STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 Weeks in Subjects with Chronic HCV Infection and Child-Pugh-Turcotte Class C Cirrhosis
Name of Test Drug:	Sofosbuvir/Velpatasvir Fixed-Dose Combination
Study Number:	GS-US-342-4022
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Analysis Type:	SVR12 and Final Analyses
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Analysis Plan Author:	PPD

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BMI	body mass index
BPM	beats per minute
CI	confidence interval
CLDQ-HCV	chronic liver disease questionnaire-HCV
CPT	Child-Pugh-Turcotte
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FACIT-F	functional assessment of chronic illness therapy-fatigue
FAS	full analysis set
FDC	fixed dose combination
FU	follow-up
FU-x	posttreatment follow-up Week x
HbA1c	hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ID	identification
INR	international normalized ratio
IWRS	interactive web response system
LLOQ	lower limit of quantitation
MELD	Model for End Stage Liver Disease
PK	pharmacokinetics
PT	preferred term
Q1, Q3	first quartile, third quartile
QOL	quality of life
RBC	red blood cell
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan

SD	standard deviation
SOC	system organ class
SOF	sofosbuvir (Sovaldi®)
SVR	sustained virologic response
SVRx	sustained virologic response x weeks after cessation of treatment
TEAEs	treatment-emergent adverse events
TND	target not detected
ULN	upper limit of the normal range
VEL	velpatasvir (previously GS-5816)
WBC	white blood cell
WPAI: Hep C	work productivity and activity impairment: hepatitis C

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-342-4022. This SAP is based on the study protocol Amendment 1 dated 22 November 2016 and the electronic case report form (eCRF). The SAP will be finalized before data finalization. Any changes to the analysis plan made after 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 efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL) fixed-dose combination (FDC) with ribavirin (RBV) for 12 weeks in subjects with chronic HCV infection and Child-Pugh-Turcotte (CPT) class C cirrhosis as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12)

- To evaluate the safety and tolerability of the treatment regimen

The secondary objectives of this study are:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of the study treatment regimen (SVR4 and SVR24)

- To evaluate the proportion of subjects with virologic failure

- To evaluate therapeutic efficacy as measured by the change of 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:

1.2. Study Design

This is a multicenter, open-label study evaluating the efficacy and safety of SOF/VEL and RBV for 12 weeks in chronic HCV infected subjects with CPT C cirrhosis.

Approximately 50 subjects will be enrolled and treated with SOF/VEL (400/100 mg) tablet once daily and RBV in a divided daily dose with food.

The total time to complete all study visits is approximately 40 weeks (42 weeks for those requiring extension of the screening period):

- 28 days (4 weeks) screening period (or 42 days for extenuating circumstances)
- 12 week study treatment period
- 24 week posttreatment period

1.3. Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The sample size is selected for practical reasons. With a sample size of approximately 50 subjects, a 2-sided 95% exact confidence interval of the SVR12 rate will extend at most 29% in length.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

2.1.1. 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.

2.1.2. Posttreatment Week 12 Analysis

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

2.2. Final Analysis

The final analysis will be performed after all subjects have completed the posttreatment Week 24 visit or have prematurely discontinued from the study, outstanding data queries have been resolved, and the database has been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and proportion 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.

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 safety and full analysis sets will be included in a by-subject listing with reasons for exclusion.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all subjects who were enrolled in the study.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled subjects who took at least 1 dose of study drug. The study drugs in this study are SOF/VEL and RBV. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.2. Subject Grouping

This study has one treatment group of SOF/VEL + RBV for 12 weeks.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule for enrolling subjects. No covariates will be included in efficacy and safety analyses.

3.4. Examination of Subject Subgroups

The following subject subgroups will be explored for the primary efficacy endpoint, SVR12:

- Age (< 65 years, ≥ 65 years)

- Sex (male, female)
- Race (white, black, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Baseline body mass index (BMI) (< 30 kg/m^2, ≥ 30 kg/m^2)
- Baseline HCV RNA (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- HCV genotype (genotype and subtypes)
- IL28B genotype (CC, non-CC; with non-CC further broken down to CT, TT)
- Baseline CPT class (CPT A [5-6], CPT B [7-9], 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 (< 80%, ≥ 80%)

3.5. Multiple Comparisons

No multiplicity adjustment will be made.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

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

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

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

If an HCV RNA data point is missing and is preceded and followed in time by values that are "< LLOQ target not detected (TND)," then the missing data point will be set to "< LLOQ TND." If a data point is missing and preceded and followed by values that are "< LLOQ detected," or preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected," then the missing value will be set to "< LLOQ detected." In these situations the data point will be termed a bracketed success; otherwise, the data point will be termed a bracketed failure (ie, ≥ LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (ie, ≥ LLOQ detected) 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 (ie, HCV RNA 14 IU/mL). No other imputation will be performed for continuous HCV RNA data.

Except for the imputation rules described above, values for other missing data (including all safety data and health-related quality of life 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 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 at all, the date that the informed consent was signed will be used for age calculation as appropriate. If only the birth year is collected on the CRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

Data that are continuous in nature but are < LLOQ 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 as < 1. For the values reported as < 1 or < 0.1, values of 0.9 or 0.09, respectively, will be used for calculation of summary statistics.

- A value that is one unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the limit of quantitation). Values with decimal points will follow the 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, version 2.0 will be used to determine HCV RNA results in this study. The LLOQ of the assay is 15 IU/mL.

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

When HCV RNA is not detected, the result will be reported as "No HCV RNA detected" or "target not detected." This result is referred to in this document as "< LLOQ target not detected" or "< LLOQ TND."

When the HCV RNA IU/mL is less than the LLOQ of the assay, the result will be reported as "< 15 IU/mL HCV RNA detected." This result is 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 the LLOQ will be set to LLOQ – 1 IU/mL. HCV RNA values returned as "target not detected" will also be set to LLOQ – 1 IU/mL.

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (eg, log10 scale), or nonparametric analysis methods may be used, as appropriate.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

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

Study day will be calculated from the date of the 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 study drug administration eCRF for the record where the "study drug was 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 the treatment group.

If there are subjects for whom the date of the last dose of study drug is unknown because the subject was lost to follow-up and not able to be contacted, the date of the 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 will not be included).

3.8.2. Analysis Visit Windows

Subject visits may 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 date of the first dose 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, CPT, MELD, vital signs and safety laboratory data are provided in Table 3-1.

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

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

HCV RNA, CPT, MELD, vital sign, 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 3-2.

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

Nominal FU [a] Visit	HCV RNA, CPT, and MELD			Vital Signs and Safety Laboratory Data [b]		
	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).

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, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be

considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

- For postbaseline visits:
  - The record closest to the nominal day for that visit will be selected, except for HCV RNA posttreatment FU 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 measurements 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, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings).
  - For postbaseline visits, if there are multiple records with the same time or no time recorded on the same day, the value with the worst severity within the window will be selected (eg, abnormal will be selected over normal for safety ECG findings).

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subjects enrolled and treated will be provided for each country and investigator. The summary will present the number and proportion of subjects in the Safety Analysis Set. The denominator for the percentage calculation will be the total number of subjects enrolled.

A summary of subject disposition will be provided for all screened subjects. The summary will present the number of subjects screened, the number of subjects not enrolled, the number of subjects enrolled, the number of subjects enrolled but never treated, and the number of subjects in each of the categories listed below:

- Treated (Safety Analysis Set)
- In FAS
- Completed study treatment
- Did not complete study treatment with reasons for premature discontinuation of study treatment
- Completed study
- Did not complete study with reasons for premature discontinuation of study

For the proportion of subjects who completed or did not complete study treatment or the 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 or discontinued study treatment, the number and proportion of subjects will be summarized for the following:

- 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 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 study drug (ie, lower bound of FU-4 visit for HCV RNA data), the subject will be 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 (id, lower bound of FU-12 visit for HCV RNA data), the subject will be categorized as having "With HCV FU-4 but No FU-12 and thereafter."

The total number of subjects who were enrolled 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 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

4.2. Extent of Exposure

The 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 proportion of subjects exposed through the following time periods: baseline /Day 1, Week 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56), and Week 12 (Day 84). A 3-day window was applied to the last planned on-treatment visit to match 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 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 eCRF 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 prescribed adherence will be expressed as a 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 (400/100 mg) prescribed for 12 weeks would require 84 SOF/VEL (400/100 mg) tablets.

Subjects will take a starting dose of 600 mg RBV with food in a divided daily dose. If the starting dose is well-tolerated, RBV can be titrated up to a maximum of 1000-1200 mg daily (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg) divided twice daily. If the starting dose is not well tolerated, the dose should be reduced as necessary. The amount of RBV prescribed at baseline is 600 mg (3 tablets) daily. The total amount of RBV prescribed for 12 weeks at baseline would require 252 tablets.

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 when virologic failure criteria were met. For virologic failure confirmed by 2 consecutive measurements, the date of the first measurement will be used. Study drug bottles that were dispensed on or after the subject first met virologic failure criteria will not be included in the calculation of adherence. If a bottle was dispensed and the bottle was returned empty, 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 proportion of subjects belonging to adherence categories (eg, < 80%, ≥ 80 to < 90%, ≥ 90%) will be provided for the Safety Analysis Set. No inferential statistics will be provided.

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

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 discontinued 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 from Day 1 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.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by HCV genotype (GT1a, GT1b, GT1 total, GT2, and GT3) and total. Age will be summarized by descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum). Age categories (< 65 years, ≥ 65 years), sex, race, and ethnicity will be summarized by the numbers and percentages of subjects. Age will be calculated in years at the date of the first dose of study drug. If a subject did not receive study drug after 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 for the Safety Analysis Set.

A by-subject demographic listing will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- Country (US, France)
- BMI (kg/m^2) as a continuous variable and as categories (< 30 kg/m^2, ≥ 30 kg/m^2)
- Baseline HCV RNA (log_{10} IU/mL) as a continuous variable and as categories (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- Genotype of HCV infection (genotype and subtypes)
- IL28B genotype (CC, CT, TT)
- Baseline ALT (U/L) as a continuous variable and as categories (≤ 1.5 × ULN, > 1.5 × ULN)
- Baseline Estimated Glomerular Filtration Rate Using the Cockcroft-Gault Equation (mL/min)
- Prior HCV treatment (treatment naive, treatment experienced)
- 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 encephalopathy (None, medication-controlled, medication-refractory)

Baseline BMI will be calculated using the following method:

BMI = (baseline weight in kilograms)/(baseline height in meters)^2

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

Females: If height ≤ 60 inches, IBW = 45.5 kg

If height > 60 inches, IBW = [(height in inches – 60) × 2.3kg/inch] + 45.5 kg

Males: If height ≤ 60 inches, IBW = 50 kg

If height > 60 inches, IBW = [(height in inches – 60) × 2.3kg/inch] + 50 kg

Note: if the subject's actual weight is less than the calculated IBW, the actual weight will be used.

For subjects with serum creatinine samples too icteric to report results via regular assay methods, serum creatinine results from the enzymatic serum creatinine test will be used (in place of serum creatinine), and also to calculate creatinine clearance.

These baseline characteristics will be summarized by HCV genotype (GT1a, GT1b, GT1 total, GT2, and GT3) and total. Continuous variables will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and categorical variables using the number and percentage of subjects. The summary of baseline characteristics will be provided for the Safety Analysis Set.

A by-subject listing of baseline characteristics will be provided by subject ID number in ascending order. A separate by-subject data listing for cirrhosis determination will be provided for all subjects at screening.

A separate by-subject listing for prior HCV treatment and response will be provided for treatment-experienced subjects. The listing will display the prior HCV treatment experience for all subjects as well as the prior HCV regimen and treatment, the treatment duration, and the prior HCV treatment response for treatment-experienced subjects.

5.3. Medical History

General medical history data will be collected at screening and a by-subject listing will be provided for Safety Analysis Set.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is SVR12 defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after cessation of treatment in the FAS.

6.1.2. Primary Analysis of the Primary Efficacy Endpoint

The point estimates of SVR12 and the 2-sided 95% exact CIs based on the Clopper-Pearson method {Clopper 1934} will be provided. Subjects who undergo on-study liver transplant will be included in the primary efficacy analysis.

6.1.3. Subgroup Analysis of the Primary Efficacy Endpoint

Point estimates and the 2-sided 95% exact CIs based on the Clopper-Pearson method will be provided for the SVR12 rate for each subgroup. 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 with HCV RNA < LLOQ at 4 and 24 weeks after cessation of treatment (SVR4, SVR24)
- The proportion of subjects with 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) by visit through the end of treatment (EOT)
- CPT score and MELD score changes from baseline
- The proportion of subjects with virologic failure, defined as follows:
  - 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 may be posttreatment), or last available on-treatment measurement with no subsequent follow-up values ie, breakthrough)

- > 1 log10 IU/mL increase in HCV RNA from nadir while on treatment confirmed with 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 with 2 consecutive values or last available posttreatment

- Characterization of HCV drug-resistant substitutions at baseline and after study treatment, as applicable.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

6.2.2.1. Analysis Methods for 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 2-sided 95% exact CI based on Clopper-Pearson method will be provided by HCV genotype (GT1a, GT1b, GT1 total, GT2, and GT3) and total for the percentage of subjects with HCV RNA < LLOQ at each visit. 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 (GT1a, GT1b, GT1 total, GT2, and GT3) and total.

Summary statistics will be presented for absolute values and change from baseline in HCV RNA (log_{10} IU/mL) by HCV genotype (GT1a, GT1b, GT1 total, GT2, and GT3) and 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 (GT1a, GT1b, GT1 total, GT2, and GT3) and total.

For the SVR12 endpoint analysis, a summary table of the number and percentage of subjects with SVR12, virologic failure, and Other will be created by HCV genotype (GT1a, GT1b, GT1 total, GT2, and GT3) and total. 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 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 (GT1a, GT1b, GT1 total, GT2, and GT3) 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 (GT1a, GT1b, GT1 total, GT2, and GT3) 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.

By-subject data listings will be provided for the HCV RNA change from baseline, subjects with virologic failure and subjects with relapse after Posttreatment Week 12.

Drug resistant substitutions will be presented in the CSR based on virology listings, which is not in the scope of this SAP.

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

For CPT and MELD scores, subjects with on-study liver transplants will have posttransplant CPT and MELD scores excluded from analysis for summary tables. 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 Scores

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):

MEASURE	1 point	2 points	3 points
Total Bilirubin (mg/dL)	< 2	2-3	> 3
Serum Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
INR	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Hepatic Encephalopathy	None	Medication-controlled	Medication-refractory *

* Note: If a subject is taking medications to control ascites or encephalopathy which has controlled the symptoms, the scoring should be 2 points (not 1 point).

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:

- 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 and change from baseline will be provided for all subjects in Safety Analysis Set.

6.2.2.2.2. MELD Scores

The MELD score will be calculated using the following formula:

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

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

The following analyses of MELD scores will be performed for subjects who achieve SVR12 and SVR24 respectively:

- The number and percentage of subjects with “no change”, “increase” and “decrease” between baseline and posttreatment visits Week 12 and Week 24 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 less than or equal to -2; and “Increase” will be assigned for differences that are greater than or equal to 2.

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints

PPD

PPD

6.3.2. Analysis Methods for Exploratory Efficacy Endpoints

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 AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high level group term, high level term, preferred term (PT), and lower level term will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events were graded by the investigator as Grade 1 (mild), 2 (moderate), 3 (severe), or 4 (life threatening) 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 the relationship to study drug will be considered to be related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing from that captured on the eCRF.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if 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 Pharmacovigilance and Epidemiology Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

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

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

7.1.5.2. Incomplete Dates

If the onset date of an 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 only) of the first dose date of study drug
- The AE onset date is the same as or before the month and year (or year only) 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 treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

A brief high-level summary of TEAEs will show the number and proportion of subjects who had the following: (1) any AE, (2) any AE of Grade 3 or above, (3) any AE of Grade 2 or above, (4) any treatment-related AE, (5) any treatment-related AE of Grade 3 or above, (6) any treatment-related AE of Grade 2 or above, (7) any SAE, (8) any treatment-related SAE, (9) any AE that led to premature discontinuation of any study drug, (10) any AE that led to modification or interruption of any study drug, (11) any AE that led to premature discontinuation of SOF/VEL, (12)any AE that led to interruption of SOF/VEL, (13) any AE that led to premature discontinuation of RBV, (14) any AE that led to modification or interruption of RBV, (15) any AE that led to premature discontinuation of all study drugs, (16) any AE that let to modification or interruption of all study drugs and (17) all deaths (including those that are treatment emergent and those that are not treatment emergent) observed during the study.

Summaries (number and percentage of subjects) of TEAEs (by SOC and PT) will be provided for the treatment group using 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 of the study drugs
- AEs leading to modification or interruption of any of the study drugs
- AEs leading to premature discontinuation of SOF/VEL
- AEs leading to premature discontinuation of RBV
- AEs leading to interruption of SOF/VEL
- AEs leading to modification or interruption of RBV
- AEs leading to premature discontinuation of all study drugs
- AEs leading to modification or interruption of all study drugs

Multiple events will be counted once only per subject in each summary. The SOCs will be presented alphabetically and the PTs within each SOC will be presented by descending order of the total frequencies. 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 within the treatment group 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 of the study drugs
- AEs leading to modification or interruption of any of the study drugs
- AEs leading to premature discontinuation of SOF/VEL
- AEs leading to premature discontinuation of RBV
- AEs leading to interruption of SOF/VEL
- AEs leading to modification or interruption of RBV
- AEs leading to premature discontinuation of all study drugs
- AEs leading to modification or interruption of all study drugs

Data listings, with a variable indicating whether the event is treatment emergent, will be provided for the following:

- All AEs
- AEs of Grade 3 or above
- SAEs
- Deaths
- AEs leading to premature discontinuation of any of the study drugs
- AEs leading to modification or interruption of any of the study drugs
- 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 date of the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units. When values are below the limit of quantitation, the closest imputed value will be used for the purpose of calculating summary statistics, but the original values will be presented in listings. 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.

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, based on the GSI 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 for the treatment group for ALT, aspartate aminotransferase (AST), albumin, total bilirubin, alkaline phosphatase, uric acid, white blood cell (WBC) counts, neutrophils, lymphocytes, hemoglobin, platelets, reticulocytes, international normalized ratio (INR), creatinine, 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 values will be displayed to the reported number of digits and the SD to the reported number of digits plus 1.

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

A summary and by-subject listing of subjects with any hemoglobin values < 10 g/dL and < 8.5 g/dL will be provided.

All laboratory test data will be listed. Central Laboratory (Covance) Reference Ranges will also be listed.

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 the date of the last dose of study drug plus 30 days. If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 at a postbaseline time point will be considered treatment emergent.

7.2.2.2. Summaries of Treatment-Emergent Laboratory Abnormalities

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

- Graded laboratory abnormalities
- Grade 3 or above laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after the date of the 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.

For subjects with at least one event of TE Grade 3 or above laboratory abnormality of glucose (either hypoglycemia or hypoglycemia), a listing of medical history and prior and concomitant medication will be provided.

For subjects with at least one event of TE Grade 3 or above laboratory abnormality of creatine kinase or lipase, a listing of AEs will be provided.

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 in vital signs at each visit will be summarized for the Safety Analysis Set using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum).. The baseline value will be defined as the last available value collected 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 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 or concomitant using the following definitions:

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

Concomitant medications will be summarized by preferred name using the number and percentage of subjects. A subject reporting the same medication more than once within each

preferred name 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 preferred name by descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

Concomitant medication 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 date of the first dose of study drug or with a start date that is after the date of the last dose of study drug 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 date of the first dose of study drug will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the date of the last dose of study drug will be excluded from the concomitant medication summary. Medications with completely missing dates will be included in the concomitant medication summary.

All collected 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, concomitant medication for ascites and hepatic encephalopathy will be summarized similarly. A listing of subjects with use of prior and concomitant medications for ascites and hepatic encephalopathy will be provided. Prior and Concomitant immunosuppressants will also be listed.

7.5. Investigator Electrocardiogram Assessment

A by-subject listing for electrocardiogram (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 numbers 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

No pharmacokinetic analysis is planned for this study.

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. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings
Appendix 2. Schedule of Assessments
Appendix 3. QOL Score Calculation Algorithms

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

Table Number	Title	Analysis Set
15.8.1.1	Subjects Enrolled and Treated by Country and Investigator	Safety Analysis Set
15.8.1.2	Subject Disposition	Screened Subjects
15.8.1.3	Reasons for Screen Failure	Screened Subjects
15.8.3	Demographics and Baseline Characteristics by HCV Genotype	Safety Analysis Set
15.8.4	Adherence to Study Drug	Safety Analysis Set
15.9.1	SVR12	Full Analysis Set
15.9.2.1.1	Virologic Outcomes by HCV Genotype	Full Analysis Set
15.9.2.1.2	Virologic Outcomes by HCV Genotype by Visit During Posttreatment Follow Up	Full Analysis Set
15.9.2.2	SVR by HCV Genotype by Visit During Posttreatment Follow Up	Full Analysis Set
15.9.2.3	Concordance Between SVR12 and SVR24 by HCV Genotype	Full Analysis Set
15.9.2.4	Proportion of Subjects with HCV RNA < LLOQ While on Treatment by HCV Genotype by Visit	Full Analysis Set
15.9.2.5	HCV RNA (log10 IU/mL) and Change from Baseline by HCV Genotype by Visit Through End of Treatment	Full Analysis Set
15.9.4.1	SVR12 by Subgroup	Full Analysis Set
15.9.5.1	Shift Table of CPT Class at Baseline and at Posttreatment Week 12	Full Analysis Set Subjects Who Achieved SVR12
15.9.5.2	Number (%) of Subjects with a Decrease, No Change, or Increase in MELD Score Between Baseline and Posttreatment Week 12	Full Analysis Set Subjects Who Achieved SVR12
15.11.1.1	Duration of Exposure to Study Regimen	Safety Analysis Set
15.11.1.2	Ribavirin Dosing Summary	Safety Analysis Set
15.11.2.1.1	Adverse Events: Brief Summary	Safety Analysis Set
15.11.2.1.2	All Treatment-Emergent Adverse Events	Safety Analysis Set

Table Number	Title	Analysis Set
15.11.2.1.3	Treatment-Emergent Adverse Events That Occurred in at Least 5% of Subjects by Preferred Term	Safety Analysis Set
15.11.2.2.1	Treatment-Emergent Adverse Events of Grade 3 or Above	Safety Analysis Set
15.11.2.2.2	Treatment-Emergent Adverse Events of Grade 3 or Above by Preferred Term	Safety Analysis Set
15.11.2.2.3	Treatment-Emergent Adverse Events of Grade 2 or Above	Safety Analysis Set
15.11.2.3.1	Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set
15.11.2.3.2	Treatment-Emergent Treatment-Related Adverse Events by Preferred Term	Safety Analysis Set
15.11.2.3.3	Treatment-Emergent Treatment-Related Adverse Events of Grade 3 or Above	Safety Analysis Set
15.11.2.3.4	Treatment-Emergent Treatment-Related Adverse Events of Grade 2 or Above	Safety Analysis Set
15.11.3.1.1	Adverse Events Leading to Modification or Interruption of Any Study Drug	Safety Analysis Set
15.11.3.1.2	Adverse Events Leading to Modification or Interruption of Any Study Drug by Preferred Term	Safety Analysis Set
15.11.3.2.1	Adverse Events Leading to Interruption of SOF/VEL	Safety Analysis Set
15.11.3.2.2	Adverse Events Leading to Interruption of SOF/VEL by Preferred Term	Safety Analysis Set
15.11.3.3.1	Adverse Events Leading to Modification or Interruption of RBV	Safety Analysis Set
15.11.3.3.2	Adverse Events Leading to Modification or Interruption of RBV by Preferred Term	Safety Analysis Set
15.11.3.4.1	Adverse Events Leading to Modification or Interruption of All Study Drugs	Safety Analysis Set
15.11.3.4.2	Adverse Events Leading to Modification or Interruption of All Study Drugs by Preferred Term	Safety Analysis Set
15.11.4.1	Treatment-Emergent Serious Adverse Events	Safety Analysis Set
15.11.4.2	Treatment-Emergent Serious Adverse Events by Preferred Term	Safety Analysis Set
15.11.4.3	Treatment-Emergent Treatment-Related Serious Adverse Events	Safety Analysis Set
15.11.5.1.1	Adverse Events Leading to Premature Discontinuation of Any Study Drug	Safety Analysis Set
15.11.5.1.2	Adverse Events Leading to Premature Discontinuation of Any Study Drug by Preferred Term	Safety Analysis Set
15.11.5.2.1	Adverse Events Leading to Premature Discontinuation of SOF/VEL	Safety Analysis Set

Table Number	Title	Analysis Set
15.11.5.2.2	Adverse Events Leading to Premature Discontinuation of SOF/VEL by Preferred Term	Safety Analysis Set
15.11.5.3.1	Adverse Events Leading to Premature Discontinuation of RBV	Safety Analysis Set
15.11.5.3.2	Adverse Events Leading to Premature Discontinuation of RBV by Preferred Term	Safety Analysis Set
15.11.5.4.1	Adverse Events Leading to Premature Discontinuation of All Study Drugs	Safety Analysis Set
15.11.5.4.2	Adverse Events Leading to Premature Discontinuation of All Study Drugs by Preferred Term	Safety Analysis Set
15.11.6.1.1	ALT (U/L) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.2	AST (U/L) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.3	Total Bilirubin (mg/dL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.4	Alkaline Phosphatase (U/L) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.5	Hemoglobin (g/dL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.6	Subjects with Postbaseline Hemoglobin < 10 g/dL and < 8.5 g/dL	Safety Analysis Set
15.11.6.1.7	Reticulocytes (x10^3/uL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.8	WBC (x10^3/uL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.9	Neutrophils (x10^3/uL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.10	Lymphocytes (x10^3/uL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.11	Platelets (x10^3/uL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.12	INR and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.13	Creatinine (mg/dL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.15	Albumin (g/dL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.16	Creatine Kinase (U/L) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.1.17	Uric Acid (mg/dL) and Change from Baseline by Visit	Safety Analysis Set
15.11.6.2	Treatment-Emergent Graded Laboratory Abnormalities	Safety Analysis Set

Table Number	Title	Analysis Set
15.11.6.3	Treatment-Emergent Grade 3 or Above Laboratory Abnormalities	Safety Analysis Set
15.11.7.1	Systolic Blood Pressure (mmHg) and Change from Baseline by Visit	Safety Analysis Set
15.11.7.2	Diastolic Blood Pressure (mmHg) and Change from Baseline by Visit	Safety Analysis Set
15.11.7.3	Pulse (bpm) and Change from Baseline by Visit	Safety Analysis Set
15.11.8.1	Concomitant Medications	Safety Analysis Set
15.11.8.2	Concomitant Medications for Ascites and Encephalopathy	Safety Analysis Set
15.12.1	Summary of SF-36 Quality of Life Questionnaire	Full Analysis Set
15.12.2	Summary of CLDQ-HCV Quality of Life Questionnaire	Full Analysis Set
15.12.3	Summary of FACIT-F Quality of Life Questionnaire	Full Analysis Set
15.12.4	Summary of WPAI: Hep C Quality of Life Questionnaire	Full Analysis Set

Figure Number	Title	Analysis Set
15.8.1	Subject Disposition	Screened Subjects
15.9.2.4	Proportion of Subjects with HCV RNA < LLOQ While on Treatment by HCV Genotype by Visit	Full Analysis Set
15.9.2.5.1	Mean ± SD Change from Baseline in HCV RNA (log10 IU/mL) by HCV Genotype by Visit Through End of Treatment	Full Analysis Set
15.9.2.5.2	Median (Q1, Q3) Change from Baseline in HCV RNA (log10 IU/mL) by HCV Genotype by Visit Through End of Treatment	Full Analysis Set
15.9.2.5.3	Mean +/- SD HCV RNA (log_{10} IU/mL) by HCV Genotype by Visit Through End of Treatment	Full Analysis Set
15.9.2.5.4	Median (Q1, Q3) HCV RNA (log_{10} IU/mL) by HCV Genotype by Visit Through End of Treatment	Full Analysis Set
15.11.6.1	Median (Q1, Q3) ALT (U/L) by Visit	Safety Analysis Set
15.11.6.2	Median (Q1, Q3) AST (U/L) by Visit	Safety Analysis Set
15.11.6.3	Median (Q1, Q3) Total Bilirubin (mg/dL) by Visit	Safety Analysis Set
15.11.6.4	Median (Q1, Q3) Alkaline Phosphatase (U/L) by Visit	Safety Analysis Set
15.11.6.5	Median (Q1, Q3) Hemoglobin (g/dL) by Visit	Safety Analysis Set
15.11.6.6	Median (Q1, Q3) Reticulocytes (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.7	Median (Q1, Q3) WBC (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.8	Median (Q1, Q3) RBC (x10^6/uL) by Visit	Safety Analysis Set
15.11.6.9	Median (Q1, Q3) Lymphocytes (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.10	Median (Q1, Q3) Platelets (x10^3/uL) by Visit	Safety Analysis Set
15.11.6.11	Median (Q1, Q3) Albumin (g/dL) by Visit	Safety Analysis Set
15.12.1	Mean +/- SD Change from Baseline in SF-36 by Visit	Full Analysis Set
15.12.2	Mean +/- SD Change from Baseline in CLDQ-HCV by Visit	Full Analysis Set
15.12.3	Mean +/- SD Change from Baseline in FACIT-F by Visit	Full Analysis Set
15.12.4	Mean +/- SD Change from Baseline in WPAI: Hep C by Visit	Full Analysis Set

Listing Number	Title	Analysis Set
16.1.6	Lot Number	Safety Analysis Set
16.2.1.1	Disposition for Subjects Who Completed Study Treatment and Study	Safety Analysis Set
16.2.1.2	Disposition for Subjects Who Did Not Complete Study Treatment and/or Study with Reasons for Premature Discontinuation of Study Treatment and/or Study	Safety Analysis Set
16.2.2.1	Inclusion and Exclusion Criteria	Subjects Not Treated
16.2.2.2	Subjects Enrolled and Treated Who Did Not Meet Eligibility Criteria	Safety Analysis Set
16.2.3	Subjects Who Were Excluded from Safety and Full Analysis Sets	All Enrolled Analysis Set
16.2.4.1	Demographics	Safety Analysis Set
16.2.4.2.1	Baseline Characteristics	Safety Analysis Set
16.2.4.2.2	Cirrhosis Determination	Safety Analysis Set
16.2.4.3.1	Medical History	Safety Analysis Set
16.2.4.3.2	Prior HCV Treatment and Response	Safety Analysis Set
16.2.4.4.1	Prior and Concomitant Medications	Safety Analysis Set
16.2.4.4.2	Prior and Concomitant Medications for Ascites and Encephalopathy	Safety Analysis Set
16.2.4.4.3	Prior and Concomitant Immunosuppressants	Safety Analysis Set
16.2.5.1	Study Drug Administration	Safety Analysis Set
16.2.5.2	Study Drug Accountability and Adherence	Safety Analysis Set
16.2.6.1	HCV RNA (log10 IU/mL) and Change from Baseline	Safety Analysis Set
16.2.6.2	Subjects with Virologic Failure	Safety Analysis Set
16.2.6.3	Subjects with 'Other' Virologic Outcome	Safety Analysis Set
16.2.6.4	Subjects with Relapse after Posttreatment Week 12	Safety Analysis Set
16.2.6.5	CPT Score and Change from Baseline	Safety Analysis Set
16.2.6.6	MELD Score and Change from Baseline	Safety Analysis Set

Listing Number	Title	Analysis Set
16.2.6.7	SF-36 Quality of Life Questionnaire	Safety Analysis Set
16.2.6.8	CLDQ-HCV Quality of Life Questionnaire	Safety Analysis Set
16.2.6.9	FACIT-F Quality of Life Questionnaire	Safety Analysis Set
16.2.6.10	WPAI: Hep C Quality of Life Questionnaire	Safety Analysis Set
16.2.7.1	All Adverse Events	Safety Analysis Set
16.2.7.2	Adverse Events of Grade 3 or Above	Safety Analysis Set
16.2.7.3	Deaths	Safety Analysis Set
16.2.7.4	Serious Adverse Events	Safety Analysis Set
16.2.7.5	Adverse Events Leading to Premature Discontinuation of Any Study Drug	Safety Analysis Set
16.2.7.6	Adverse Events Leading to Modification or Interruption of Any Study Drug	Safety Analysis Set
16.2.7.7	Adverse Events with Changes Other than Resolution Dates Between Posttreatment Week 12 and final Analyses	Safety Analysis Set
16.2.8.1.1	Subjects with Postbaseline Hemoglobin < 10 g/dL and < 8.5 g/dL	Safety Analysis Set
16.2.8.1.2	Central Laboratory (Covance) Reference Ranges	Safety Analysis Set
16.2.8.1.3.1	Subjects with Treatment-Emergent Grade 3 or Above Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.3.2	Medical History and Prior and Concomitant Medications for Subjects with Treatment-Emergent Grade 3 or Above Laboratory Abnormalities of Glucose	Safety Analysis Set
16.2.8.1.3.3	Adverse Events for Subjects with Treatment-Emergent Grade 3 or Above Laboratory Abnormalities of Creatine Kinase or Lipase	Safety Analysis Set
16.2.8.1.4	Screen Labs: HBsAg, HBsAb, HBcAb, Anti-HIV Ab, Anti-HCV Ab, HIV Screen, and Serum Beta hCG	Safety Analysis Set
16.2.8.1.5.1	Hematology: Hematocrit, Hemoglobin, Reticulocytes, MCV, RBC, WBC, and Platelets	Safety Analysis Set
16.2.8.1.5.2	Hematology: WBC, Neutrophils, and Lymphocytes	Safety Analysis Set
16.2.8.1.5.3	Hematology: Eosinophils, Basophils, and Monocytes	Safety Analysis Set
16.2.8.1.6	Coagulation: INR and APTT	Safety Analysis Set

Listing Number	Title	Analysis Set
16.2.8.1.7.1	Serum Chemistry: Sodium, Potassium, Creatine Kinase, Creatinine, Estimated GFR (Cockcroft-Gault), Glucose and Uric Acid	Safety Analysis Set
16.2.8.1.7.2	Serum Chemistry: AST, ALT, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, GGT, Albumin, Lipase and Phosphate	Safety Analysis Set
16.2.8.1.8	Urinalysis: Urine Blood, Glucose, pH, Protein, Urobilinogen, and Leukocyte Esterase	Safety Analysis Set
16.2.8.1.9	Microscopic Urinalysis for Subjects with Abnormal Leukocyte Esterase	Safety Analysis Set
16.2.8.2.1	Vital Signs	Safety Analysis Set
16.2.8.2.2	Height, Weight, and BMI	Safety Analysis Set
16.2.8.2.3.1	12-Lead Electrocardiogram Results	Safety Analysis Set
16.2.8.2.3.2	12-Lead Electrocardiogram Results for Subjects with Clinically Significant Abnormalities	Safety Analysis Set
16.2.8.3	Pregnancy	Safety Analysis Set
16.2.8.4	Pre and On-study Liver Transplants	Safety Analysis Set

Appendix 2. Schedule of Assessments

			On-treatment Study Week (± 3 days)				Posttreatment Study Week (± 5 days)		
	Screen	Day 1a	2	4	8	12/ET	4	12	24
Informed Consent	X								
Determine Eligibility	X	X							
Medical History	X								
Physical Examination	X	X				X		X	X
Assess ascites and hepatic encephalopathy	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X							
AEs	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling	X	X		X	X	X	X	X	X
Health Related Quality of Life[c]		X				X		X	
Study Drug Dispensing[d]		X		X	X				
Review of Study Drug Compliance[e]			X	X	X	X			
Hematology, Chemistry	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X	X	X	X	X	X	X	X
Urinalysis	X	X				X			

	Screen	Day 1a	On-treatment Study Week (± 3 days)				Posttreatment Study Week (± 5 days)		
			2	4	8	12/ET	4	12	24
HCV RNA	X	X	X	X	X	X	X	X	X
HBV DNA[f]		X		X	X	X	X	X	X
Viral Sequencing		X	X	X	X	X	X	X	X
Single PK			X	X	X	X			
Serum β-hCG or Urine Pregnancy Test[g]	X	X		X	X	X	X	X	X
Urine Drug Screen	X								
HbA1c	X								
HCV & IL28B Genotyping	X								
HCV, HIV, HBV Serology	X								
Fibrotest®	X								
PPD									
PPD									

a Day 1 assessments must be performed prior to dosing.
b Vital signs include resting blood pressure, pulse, respiratory rate and temperature.
c There are four Health Related Quality of Life surveys to provide to subjects: SF-36, CLDQ-HCV, FACIT-F, and WPAI.
d The IWRS will provide direction on the specifics of each subject's study drug dispensing.
e Instruct the subject to bring back all study drugs and study drug containers (used/unused).
f Only for subjects who are HBcAb+ at Screening
PPD
PPD

Appendix 3. 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 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 {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 40 questions 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 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.

GS-US-342-4022 SAP v1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	31-Oct-2018 17:42:28
PPD	Clinical Research eSigned	01-Nov-2018 21:49:04