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-342-3921. This SAP is based on the study protocol Amendment 3 dated 13 June 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) and ribavirin for 12 or 24 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 regimen as assessed by review of the accumulated safety data

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 the kinetics of circulating HCV RNA during treatment and after cessation of each treatment regimen
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

Exploratory objectives of this study are as follows

1.2. Study Design

This is a multicenter, randomized, open-label study in subjects who previously failed a DAA-containing regimen with chronic HCV infection with or without cirrhosis. All subjects with HCV genotype 1 will have failed prior treatment with an NS5A inhibitor. Subjects with HCV genotype 2 can have failed any DAA-containing treatment regimen.

Approximately 110 eligible subjects (please refer to the protocol for the complete inclusion and exclusion criteria) will be randomized in a 1:1 ratio to one of the following two treatment groups:

- SOF/VEL(400/100 mg) + RBV for 12 weeks (N = 55)
- SOF/VEL(400/100 mg) + RBV for 24 weeks (N = 55)

Randomization will be stratified by cirrhosis status (presence/absence) and HCV genotype (genotype 1/genotype 2). Approximately 20 subjects will have Child-Pugh-A compensated cirrhosis.

HCV Genotype	Number of Subjects Enrolled
1	approximately 90
2	approximately 20
Total	approximately 110

The schedule of assessments is provided as an appendix to the SAP (Appendix 1).

The total time to complete all study visits is up to approximately 42 or 54 weeks, including the following periods:

- 42-day (6-week) screening period
- 12-week or 24-week treatment period
- Up to 24-week posttreatment period

1.3. Sample Size and Power

Approximately 110 subjects will be randomized in this study with approximately 90 subjects with genotype 1 HCV infection and approximately 20 subjects with genotype 2 HCV infection. Due to the limited number of genotype 2 subjects in this study, the sample size justification will be based on genotype 1 subjects only.

A sample size of 45 genotype 1 subjects in each treatment group will provide over 90% power to detect at least 27% improvement in SVR12 rate from the historical control rate of 50% using a two-sided exact one-sample binomial test at significance level of 0.025.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee

This study does not have a data monitoring committee (DMC).

2.2. Interim Analysis

2.2.1. Posttreatment Week 12 Analysis

The analysis for the primary endpoint SVR12 will occur after all subjects have completed 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

The final analysis will be conducted when all subjects have completed the post treatment week 24 visit or prematurely discontinued from study. The data will be finalized after all data queries are resolved for study visits through completion of the post treatment week 24 visit. At the conclusion of data finalization, the study statistician and statistical programmers will run the final version of tables, figures and listings (TFLs).

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 in Section 6.1.

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.

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 analysis set.

3.1.1. All Randomized Analysis Set

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 were randomized to receive.

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. 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 study drug, and have 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.

3.1.5. PK Substudy Analysis Set

The PK Substudy Analysis Set includes all subjects who are enrolled in the PK substudy, have been administered at least 1 dose of study drug, and have at least 1 nonmissing postdose concentration value for the corresponding analyte in plasma. The analytes of interest may include SOF, GS-566500, GS-331007, or VEL. The PK Substudy Analysis Set will be used for intensive PK profiles of these analytes.

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 differed 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:

- Cirrhosis status (presence versus absence)
- HCV genotype (genotype 1 versus 2).

3.4. Examination of Subject Subsets

Subsetting of subjects based on randomization stratification factors will be explored for subgroup analyses. 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.

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 body mass index (BMI) (< 25 kg/m^2, ≥ 25 kg/m^2)
- HCV genotype/subtype (1 [1a, 1b, 1 other], 2)
- Number of prior DAAs (1, 2, 3, >3)

- Number of prior HCV treatment regimens (1, 2, 3, 4, 5, >5)
- Prior DAAs (NS5A only, NS5A + NS5B, NS5A + NS3, NS5A + NS5B + NS3, NS5B only, NS5B + NS3)
- cirrhosis (cirrhosis, absence of cirrhosis, missing)
- 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 alanine aminotransferase (ALT) (≤ 1.5 × upper limit of normal range (ULN), > 1.5 × ULN)
- most recent HCV treatment response (non-responder, relapse/breakthrough, early treatment discontinuation, met a virologic stopping rule not otherwise listed, or unknown)
- study treatment status (completed study treatment, discontinued study treatment)
- adherence to study regimen (< 80%, ≥ 80%)

3.5. Multiple Comparisons

The SVR12 rate for genotype 1 patients in each of the two treatment groups will be compared to the historical control rate of 50% using two-sided exact one-sample binomial test with the Bonferroni correction (each at significance level 0.025).

Adjustments for multiplicity will not be made in genotype 2 subjects because no statistical testing will be performed for those subjects.

No between-treatment comparison will be performed for this study.

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 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 "< 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 data management and data analysis processes, but no sensitivity analyses will be conducted. All available 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 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 instead of the first dose date of study drug. For some countries, only birth year is collected on the case report form (CRF). In those cases, "01 January" will be used for the unknown birth day and month for the purpose of age calculation, unless age is captured on the CRF.

Non-pharmacokinetics (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 < 1. For the values reported as < 1 or < 0.1, values of 0.9 or 0.09 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 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, then the result will be report as "<< numeric value>> IU/mL." This result is 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. HCV RNA values returned as "NO HCV RNA 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).

Natural logarithm transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are below the lower limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing.

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 date of the first dose of study drug administration.

Study day will be calculated from the date of first dose of study drug 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 the study drug administration eCRF for the record where the "subject permanently discontinued" 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 purposes 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, 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, 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 3-1.

Table 3-1. Analysis Windows for On-treatment HCV RNA, Vital Signs and Safety Laboratory Data

	SOF/VEL + RBV 12 Weeks			SOF/VEL + RBV 24 Weeks		
Nominal Visit	**Nominal Day**	**Lower Limit**	**Upper Limit**	**Nominal Day**	**Lower Limit**	**Upper Limit**
Baseline	1	(none)	1	1	(none)	1
Week 1	7	2	11	7	2	11
Week 2	14	12	18	14	12	18
Week 3	21	19	25	21	19	25
Week 4	28	26	32	28	26	32
Week 5	35	33	39	35	33	39
Week 6	42	40	49	42	40	49
Week 8	56	50	63	56	50	63
Week 10	70	64	77	70	64	77
Week 12	84	78	≥ 85	84	78	98
Week 16	NA	NA	NA	112	99	126
Week 20	NA	NA	NA	140	127	154
Week 24	NA	NA	NA	168	155	≥ 169

HCV RNA, vital sign, and safety laboratory data collected after the last dose date + 3 days will be assigned to the posttreatment follow-up (FU) visit. Visit windows will be calculated from the last dose date (ie, FU Day = collection date minus the last dose date) as shown in Table 3-2.

Table 3-2. Analysis Windows for Posttreatment HCV RNA, Vital Signs and Safety Laboratory Data

	HCV RNA/Vital Sign			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 FU-4 visit (up to 30 days after last dose).

ECG data is collected at baseline only. Qualitative assessments of whether the ECG is normal or abnormal will be assessed at baseline.

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 one value per analysis window.

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

- 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 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 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 total. 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 randomization table will be provided by randomization stratum for each treatment group and total. The denominator for the percentage of subjects in the stratum will be the total number of subjects in the Safety Analysis Set within that stratum for each treatment group and total. If there are discrepancies in the value used for stratification assignment between the Interactive Web Response System (IWRS) and the clinical database including CRF and laboratory data, the value collected in the clinical database will be used for the summary. A listing of subjects with the IWRS randomization strata that differ from stratification factor data entered in the clinical database at the time of data finalization will be provided.

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 total. This summary 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, randomized and treated (ie, safety analysis set), FAS, PK analysis set, and the number and percentage of subjects in each of the categories listed below. For the "Treated" category, the denominator for the percentage calculation will be the total number of subjects randomized for each column. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column:

- Completed study treatment
- Did not complete study treatment (with reasons for premature discontinuation of study treatment)
- Completed study
- Did not complete study (with reason for premature discontinuation of study)

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

- Who had no HCV posttreatment Week 4 assessment and thereafter (No HCV FU-4 and thereafter)
- Who had HCV posttreatment Week 4 assessment but no HCV posttreatment Week 12 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 identification (ID) number in ascending order to support the above summary tables:

- Disposition for subjects who complete 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 as specified in the study protocol.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dose date − first dose date + 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 and percentage of subjects (ie, cumulative counts) exposed through the following time periods: baseline (Day 1), Week 1 (Day 7), Week 2 (Day 14), Week 3 (Day 21), Week 4 (Day 28), Week 5 (Day 35), Week 6 (Day 42), Week 8 (Day 56), Week 10 (Day 70), Week 12 (Day 84), and for the 24-week arm only, Week 16 (Day 112), Week 20 (Day 140), and Week 24 (Day 168). 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 or Week 24 will be calculated as the number of subjects who were exposed to study drug for at least 81 days or 165 days, respectively). Summaries will be provided by treatment group for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

The total number of tablets administered will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum).

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 this study, the total amount of SOF/VEL (400 mg/100 mg) prescribed for 12 and 24 weeks would require 84 and 168 tablets, respectively; weight-based RBV (200 mg) prescribed for 12 and 24 weeks would require 252 / 504 (3 tablets/day for baseline weight ≤ 60 kg) , 336 / 672 (4 tablets/day for baseline weight > 60 kg to ≤ 80 kg) tablets, or 420 / 840 (5 tablets/day for baseline weight > 80 kg), respectively.

Subjects who prematurely discontinue study drug due to lack of efficacy (ie, virologic failure) will have the total amount of study drug prescribed calculated up to the first date that 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 date that 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 and total for the Safety Analysis Set. Categorical displays will be provided for the number of subjects who were at least 80% adherent to their study drug regimen (ie, adherence was ≥ 80% for each of the study drugs). No inferential statistics will be provided.

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).

4.3. Protocol Deviations

A summary of important protocol deviations will be provided by the Gilead 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, genotype (1, 2, and total), and total 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, 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:

- body mass index (BMI; in kg/m2) as a continuous variable and as categories (< 25 kg/m2, ≥ 25 kg/m2)
- HCV genotype/subtype (1 [further broken down to 1a, 1b, and 1 other if applicable], 2 [further broken down to 2a, 2b, and 2 other if applicable])
- Number of prior DAAs (1, 2, 3, >3)
- Number of prior HCV treatment regimens (1, 2, 3, 4, 5, >5)
- Prior DAAs (NS5A only, NS5A + NS5B, NS5A + NS3, NS5A + NS5B + NS3, NS5B only, NS5B + NS3)
- cirrhosis (cirrhosis, absence of cirrhosis, missing)
- IL28B (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)
- most recent prior HCV treatment response (non-responder, relapse/breakthrough, early treatment discontinuation, met a virologic stopping rule not otherwise listed, or unknown)
- 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, genotype (1, 2, and total), and total 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

General medical history data will not be coded, but will be listed only.

A by-subject listing of disease-specific medical history will be provided by subject ID number in ascending 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 for genotype 1 subjects in each of the two treatment groups will be compared to the performance goal of 50% using a 2-sided exact 1-sample binomial test at the 0.025 significance level. The null (H_0) and alternative (H_1) hypotheses used to assess superiority of SOF/VEL+RBV relative to the performance goal of 50% are:

- H_0: SVR12 rate = 50%
- H_1: SVR12 rate ≠ 50%

The 50% SVR null rate is derived from SVR rates of 43% (59/137) and 59% (57/96) for treatment naive patients with genotype 1 HCV infection and high viral loads treated with PEG IFN and RBV for 48 weeks cited in the Japanese package inserts for REBETOL® Capsules 200 mg (MSD, July 2015, 19_{th} version) and COPEGUS® Tablets 200 mg (Chugai Pharmaceuticals, July 2015, 6^{th} version), respectively. The weighted average rate then is 50% ((59+57)/(137+96) = 50%).

It is important to note that this historical control rate is a conservative estimate. Because there are no currently available IFN-free treatment options for these subjects and because many of these subjects will have a history of treatment failure with IFN-based therapy and/or medical comorbidities precluding the use of IFN, the actual response rate of this population would likely be much lower than 50%.

No statistical hypothesis testing will be performed in genotype 2 subjects.

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. The 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method {Clopper 1934} will be provided for the SVR12 rate for each of the two treatment groups and HCV genotype (1[1a, 1b, 1 other], 2, and total).

6.1.4. Subgroup Analysis of the Primary Efficacy Endpoint

Point estimates and 95% exact CIs of the SVR12 rates for each treatment group will be displayed by HCV genotype (1[1a, 1b, 1 other], 2, and total). Subgroups are 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 who attain SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- The percentage of subjects with HCV RNA < LLOQ while on treatment by study visit
- HCV RNA ($\log_{10}$ IU/mL) and change from baseline in HCV RNA ($\log_{10}$ IU/mL) through end of treatment (EOT)
- The percentage 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 by 2 consecutive values (Note: second confirmation value may 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 by 2 consecutive values (Note: second confirmation value may 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 EOT, confirmed by 2 consecutive values or last available posttreatment measurement
- Characterization of HCV drug resistance substitutions at baseline, during, and after therapy with SOF/VEL+RBV

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

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 two-sided 95% exact confidence interval based on the Clopper-Pearson method will be provided by HCV genotype (1[1a, 1b, 1 other], 2, and total) for the percentage of subjects with HCV RNA < LLOQ at each visit within each treatment

group and total. The overall category for "HCV RNA < LLOQ" will be divided into the following 2 subcategories: "< LLOQ TND" for subjects with target not detected and "< LLOQ detected" for subjects with < LLOQ in tabular displays.

Graphs for the percentage of subjects with HCV RNA < LLOQ over time during treatment will be displayed by HCV genotype (1[1a, 1b, 1 other], 2, and total).

Summary statistics will be presented for absolute values and change from baseline in HCV RNA (log_{10} IU/mL) by HCV genotype (1[1a, 1b, 1 other], 2, and total) and visit through EOT. Imputation rules described in Section 3.6.1 will be used to assign HCV RNA values for missing values at visits 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 (1[1a, 1b, 1 other], 2, and 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 (1[1a, 1b, 1 other], 2, and total). All subjects who achieved 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 virologic failure 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.

A concordance table between SVR12 and SVR24 will be provided by HCV genotype (1[1a, 1b, 1 other], 2, and total) for each treatment group and total. Subjects with both observed SVR12 and observed SVR24 data will be included for this analysis.

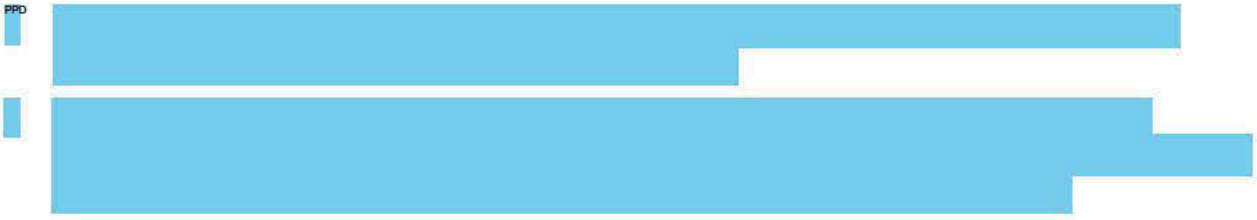
In addition, a summary table of the number and percentage of subjects with HCV RNA < LLOQ and ≥ LLOQ at the posttreatment follow-up visit (observed and imputed, with reasons for imputed) will be provided by HCV genotype (1[1a, 1b, 1 other], 2, and total) for each posttreatment follow-up visit; 95% Clopper-Pearson 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.

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints

Exploratory efficacy endpoints may include:



6.3.2. Analysis Methods for Exploratory Efficacy Endpoints

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 an AE is incomplete, then the month and year (or year alone if month is not recorded) of onset will 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 will be 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 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 by treatment group and total 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 that led to premature discontinuation of any study drug, any AE that led to premature discontinuation of SOF/VEL, any AE that led to premature discontinuation of RBV, any AE that led to premature discontinuation of all study drugs, any AE that led to modification or interruption of any study drug, any AE that led to interruption of SOF/VEL, any AE that led to modification or interruption of RBV, any AE that led to modification or interruption of all study drugs. All deaths (including those that were treatment emergent and those that were not treatment emergent) observed during the study will also be summarized and included in this table.

A brief summary of AEs by age group (ie, <65 years, ≥65 years) and by cirrhosis status will also be explored.

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT, by age group, by treatment group and total 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 first in alphabetic order of SOC and then by PT in order of descending incidence in the overall group 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 also be summarized by PT only, in order of descending incidence for:

- AEs that occurred in at least 5% of subjects
- 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
- 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 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 and total for ALT, aspartate aminotransferase (AST), total bilirubin, alkaline

phosphatase, hemoglobin, reticulocytes, red blood cell (RBC), white blood cell (WBC) counts, neutrophils, lymphocytes, platelets, Albumin, and international normalized ratio (INR) 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 the first dose of study drug. Change from baseline to a postbaseline visit will be defined as visit value − baseline value. The mean, median, Q1, Q3, minimum, and maximum will be displayed to the reported number of digits, with SD to the reported number of digits plus 1.

The median (Q1, Q3) of the observed values for ALT, AST, total bilirubin, alkaline phosphatase, hemoglobin, reticulocytes, WBC, neutrophils, lymphocytes, and platelets will be plotted using a line plot by treatment group and total and by 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 visits (up to 30 days after the last dose of any study drug) will be summarized by treatment group and age group and total.

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 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 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 [°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 prior to the initial study drug dosing date
- Concomitant medications: any medications initially taken on or after the initial study drug dosing date and within the study drug's treatment period (including study drug's 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 total. 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 will be sorted alphabetically by drug class and then by decreasing total frequency of generic name within a 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 the 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.

7.5. Other Safety Measures

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

7.6. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSIS

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 (intensive and sparse) 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 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 9.4. SAS Institute Inc., Cary, NC, USA.

11. APPENDICES

Appendix 1. Study Procedures Table
Appendix 2. QOL Score Calculation Algorithms

Appendix 1. Study Procedures Table

			Treatment Week (±3 days)												ET[c]	Posttreatment Week (±5 days)		
	Screening	Day 1[a]	1	2	3	4	5	6	8	10	12	16[b]	20[b]	24[b]		4	12	24
Clinical Assessments																		
Informed Consent	X																	
Determine Eligibility	X	X																
Medical History	X																	
Physical Examination	X	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	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X																	
Adverse Events and Concomitant Medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling		X									X			X	X	X	X	X
Health Related Quality of Life[g]		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	X			
Study Drug Dispensing[j]		X				X			X		X[b]	X	X					
Laboratory Assessments																		
Hematology & Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation (PT, aPTT and INR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
HCV RNA (Plasma)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral RNA Sequencing /Phenotyping Sample (Plasma)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single PK			X	X	X	X	X	X	X	X	X	X	X	X	X			
Intensive PK Substudy Collection[k]				X	X	X												
Serum or Urine Pregnancy Test[l]	X	X				X			X		X	X	X	X	X	X	X	X

	Screening	Day 1[a]	Treatment Week (±3 days) 1	2	3	4	5	6	8	10	12	16[b]	20[b]	24[b]	ET[c]	Posttreatment Week (±5 days) 4	12	24
Urinalysis	X																	
HCV Genotype, IL28B Genotype	X																	
HCV Ab, HIV Ab, HBsAg, HBsAb, HBcAb	X																	
HbA1c	X																	
FibroTest®	X																	
Archive plasma sample[m]		X									X			X	X			
Single Genomic Sample[n]		X																

a Day 1 assessments must be performed prior to dosing.
b Only to be completed for subjects on the 24 week treatment regimen
c ET = Early Termination.
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.
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, Week 12, Week 24 (if applicable), and posttreatment Week 12.
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. For subjects without cirrhosis, imaging must have been performed within 6 months prior to Day 1. For subjects with cirrhosis, imaging must have been performed 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 Dispense study drugs as directed by the IWRS
k Subjects that consent to the optional PPD .
l 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 during the dosing period. Females of childbearing potential 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. Pregnancy test kits will be dispensed to female subjects of childbearing potential after the posttreatment Week 4 visit. 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.
m Only for subjects who have provided separate consent for this sample and testing
n 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 Algorithms

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 non-missing 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 as follows:

Not at all = 0
A little bit = 1
Somewhat = 2
Quite a bit = 3
Very much = 4.

All FACIT-F scales are scored so that a high score is good. To achieve this, scores for following 23 questions are reversed by taking the difference from 4 (i.e. 4 – reported response).

GP1=4-GP1;
GP2=4-GP2;
GP3=4-GP3;
GP4=4-GP4;
GP5=4-GP5;
GP6=4-GP6;
GP7=4-GP7;
GE1=4-GE1;
GE3=4-GE3;
GE4=4-GE4;
GE5=4-GE5;
GE6=4-GE6;
HI7=4-HI7;

HI12=4-HI12;
AN1=4-AN1;
AN2=4-AN2;
AN3=4-AN3;
AN4=4-AN4;
AN8=4-AN8;
AN12=4-AN12;
AN14=4-AN14;
AN15=4-AN15;
AN16=4-AN16;

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}
- FACIT-F Trial Outcome Index (TOI) = PWB+FWB+FS
- 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 had been in a paid employment during the week prior to assessment.

If the patient has 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