STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination (FDC) and Sofosbuvir/Velpatasvir FDC and Ribavirin in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis
Name of Test Drug:	Sofosbuvir/Velpatasvir Fixed-Dose Combination
Study Number:	GS-US-342-2097
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Analysis Plan Version:	Version 1.0
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Analysis Plan Author:	PPD

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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
CSR	clinical study report
DAA	direct-acting antiviral
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FAS	full analysis set
FDC	fixed dose combination
FU	follow-up
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ID	identification
INR	international normalized ratio
IWRS	interactive web response system
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
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
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings

TND	target not detected
ULN	upper limit of the normal range
VEL	velpatasvir (previously GS-5816)
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-342-2097. This SAP is based on the study protocol Amendment 1 dated 04 April 2016 and the electronic case report form (eCRF). The SAP will be finalized before data finalization. Any changes 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 study treatment with sofosbuvir (SOF)/velpatasvir (VEL) fixed-dose combination (FDC) and SOF/VEL FDC+ ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after cessation of treatment regimen (SVR12)

- To evaluate the safety and tolerability of each treatment regimen

The secondary objectives of this study are as follows:

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

- 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 each treatment regimen

The exploratory objective of this study is as follows:

- PPD [redacted]

1.2. Study Design

This is a multicenter, randomized, open-label study that will evaluate the safety, tolerability, and antiviral efficacy of SOF/VEL FDC±RBV for 12 weeks in subjects with chronic genotype 3 HCV infection and compensated cirrhosis with or without human immunodeficiency virus (HIV) coinfection.

Approximately 200 subjects with chronic genotype 3 HCV infection and compensated cirrhosis will be randomized (1:1) to either:

- Group 1 (n = 100): SOF/VEL (400/100 mg) once daily for 12 weeks

OR

- Group 2 (n = 100): SOF/VEL (400/100 mg) once daily + RBV (1000 or 1200 mg divided into 2 daily doses) for 12 weeks

Randomization will be stratified by prior treatment experience (treatment naive or treatment experienced); treatment naive is defined as never having been exposed to an approved or experimental HCV-specific direct-acting antiviral (DAA) or having had prior treatment of HCV with interferon or RBV. All other subjects will be considered treatment experienced.

1.3. Sample Size and Power

Approximately 200 subjects with chronic genotype 3 HCV infection and compensated cirrhosis will be enrolled in this study. This sample size is based on the number of subjects who meet the eligibility criteria and could practically be enrolled. With a sample size of 100 for each treatment, a 2-sided 95% exact confidence interval (CI) will extend 21% in length, at most, for each treatment group.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

No formal interim analysis is planned.

2.2. Final Analysis

The final analysis will be performed after all subjects have completed the posttreatment Week 12 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 each analysis set will be included in a by-subject listing with reasons for exclusion.

3.1.1. All Randomized/Enrolled Analysis Set

The All Randomized Analysis Set includes all subjects who were randomized in the study. Subjects will be grouped within the All Randomized Analysis Set by the treatment group to which they were randomized.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who took at least 1 dose of any study drug. The study drugs in this study are SOF/VEL and RBV. Subjects will be 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 took at least 1 dose of any study drug. Subjects will be grouped within the Safety Analysis Set according to the treatment they 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 took at least 1 dose of study drug and have at least 1 nonmissing postdose plasma concentration value for the corresponding analyte. The analytes of interest may include SOF (and its metabolites GS-566500 and GS-331007), VEL, and RBV if applicable. The PK Analysis Set will be used for the listing of concentration data.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set or FAS, subjects will be grouped according to the treatment group to which they were randomized. For analyses based on the Safety Analysis Set or the PK 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 such cases, the actual treatment received will be defined as the treatment received for the entire treatment duration.

3.3. Strata and Covariates

Approximately 200 subjects with chronic genotype 3 HCV infection and compensated cirrhosis will be randomized in a 1:1 ratio to treatment Group 1 or Group 2 using an interactive web response system (IWRS). Randomization will be stratified by prior HCV treatment experience (treatment naive or treatment experienced).

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.

3.4. Examination of Subject Subsets

The following subject subsets will be explored for the primary efficacy endpoint:

- Age (< 65 years, ≥ 65 years)
- Sex (male, female)
- Race (White, Asian)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline body mass index (BMI) (< 30 kg/m^2, ≥ 30 kg/m^2)
- 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)
- Baseline alanine aminotransferase (ALT; ≤ 1.5 × upper limit of normal [ULN], > 1.5 × ULN)
- Prior HCV treatment experience (treatment naive, treatment experienced)
- HIV coinfection (yes, no, missing)
- Prior HCV treatment response (nonresponder, relapse/breakthrough, other) for treatment-experienced subjects

- Completed study treatment, discontinued study treatment
- Adherence to study regimen (< 80%, ≥ 80%)
- Adherence to SOF/VEL (< 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 7.5.

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).

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.

For the analyses of continuous HIV RNA data, for subjects with a missing HIV RNA value in a visit window that is bracketed by prior and subsequent values, the numerical value of HIV RNA will be imputed using the larger value. No other imputation will be performed for HIV RNA data.

Except for the imputation rules described above, values for other missing data (including all safety 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. For some countries, only birth year is collected on the eCRF. 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 eCRF.

Non-PK 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.

HIV RNA in this study will be measured using the AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0. The LLOQ of the assay is 20 copies/mL.

For the analyses of continuous HIV RNA data, for missing HIV RNA values in a visit window that are bracketed by prior and subsequent values, the numerical value of HIV RNA will be imputed using the larger value. Values returned as "< 20 copies/mL HIV-1 RNA detected" or "No HIV-1 RNA detected" will be set to the LLOQ minus 1 (ie, HIV RNA 19 copies/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

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, vital signs, safety laboratory data, HIV-1 RNA and CD4 counts (HIV-1 RNA and CD4 counts will be assessed for subjects with HIV coinfection only) collected up to the date of the last dose of study drug plus 3 days will be considered to be on-treatment data; HCV RNA, vital signs, safety laboratory data, and HIV-1 RNA and CD4 counts collected after the date of the last dose of study drug plus 3 days will be considered posttreatment data. The analysis windows for on-treatment HCV RNA, vital signs, safety laboratory data, and HIV-1 RNA and CD4 counts are provided in Table 3-1.

Table 3-1. Analysis Windows for On-treatment HCV RNA, Vital Signs, Safety Laboratory Data, HIV-1 RNA and CD4 Counts

	HCV RNA, Vital Signs, Safety Laboratory Data, HIV-1 RNA and CD4 Counts			Urinalysis, Coagulation Tests, CPT Score and Body Weight		
Nominal Visit	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, vital signs, safety laboratory data, and HIV-1 RNA and CD4 counts collected after the date of the last dose of study drug plus 3 days will be assigned to the posttreatment follow-up (FU) visit. Visit windows will be calculated from the date of the last dose (ie, FU Day = collection date − 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, HIV-1 RNA and CD4 Counts

	HCV RNA			Vital Signs, HIV-1 RNA, CD4 Counts and Other 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

a FU-x visit = posttreatment Week-x follow-up visit.
b Posttreatment vital signs, safety labs, HIV-1 RNA, and CD4 counts will be summarized only for the FU-4 visit (ie, 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, a single value 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 for each analysis window.

If there are multiple valid nonmissing numeric observations 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 arithmetic mean will be used for 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 arithmetic mean will be used, unless otherwise specified.

- If there are multiple valid nonmissing categorical observations in an analysis 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).

  — For postbaseline visits, the same rules described above for postbaseline numeric observations will be followed, except if there are multiple records on the same day, in which case 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 all enrolled subjects will be provided for each investigator by treatment group and overall. The summary will present the number and proportion of subjects in all enrolled subjects. For each column, the denominator for the percentage calculation will be the total number of subjects for that column.

A similar enrollment table will be provided by treatment group and overall by prior HCV treatment (treatment naive or treatment experienced). The denominator for the proportion of subjects in the stratum will be the total number of subjects in the Safety Analysis Set within that stratum. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database, 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 for each treatment group and overall for all screened subjects. The 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, and the number of subjects in each of the categories listed below:

- Treated (Safety Analysis Set)
- In the FAS
- In the PK Analysis Set
- 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 of subjects will be summarized for the following:

- No HCV posttreatment Week 4 assessment and thereafter (No HCV FU-4 and thereafter)
- With 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 (ie, 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 randomized and the number of subjects in each of the disposition categories listed above will be depicted by a flowchart.

A summary of reasons for screen failure will also be provided.

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 and kit ID (if applicable)

4.2. Extent of Exposure and Adherence

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 regimen/drug specified in the protocol for subjects in Safety Analysis Set.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to the study regimen is defined as the date of the last dose of study regimen – the date of the first dose of study regimen + 1, regardless of any temporary interruptions in study drug dosing, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). The date of first/last dose of study regimen is defined as the date of first/last dosing of SOV/VEL for subjects who were assigned to SOF/VEL treatment group, and the date of the earliest/latest dosing of SOF/VEL or RBV for subjects who were assigned to SOF/VEL+RBV treatment group.

The total duration of exposure to individual study drug is defined as the date of the last dose of study drug (either SOF/VEL or RBV) – the date of the first dose of study drug (either SOF/VEL or RBV) + 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place.

The total duration of exposure to the study regimen and to each individual study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and the number (ie, cumulative counts). The proportion of subjects exposed to the

study regimen 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) will also be presented. A 3-day window was applied to the last planned on-treatment visit to match the protocol-specified visit window. Summaries will be provided by treatment group and overall 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 adherence to study drug 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 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. For Group 2 subjects, the prescribed weight-based RBV (200 mg tablet) would require 420 tablets (5 tablets/day × 84 days for subjects with baseline weight < 75 kg) or 504 tablets (6 tablets/day × 84 days for subjects with baseline weight ≥ 75 kg) for the 12 week treatment period.

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 (e.g., < 80%, ≥ 80 to < 90%, ≥ 90%) will be provided by treatment group 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).

4.3. Protocol Deviations

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

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

A by-subject listing will be provided for those subjects who violate at least 1 inclusion or exclusion criterion. The listing will present the entry criterion (or criteria if more than 1 violation) that subjects did not meet and related comments, if collected.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables ie, age, sex, race, and ethnicity) will be summarized for each treatment group and overall. 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 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:

- BMI (kg/m^2) as a continuous variable and as categories (< 30 kg/m^2, ≥ 30 kg/m^2)
- HCV genotype/subtype
- IL28B genotype (CC, non-CC; further broken down to CT, TT)
- Baseline HCV RNA (log_{10} IU/mL) as a continuous variable and as categories (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- Baseline ALT (U/L) as a continuous variable and as categories (≤ 1.5 × ULN, > 1.5 × ULN)
- Prior HCV treatment (treatment naive, treatment experienced)
- Prior HCV treatment (DAA±Peg-IFN±RBV, Peg-IFN+RBV, Other) and treatment response to the last prior HCV treatment (non responder, relapse/breakthrough, other) for treatment-experienced subjects
- HIV coinfection (yes, no, missing)
- Baseline HIV RNA (subjects with HIV coinfection) as a continuous variable and as categories (<50 copies/mL, >=50 copies/mL)
- Baseline CD4 T-cell counts (subjects with HIV coinfection)

- Baseline CD4 T-cell counts by category for subjects with HIV coinfection (100−200 cells/uL, 201−350 cells/uL, 351−500 cells/uL, > 500 cells/uL)
- Estimated glomerular filtration rate (eGFR)
- Baseline Cirrhosis status (yes, no, not determined)
- Cirrhosis determination method (FibroTest and APRI, Liver Biopsy, and Transient Elastography)

Estimated glomerular filtration rate 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.

Baseline BMI will be calculated using the following method:

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

These baseline characteristics will be summarized for each treatment group and overall. 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 discontinuation of the study drug for 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 for each treatment group.

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 by treatment group. Subsets are outlined in Section 3.4.

SVR12 rates will be summarized by categories of early viral response to explore possible early on-treatment predictors of SVR12. The relationship between SVR12 and study drug modification may also be explored.

A Forest plot will graphically present the point estimates and the 2-sided 95% exact CIs of SVR12 rates for each subgroup by treatment group.

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 weeks after discontinuation of treatment (SVR4)
- The proportion 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 the end of treatment (EOT)
- 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)

- $> 1 \log_{10}$ 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 measurement

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

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 2-sided 95% exact CI based on the Clopper-Pearson method will be provided for the proportion of subjects with HCV RNA < LLOQ at each visit for each treatment group. 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 HCV RNA detected in tabular displays.

A plot of the proportion of subjects with HCV RNA < LLOQ over time during treatment will be provided.

Summary statistics will be presented for absolute values and change from baseline in HCV RNA ($\log_{10}$ IU/mL) by visit through the 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) absolute values and changes from baseline in HCV RNA through EOT will be provided.

For the virologic outcome analysis, a summary table of the number and proportion of subjects with SVR12, virologic failure, and other ie, subjects who did not achieve SVR12 and did not meet criteria for virologic failure) will be created. 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). 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. Virologic outcomes will also be provided by randomization stratum by treatment group and overall for the FAS.

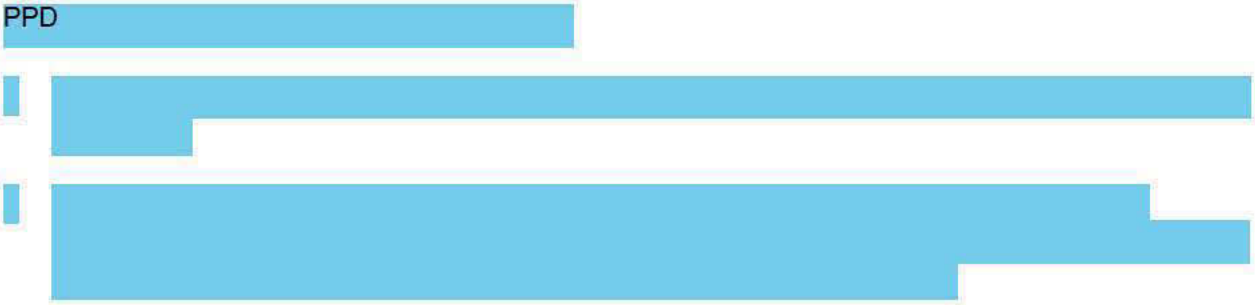
In addition, a summary table of the number and proportion of subjects with HCV RNA < LLOQ and ≥ LLOQ at each posttreatment follow-up visit (observed and imputed, with reasons for imputed) will be provided. Two-sided 95% exact CIs based on the Clopper-Pearson method will be presented for the proportion of subjects with HCV RNA < LLOQ by treatment group.

By-subject data listings will be provided for the HCV RNA change from baseline for subjects with virologic failure and subjects with other virologic outcomes.

Drug-resistant substitutions will be summarized and listed as applicable.

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints



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 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 GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (01 April 2015). 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 will be considered the least severe for the purposes of sorting for 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 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 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, by treatment group, 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 discontinuation of RBV, (14) any AE that led to modification or interruption of RBV, and (15) all deaths.

Summaries (number and percentage of subjects) of TEAEs (by SOC and PT) will be provided by 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 study drug
- AEs leading to modification or interruption of any study drug

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 overall treatment group for:

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

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 study drug

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 by treatment group for ALT, aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, white blood cells (WBC) counts, neutrophils, lymphocytes, hemoglobin, platelets, CD4 T-cell counts (absolute and percentage for HIV coinfected subjects only), reticulocytes, 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 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, total bilirubin, alkaline phosphatase, WBC, neutrophils, lymphocytes, hemoglobin, platelets, CD4 T-cell counts (absolute and percentage for HIV coinfected subjects only), and reticulocytes will be plotted using a line plot by treatment group and visit. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

A 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 GSI Scale for Severity of Adverse Events and Laboratory Abnormalities (01 April 2015) will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; 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 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 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.

7.3. HIV RNA for HIV Coinfected Subjects

The analysis of HIV RNA will be performed for HIV coinfected subjects in Safety Analysis Set using data collected up to the date of the last dose of any study drug plus 30 days.

The proportion of subjects with HIV virologic rebound during the study will be summarized. Subjects with HIV virologic rebound are defined as those with HIV RNA ≥ 400 copies/mL at at least 2 consecutive postbaseline on-treatment visits which are at least 2 weeks apart based on actual dates.

By-subject listings of HIV virologic rebound will be provided and include HIV RNA, CD4 counts (absolute and percentage), HCV RNA, HIV current antiretroviral medication, and HCV treatment during the study.

A contingency table of the number of subjects with HIV RNA < 400 or ≥ 400 copies/mL at baseline and postbaseline visits by CD4 count < 200 cells/μL or ≥ 200 cells/μL at baseline will be generated. The number and proportion of subjects with HIV RNA < 50 or ≥ 50 copies/mL will be summarized by visit. Median (Q1, Q3) and mean (± SD) change from baseline in HIV RNA (copies/mL) will be summarized and plotted by visit for subjects with detectable HIV RNA at baseline. A listing of subjects with HIV RNA ≥ 50 copies/mL will be provided.

The denominator for proportion of subjects with HIV rebound, the contingency table of HIV RNA by CD4 counts, and the proportion of subjects with HIV RNA < 50 or ≥ 50 copies/mL will be the number of subjects in the Safety Analysis Set with HIV coinfection.

7.4. 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) by treatment group. 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.

7.5. 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 Anatomical Therapeutic Chemical (ATC) drug class Level 2, and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be

counted only once when calculating the number and percentage of subjects who received that medication. The summary of concomitant medications will be ordered by descending frequency of ATC drug classes for overall, and then preferred names within an ATC medical class. 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.

For HIV coinfected subjects, the proportion of subjects who were treated with HIV antiretroviral therapy at baseline will be summarized. The prior and current HIV antiretroviral therapy will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.6. Investigator Electrocardiogram Assessment

A by-subject listing for electrocardiogram (ECG) assessment results will be provided by subject ID number and visit in chronological order.

7.7. Other Safety Measures

A data listing will be provided for subjects who become pregnant during the study. A data listing of Child-Pugh-Turcotte (CPT) scores will be provided.

7.8. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

Plasma concentrations of SOF (and its metabolites GS-566500 and GS-331007), and VEL will be determined using validated bioanalytical assays. All plasma concentrations will be provided in a by-subject listing sorted by subject ID number and study drug administration date in chronological order.

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

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15.8.4	Adherence to Study Drug	Safety Analysis Set
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Figure Number	Title	Analysis Set
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Listing Number	Title	Analysis Set
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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 Current HIV Medications	Safety Analysis Set with HIV Coinfection
16.2.5.1	Study Drug Administration	Safety Analysis Set
16.2.5.2	Study Drug Accountability and Adherence	Safety Analysis Set
16.2.5.3	Plasma PK Sampling Details and PK Concentrations	PK Analysis Set
16.2.6.1	HCV RNA ($\log_{10}$ 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
16.2.7.1	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

Listing Number	Title	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
16.2.8.1.1	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	Subjects with Treatment-Emergent Grade 3 or Above Laboratory Abnormalities	Safety Analysis Set
16.2.8.1.4	Screen Labs: HBsAg, Anti-HIV Ab, Anti-HCV Ab, HbA1c, 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, Prothrombin Time, and APTT	Safety Analysis Set
16.2.8.1.7.1	Serum Chemistry: Sodium, Potassium, Uric Acid, Creatine Kinase, Serum Creatinine, Estimated GFR (Cockcroft-Gault), and Glucose	Safety Analysis Set
16.2.8.1.7.2	Serum Chemistry: AST, ALT, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, GGT, Albumin, and Lipase	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
16.2.8.1.10	Subjects with HIV Virologic Rebound During Study	Safety Analysis Set with HIV Coinfection
16.2.8.1.11	HIV RNA by Visit for Subjects with HIV RNA ≥ 50 copies/mL	Safety Analysis Set with HIV Coinfection
16.2.8.1.12	CD4 T-Lymphocyte Absolute Count (cells/μL and %) and HIV RNA (copies/mL)	Safety Analysis Set with HIV Coinfection
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
16.2.8.3	Pregnancy	Safety Analysis Set
16.2.8.4	Child-Pugh-Turcotte (CPT) scores by Visit	Safety Analysis Set

Appendix 2. Schedule of Assessments

	Screen	Baseline/Day 1[b]	On-treatment Week				Post-treatment Week	
			2	4	8	12/ET	4	12
Clinical Assessments								
Informed Consent	X							
Determine Eligibility	X	X						
Medical History	X							
Physical Examination	X	X				X	X	X
Height	X							
Weight	X	X				X		
Vital Signs	X	X	X	X	X	X	X	X
12-Lead ECG	X							
CPT score	X					X		
Adverse Events and Concomitant Medications	X	X	X	X	X	X	X	
Pregnancy Prevention Counseling		X		X	X	X	X	X
Review of Study Medication Compliance			X	X	X	X		
Study Drug Dispensing[a]		X		X	X			
Laboratory Assessments								
Hematology, Chemistry[g]	X	X	X	X	X	X	X	X
Coagulation Tests	X	X				X		
Urinalysis	X	X				X		
HCV RNA[c]	X	X	X	X	X	X	X	X[f]

	Screen	Baseline/Day 1[b]	On-treatment Week				Post-treatment Week	
			2	4	8	12/ET	4	12
HIV-1 RNA[h]	X	X	X	X	X	X	X	X
Viral Sequencing[c]		X	X	X	X	X	X	X[f]
Single PK			X	X	X	X		
Serum β-hCG or Urine Pregnancy Test[d]	X	X		X	X	X	X	X
Urine Drug Screen	X							
HCV Genotyping, IL28B	X							
HCV, HIV, HBV Serology	X							
HbA1c, Fibrotest®	X							
Archive Sample[e]		X				X		
Pharmacogenomic Sample[e]		X						

a The IWRS will provide direction on the specifics of each subject's study drug dispensing
b Baseline/Day 1 assessments must be performed prior to dosing
c Viral sequencing samples for virologic sequencing required at baseline and after any visit where a previously undetectable HCV RNA becomes detectable
d Serum β-hCG pregnancy test performed at screening and for confirmation of positive urine pregnancy test.
e Only for subjects who have provided consent for this sample and testing. The Week 12 / Early Termination visit will be the last opportunity for this to be collected.
f Only for subjects with HCV RNA ≥LLOQ at post-treatment week 12 visit will be asked to return after for a confirmatory visit where additional samples are collected.
g CrCl will be calculated at all visits where a blood sample is drawn
h HIV-1 RNA will only be collected and analyzed for coinfected subjects

Appendix 3. Child-Pugh-Turcotte[a] Classification of the Severity of Cirrhosis

	POINTS*		
	1	**2**	**3**
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)**
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
PT (sec prolonged) or INR***	< 4 < 1.7	4-6 1.7-2.3	> 6 > 2.3

* CPT score is obtained by adding the score for each parameter

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

** 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).

*** Either PT or INR can be used to determine the CPT Score; however, if both tests have been performed, INR will be chosen as the primary test for the calculation.

a U.S. Department of Veterans Affairs. Child -Pugh-Turcotte Classification of the severity of cirrhosis. Available at http://www hepatitis.va.gov/provider/tools/child-pugh-calculator.asp, Accessed May 29, 2012.