STATISTICAL ANALYSIS PLAN

Study Title:	An Open-Label Study to Evaluate the Safety And Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination for 12 Weeks in Subjects who Participated in a Prior Gilead-Sponsored HCV Treatment Study
Name of Test Drug:	Sofosbuvir/Velpatasvir/Voxilaprevir
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Analysis Plan Author:	PPD

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DAA	direct-acting antiviral
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FAS	full analysis set
FDC	fixed-dose combination
FU	follow-up
FU-x	posttreatment follow-up Week x
Gilead	Gilead Sciences, Inc.
Hb	hemoglobin
HCV	hepatitis C virus
HLGT	high-level group term
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification
INR	international normalization ratio
IWRS	Interactive Web Response System
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PP	per protocol
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization

QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SF-36	short form health survey
SOC	system organ class
SOF	sofosbuvir (Sovaldi®)
SVR	sustained virologic response
SVRx	sustained virologic response x weeks after cessation of treatment
TEAE	treatment-emergent adverse events
TFLs	tables, figures, and listings
ULN	upper limit of normal
VEL	velpatasvir (GS-5816)
VOX	voxilaprevir (GS-9857)
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-367-4181. This SAP is based on the study protocol dated 19JAN2017 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To determine the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL)/voxilaprevir (VOX) fixed dose combination (FDC) for 12 weeks 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 treatment with SOF/VEL/VOX FDC

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 weeks after cessation of treatment (SVR4)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF, VEL, and VOX during treatment and after cessation of treatment

1.2. Study Design

This is a multicenter, open-label Phase 3 study that will evaluate the safety and efficacy of SOF/VEL/VOX FDC for 12 weeks in subjects with chronic HCV infection with or without cirrhosis, who have received prior treatment in a Gilead sponsored HCV treatment study of DAA containing regimens. There will be one treatment group of approximately 50 subjects:

- SOF/VEL/VOX FDC (400/100/100 mg) once daily with food for 12 weeks

The schedules of assessments for the study are provided as appendixes to the SAP (see Study Procedures Table, Appendix 1).

The total time to complete all study visits is up to approximately 30 weeks including the following periods:

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

1.3. Sample Size and Power

Approximately 50 subjects will be enrolled in this study. The sample size is based on the number of subjects who failed to achieve SVR12 in prior Gilead-sponsored HCV treatment studies and are eligible to be enrolled into this study.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee

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

2.2. Interim Analysis

No formal interim analysis is planned.

2.3. Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved, and the database has been cleaned and finalized, the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

3.1. Analysis Sets

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

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all subjects enrolled in the study after screening.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled subjects who took at least 1 dose of study drug. This is a single arm study. The study drug received in this study is SOF/VEL/VOX FDC.

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

There will be single treatment group for efficacy and safety analyses:

- SOF/VEL/VOX FDC (400/100/100 mg) once daily with food 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 Subsets

The primary efficacy endpoint SVR12 will be analyzed for the following subsets:

- age (< 65 years, ≥ 65 years)
- sex (male, female)
- race (black, non-black)
- ethnicity (Hispanic or Latino, non-Hispanic or Latino)
- region (US, non-US)
- baseline body mass index (BMI) (< 30 kg/m2 , ≥ 30 kg/m2)
- cirrhosis (presence, absence, missing)
- baseline HCV RNA (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- HCV genotype (1 further broken down to 1a and 1b, 2, 3, 4, 5, 6, or other, as appropriate)
- baseline ALT (≤ 1.5 × upper limit of normal [ULN], > 1.5 × ULN)
- IL28B (CC, non-CC; with non-CC further broken down to CT, TT)
- prior Gilead study assigned HCV treatment (SOF/VEL/VOX 8 weeks, SOF/VEL 12 weeks and other)
- adherence to study regimen (<80%, ≥80%)
- study treatment status (completed study treatment, discontinued study treatment)

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made because no statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

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

For analyses of categorical HCV RNA data, missing posttreatment HCV RNA data will have the missing data imputed. Missing on-treatment HCV RNA will have the missing data imputed up to the time of the last dose (for on-treatment displays). If the study day associated with the last dosing date is greater than or equal to the lower bound of a visit window, and the value at the visit is missing, the value will be imputed. If the study day associated with the last dosing date is less than the lower bound of a visit window then the on-treatment value at that visit will remain missing.

If a 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. No other imputation will be performed for continuous HCV RNA data.

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 will be used for analyses and presentation in listings.

If a subject was not dosed with study drug at all, then the date the informed consent was signed will be used instead of the first dose date of study drug. For some countries, only birth year or birth year and month are collected on the eCRF. In those cases, "01 January" will be used for the unknown birth day and month, and "15" will be used for the unknown birth day for the purpose of age calculation, unless age is captured on the CRF.

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

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

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

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

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

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

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

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

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

For numerical HCV RNA data, values below LLOQ will be set to the LLOQ – 1 IU/mL. HCV RNA values returned as "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. Visit Windows

3.8.1. Definition of Study Day

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

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

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

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

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

3.8.2. Analysis Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

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

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

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

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

HCV RNA, vital sign, and safety laboratory data collected after the last dose date + 3 days will be assigned to the posttreatment follow-up (FU) 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, Vital Sign and Safety Laboratory Data

Nominal FU [a] Visit	HCV RNA			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

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

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, average (arithmetic mean) will be used for the baseline value. If multiple ECG measurements occur on the same day prior to first dose of any study drug, the average will be used as baseline for continuous data, regardless of the timing of these multiple ECG measurements.

- For postbaseline visits:

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

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

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

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

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided for each country, investigator within a country. The summary will present the number and percentage of subjects in the Safety Analysis Set. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set.

A summary of subject disposition will be provided for the study overall. This summary will present the number of subjects screened, the number of subjects enrolled, the number of subjects enrolled but never treated, and the number and percentage of subjects in each of the categories listed below. For the "Treated" category, the denominator for the percentage calculation will be the total number of subjects enrolled. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set.

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

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

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

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

In addition, the total number of subjects who were enrolled, and the number of subjects in each of the disposition categories listed above will be displayed in 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 drug and/or study
- Lot number and kit ID (if applicable)

4.2. Extent of Exposure

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

4.2.1. Duration of Exposure to Study Drug

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

The total duration of exposure to study drug will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum) and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: Baseline (Day 1), Week 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56), Week 12 (Day 84). A 3-day window is applied to the last planned on-treatment visit to match with the protocol-specified visit window. Summaries will be provided for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

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

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

$$\text{Total Number of Doses Administered} = \left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets not administered}\right)$$

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

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

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

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

In this study, the total amount of SOF/VEL/VOX (400/100/100 mg) prescribed for 12 weeks of treatment would require 84 tablets.

Subjects who prematurely discontinue study drug for lack of efficacy (ie, virologic failure) will have the total amount of study drug prescribed calculated up to the first date when virologic failure criteria were met. For virologic failure confirmed by 2 consecutive measurements the date of the first measurement will be used. If there are study drug bottles dispensed on or after the subject first met virologic failure criteria, these bottles will not be included in the calculation of adherence. If a bottle is dispensed and the bottle is returned empty, then the number of tablets returned will be entered as zero. If a bottle is dispensed but not returned (missing), the number of tablets taken from that bottle will be counted as zero.

Descriptive statistics for the level of adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) with the number and percentage of subjects belonging to adherence categories (eg, {< 80%, ≥ 80 to < 90%, ≥ 90%}) will be provided 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 enrollment will be listed with the start and stop dates that they received incorrect study treatment.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized for study overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for age, and using the numbers and percentages of subjects for age categories (< 65 years, ≥ 65 years), sex, race, and ethnicity. Age is calculated in years at the date of initial study drug administration. If a subject did not receive study drug after enrollment, the subject's age will be calculated from the date that the subject signed the informed consent form. The summary of demographic data will be provided for the Safety Analysis Set.

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- region (US, non-US)
- body mass index (BMI; in kg/m^2) as a continuous variable and as categories (< 30 kg/m^2, ≥ 30 kg/m^2)
- HCV genotype (1 [further broken down to 1a and 1b], 2, 3, 4, 5, 6, or other)
- cirrhosis (presence, absence, missing)
- cirrhosis determination method (FibroTest and APRI, liver biopsy, transient elastography)
- IL28B (CC, non-CC; with non-CC further broken down to CT, TT)
- baseline HCV RNA (log10 IU/mL) as a continuous variable and as categories (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- baseline ALT (U/L) as a continuous variable and as categories (≤1.5 x ULN, > 1.5 x ULN)
- prior Gilead study assigned HCV treatment (SOF/VEL/VOX 8 weeks, SOF/VEL 12 weeks and other)
- estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation

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

These baseline characteristics will be summarized for study overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using the numbers and percentages of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set.

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

5.3. Medical History

General medical history (ie, conditions not specific to the disease being studied) data will be collected at screening and listed only. General medical history data will not be coded. A by-subject listing of disease-specific medical history will be provided by subject ID number (in ascending order) and medical history of abnormalities (in chronological order).

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is SVR12 defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after cessation of treatment in the FAS. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test v2.0 will be used to measure HCV RNA.

6.1.2. Primary Analysis of the Primary Efficacy Endpoint

No inferential statistics will be provided for efficacy endpoints. No statistical comparison will be conducted.

The point estimate of SVR12 rate and 2-sided 95% exact confidence interval (CI) based on Clopper-Pearson method will be provided {Clopper 1934} for the FAS.

6.1.3. Subgroup Analysis of the Primary Efficacy Endpoint

The point estimate of SVR12 rate and 2-sided 95% exact confidence interval (CI) based on Clopper-Pearson method will be provided {Clopper 1934} for the FAS, and also for each subgroup specified in Section 3.4.

A Forest plot will graphically present estimates and 95% confidence intervals of SVR12 rates for each subgroup.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- The percentage of subjects who attain SVR at 4 weeks after stopping therapy, defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 4 weeks after stopping treatment (SVR 4)
- The percentage of subjects with HCV RNA below LLOQ on treatment
- HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through end of treatment (EOT)

- The percentage of subjects with virologic failure as the following:

  On-treatment virologic failure

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

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

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

  Relapse

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

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

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 confidence interval based on Clopper-Pearson method will be provided for the percentage of subjects with HCV RNA < LLOQ at each visit for FAS. 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.

Summary statistics will be presented for absolute values and change from baseline in HCV RNA ($\log_{10}$ IU/mL) 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.

For the SVR12 endpoint analysis, a summary table of the number and percentage of subjects with SVR12, virologic failure (VF), and Other will be created. All subjects who achieve SVR12 will be categorized as SVR12. Virologic failure will be descriptively summarized as "on-treatment virologic failure" and relapse (which will be broken down by study drug completed yes/no). Subjects who do not achieve SVR12 and do not meet criteria for VF will be categorized as Other. The denominator for relapse will be the number of subjects who had HCV RNA < LLOQ on their last observed on-treatment HCV RNA measurement; otherwise, the denominator will be the number of subjects in the FAS.

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

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints

PPD

6.3.2. Analysis Methods for Exploratory Efficacy Endpoints

PPD

6.4. Changes From Protocol-Specified Efficacy Analyses

PPD

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

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 one or both of the following:

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

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent, as long as the AE stop date is not prior to the first dose date of study drug. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset and end dates are the same as or after the month and year (or year) of the first dose date of study drug
- The AE onset date is the same as or before the month and year (or year) of the 30th day after the date of the last dose of study drug

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

7.1.6. Summaries of Adverse Events and Deaths

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

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT based on the Safety Analysis Set as follows:

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- All treatment-related SAEs
- All AEs leading to premature discontinuation of study drug
- All AEs leading to interruption of study drug
- Deaths

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

In addition to the above summary tables, TEAEs will be summarized by PT only, in order of descending incidence 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 study drug
- All AEs leading to interruption of study drug

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

- All AEs (with a variable indicating whether the event is treatment emergent)
- AEs of Grade 3 or above
- SAEs
- Deaths
- AEs leading to premature discontinuation of 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 last dose of study drug plus 30 days for subjects who have permanently discontinued study drug or all available data at the time of the database snapshot for subjects those who were ongoing at the time of an interim analysis. The analysis will be based on values reported in conventional units. When values are below the limit of quantitation, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics. For example, if "< 0.2" was recorded, a value of 0.1 will be used for the purpose of calculating summary statistics; if "< 0.1" was recorded, a value of 0.09 will be used for the purpose of calculating summary statistics.

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

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided for ALT, AST, total bilirubin, alkaline phosphatase, hemoglobin, reticulocytes, white blood cell (WBC), neutrophils, lymphocytes, platelets, and INR as follows:

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

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

Median (Q1, Q3) of the observed values for ALT, AST, total bilirubin, alkaline phosphatase, hemoglobin, reticulocytes, RBC, WBC, neutrophils, lymphocytes, and platelets 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 (Selection of Data in the Event of Multiple Records in a Window).

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning toxicity grades (0 to 4) to laboratory results 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 and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug, or all available data in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

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

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by analyte; 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 last dose for the laboratory parameter of interest.

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

7.3. Body Weight, Height, and Vital Signs

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

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3 (Selection of Data in the Event of Multiple Records in a Window). No inferential statistics will be generated.

A by-subject listing of vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min], respiration [breaths/min], and body temperature [^{o}C]) will be provided by subject ID number and visit in chronological order. In the same manner, a by-subject listing of body weight, height, and BMI at baseline 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 and stopped prior to or on the date of first study drug administration
- Concomitant medications: any medications taken after the date of first study drug administration and up to the last dosing date of study drug

Concomitant medications will be summarized by preferred name using the number and percentage of subjects for each treatment group. 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 preferred term in descending frequency. For drugs with the same frequency, sorting will be done alphabetically.

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

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

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

7.5. Electrocardiogram Results

A by-subject listing for ECG assessment results at Screening will be provided by subject ID number.

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. REFERENCES

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Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989:pp. 414-21.

9. SOFTWARE

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

10. SAP REVISION

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

11. APPENDICES

Appendix 1. Study Procedures Table

			On-Treatment Study Week (±3 Days)					Posttreatment Study Week (±5 Days)	
	Screen[a]	Day 1[b]	2	4	8	12/EoT	ET	4	12
Informed Consent	X								
Determine Eligibility	X	X							
Medical History	X								
Physical Examination	X	X				X	X		
Height	X								
Weight	X								
Vital Signs	X	X	X	X	X	X	X	X	
12-Lead ECG	X						X		
Imaging for HCC[c]	X								
AEs/ SAEs[h]	X	X	X	X	X	X	X	X	X[h]
Concomitant Medications	X	X	X	X	X	X	X	X	
Review of Study Drug Compliance (Pill Count)[d]			X	X	X	X	X		
Study Drug Dispensing		X		X	X				
Hematology, Chemistry	X	X	X	X	X	X	X	X	
Coagulation Tests	X	X				X	X		
HCV RNA	X	X	X	X	X	X	X	X	X
HBV DNA[i]				X	X	X	X	X	X
Viral Sequencing/phenotyping[d]		X	X	X	X	X	X	X	X
Pregnancy Testing[e]	X	X		X	X	X	X	X	

	Screen[a]	Day 1[b]	On-Treatment Study Week (±3 Days)					Posttreatment Study Week (±5 Days)	
			2	4	8	12/EoT	ET	4	12
Urinalysis, Urine Drug Screen	X								
HCV Genotyping[f], IL28B	X								
HCV, HIV, HBV Testing	X								
HbA1c, Fibrotest®	X								
Archive Plasma Sample[g]		X				X	X		
Single PK Sample			X	X	X	X	X		

a. Screening assessments to be completed within 28 days of the Day 1 visit. The screening window can be extended to 42 days for subjects requiring a liver biopsy, or for extenuating circumstances with sponsor approval.
b. Day 1 assessments must be performed prior to dosing
c. Cirrhotic subjects will have liver imaging within 6 months of Day 1 to exclude HCC.
d. Plasma will be collected for possible viral resistance or other virology studies.
e. For females of childbearing potential only: serum β-hCG at Screening, urine pregnancy testing will occur every 4 weeks during the dosing period and for 30 days following the last dose of study drug.
f. HCV genotyping to be performed by the central laboratory utilizing the LiPa assay.
g. Subjects may opt out of archive sample collection.
h. Only SAEs will be collected at post-treatment week visits.
i. Only for subjects who are HBcAb+ at Screening.