STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) infection
Name of Test Drug:	Sofosbuvir/Velpatasvir
Study Number:	GS-US-342-1521
Protocol Version (Date):	Original: 12 February 2016
Analysis Type:	SVR12
Analysis Plan Version:	1.0
Analysis Plan Date:	14 March 2018
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DAA	direct acting antiviral
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDC	fixed dose combination
Gilead	Gilead Sciences, Inc.
GT	genotype (viral)
Hb	hemoglobin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IFN	interferon
INR	international normalized ratio of prothrombin time
LLOQ	lower limit of quantification
LLT	lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
Peg-IFN	pegylated interferon
PP	per protocol
PT	preferred term
Q1	first quartile
Q3	third quartile
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SI (units)	International system of units
SOC	system organ class
SOF	Sofosbuvir
SVR	sustained virologic response

TEAE	treatment-emergent adverse events
TFLs	tables, figures, and listings
ULN	upper limit of normal
VEL	Velpatasvir
WBC	white blood cell count
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-342-1521. This SAP is based on the study protocol dated 12 February 2016 and the electronic case report form (eCRF).This 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 objective of this study is as follows:

- To evaluate the efficacy of treatment with SOF/VEL FDC for 12 weeks in subjects with chronic HCV infection 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 FDC for 12 weeks.

1.2. Study Design

This is a multicenter, open-label study to evaluate the safety, tolerability, and antiviral efficacy of SOF/VEL FDC for 12 weeks in subjects with chronic HCV infection. Subjects with or without cirrhosis will be enrolled.

Approximately 125 subjects with chronic HCV infection will be enrolled in the study and all subjects will receive SOF/VEL FDC once daily for 12 weeks. Approximately 20% of subjects may be treatment experienced, and up to 20% of subjects may have compensated cirrhosis at baseline.

The total time to complete all study visits is up to approximately 28 weeks, including the following periods:

- 28-day (4-week) screening period

- 12-week treatment period

- Up to 12-week posttreatment period

1.3. Sample Size and Power

A sample size of 125 subjects will provide 95% power to detect an improvement in SVR12 rate from 85% to 95% using a two-sided exact one-sample binomial test at a significance level of 0.05.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee

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

2.2. Final Analysis

After all subjects have completed through the posttreatment Week 12 visit or have prematurely discontinued from the study, the final analysis of the data will be performed once all 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 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. The study drug in this study is SOF/VEL FDC (400/100 mg).

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

Generally speaking, efficacy analyses will be performed on the FAS. Subjects will be grouped by HCV genotype (GT1a, GT1b, GT1 (total), GT2, GT3, GT4, GT5, GT6, Indeterminate, and Total). For subjects with missing or mixed genotype or indeterminate genotype 1 subtype determined by LiPA 2.0 at enrollment, further Sanger sequencing will be performed to determine their HCV genotype and subtype. The analysis of HCV RNA less than the lower limit of quantitation (< LLOQ) at the end of treatment and during the posttreatment (ie, SVR) follow-up period will be performed on the FAS by genotype as described above.

For analyses based on other analysis sets, such as the Safety Analysis Set, data will be summarized based on the treatment subjects received.

3.3. Examination of Subject Subsets

The primary efficacy endpoint will be examined using the following subsets:

- Age (< 65 years, ≥ 65 years)
- Sex (male, female)
- Baseline body mass index BMI (<25 kg/m^2 , ≥ 25 kg/m^2)
- HCV genotype and subtype
- Cirrhosis (presence, absence, missing)
- 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 naïve, treatment experienced)
- Prior HCV treatment for treatment-experienced subjects (Peg-IFN + RBV and Other)
- Response to prior HCV treatment (non-responder, relapse/breakthrough, early treatment discontinuation) for treatment experienced subjects
- Adherence to study regimen (<80%, ≥80%)

3.4. Multiple Comparisons

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

3.5. Missing Data and Outliers

3.5.1. 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 3.7.1. The handling of missing or incomplete dates for adverse event (AE) onset is described in Section 7.2.5.2, and for prior and concomitant medications in Section 7.5.

For analyses of categorical HCV RNA data, missing posttreatment week 12 HCV RNA data will have the missing data imputed.

If a posttreatment week 12 HCV RNA data point is missing and is preceded and followed in time by values that are less than the lower limit of quantitation (LLOQ) target not detected (TND) (ie, "< LLOQ 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", 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 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.

3.5.2. 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 analyses.

3.6. 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, the date the informed consent was signed will be used instead of the first dose date of study drug. "01 January" will be used for the unknown birth day and month for the purpose of age calculation.

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 to this rule is any value reported as < 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 LLOQ of the assay is 15 IU/mL.

When the calculated 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 is reported as "HCV RNA not 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 < LLOQ of the assay, the result is 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 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.

3.7. Visit Windows

3.7.1. 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 the study drug administration eCRF for the record where the "subject permanently discontinued" flag is 'Yes'. The last dose date will be defined as the maximum of the last dose dates of study drugs.

If there are subjects for whom the date of last dose of 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 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 are not included).

3.7.2. 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. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dose of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be considered the baseline value.

HCV RNA, vital signs, and safety laboratory data collected up to the last dose date + 3 days are considered 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 12	84	2	98

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

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

	HCV RNA			Vital Signs and Safety Laboratory Data[b]		
Nominal FU[a] Visit	Nominal FU Day	Lower Limit	Upper Limit	Nominal FU Day	Lower Limit	Upper Limit
FU-4	NA	NA	NA	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).

3.7.3. 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 a single 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, the average (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 follow-up visits, for which the most recent record in the analysis window will be selected.

  — If there are 2 records that are equidistant from the nominal day, the more recent 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).

- 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 and investigator. The summary will present the number and percentage of subjects in the Safety Analysis Set. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A summary of subject disposition will be provided by genotype and overall. This summary will present the number of subjects screened, the number of subjects enrolled, the number of subjects enrolled but never treated, the number of subjects enrolled and treated (ie, Safety Analysis Set), in FAS, and the number and percentage of subjects in each of the categories listed below. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column.

- Continuing study treatment (if applicable)
- Completed study treatment
- Did not complete study treatment with reasons for premature discontinuation of study treatment
- Completed study
- Did not complete the study with reasons for premature discontinuation from study

Among subjects who completed study treatment and who discontinued study treatment, the number and percentage of subjects will be summarized for the subjects who had an HCV RNA posttreatment Week 12 assessment.

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

4.2. Extent of Exposure

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

4.2.1. Duration of Exposure to Study Drug

The 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 1 decimal place (eg, 4.5 weeks).

The total duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median Q1, Q3, minimum, and maximum) and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: baseline (Day 1), 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 by treatment group for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

The total number of study drug 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 eCRF using the following formula:

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

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

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

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

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

In this study, the total amount of SOF/VEL (400/100 mg) prescribed for 12 weeks 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. If study drug bottles are dispensed on or after the subject first met virologic failure criteria, the bottles will not be included in the calculation of adherence. If a bottle is dispensed and the bottle is returned empty, 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 by genotype for the Safety Analysis Set. Categorical displays will also be provided for the number of subjects who are at least 80% adherent to the study drug (ie, adherence to study drug is ≥ 80%).

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

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

4.3. Protocol Deviations

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

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographics (ie, age, sex, race, and ethnicity) will be summarized for the Safety Analysis Set overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for age and the number and percentage 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.

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- Body mass index (BMI; in kg/m^2) as a continuous variable and as categories (< 25 kg/m^2, ≥ 25 kg/m^2)
- HCV genotype and subtype
- Cirrhosis (presence, absence, missing)
- 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 experience (treatment naive, treatment experienced)
- Prior HCV treatment for treatment-experienced subjects (Peg-IFN + RBV, Other)
- Estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation

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.

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

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

A separate by-subject data listing for cirrhosis determination at screening will be provided for all subjects.

A separate by-subject data listing for prior HCV treatment and response will be provided for all treatment-experienced subjects. The listing will display the prior HCV regimen(s) and treatment(s) including treatment duration and the prior HCV treatment response.

5.3. Medical History

A by-subject listing of disease-specific medical history will be provided by subject ID number (in ascending order) and medical history 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 12 weeks after discontinuation of study drug in the FAS. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 will be used to measure HCV RNA. The LLOQ of the assay is 15 IU/mL.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

In the primary efficacy analysis, the SVR12 rate will be compared to the pre-specified performance goal of 85% by using a two-sided exact one-sample binomial test at the 0.05 significance level. The null (H0) and alternative (H1) hypotheses used to assess superiority of SOF/VEL FDC relative to the performance goal of 85% are:

- • H0: SVR12 rate = 85%
- • H1: SVR12 rate ≠ 85%

It is difficult to characterize a single historical control rate for all genotypes included in this study given the different standards of care of each genotype (some of which include interferon), and the lack of historical data for genotype 4, 5, and 6 participants. Given these difficulties, rather than use a historical control rate as the basis for assessing the primary endpoint, a pre-specified performance goal is defined as a benchmark against which the efficacy of SOF/VEL FDC will be tested. The benchmark sets a high bar of 85%. The basis for this benchmark includes the overall trend toward increasing SVR rates in recent years, the higher SVR rates observed with Peg-IFNα + RBV treatment in Asian subjects {Yu 2009} compared with other races, and the general appeal of using a fixed clinically relevant threshold as a measure of treatment benefit {Weins 2013} of SOF/VEL FDC.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The 2-sided 1-sample exact binomial test will be used to test the statistical hypotheses described above. The 2-sided 95% exact confidence interval (CI) and p-value based on the Clopper-Pearson method {Clopper 1934} will be provided for the SVR12 rate for total subjects.

6.1.4. Subgroup Analysis of the Primary Efficacy Endpoint

The point estimates and 95% exact CIs of the SVR12 rates will be displayed by genotype and subtype for the subgroups outlined in Section 3.3

A forest plot will graphically present estimates and 95% CIs in SVR12 rates for each of the subgroups.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoint is the proportion of subjects with virologic failure.

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

  On-treatment virologic failure

  – HCV RNA persistently ≥ LLOQ through 12 weeks of treatment (ie, nonresponse)

  Relapse

  – HCV RNA ≥ LLOQ at posttreatment Week 12 having achieved HCV RNA < LLOQ at EOT

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

For analyses of HCV RNA < LLOQ at end of treatment and during the posttreatment (SVR) follow-up period, subjects will be assigned a value at end of treatment or posttreatment week 12 based on windows specified in Section 3.7.2. Missing values will be imputed based on the categorical imputation rules described in Section 3.5.1. The two-sided 95% exact CI based on Clopper-Pearson method will be provided for the percentage of subjects with HCV RNA < LLOQ at each visit by genotype. 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 in tabular displays.

Summary statistics will be presented for absolute values and change from baseline in HCV RNA ($\log_{10}$ IU/mL), by genotype at EOT. Imputation rules described in Section 3.5.1 will be used to assign HCV RNA values for missing values at posttreatment week 12 that are bracketed by "< LLOQ TND" and/or "< LLOQ detected". Otherwise, a missing = excluded analysis will be performed.

For the SVR12 endpoint analysis, a summary table of the number and percentage of subjects with SVR12, virologic failure, and Other by genotype 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 or no). Subjects who do not achieve SVR12 and do not meet criteria for virologic failure will be categorized as "Other." The denominator for relapse will be the number of subjects who had HCV RNA < LLOQ at EOT HCV RNA measurement; otherwise, the denominator will be the number of subjects in the FAS.

6.3. Changes From Protocol-Specified Efficacy Analyses

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

7. SAFETY ANALYSES

7.1. Safety Endpoints

The primary safety endpoint is any AE leading to permanent discontinuation of study drug(s).

7.2. Adverse Events and Deaths

7.2.1. Adverse Event Dictionary

Clinical and laboratory 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.

7.2.2. 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.

7.2.3. 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 related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing from that captured on the eCRF.

7.2.4. 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.

7.2.5. Treatment-Emergent Adverse Events

7.2.5.1. 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.

7.2.5.2. Incomplete Dates

If the onset date of 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 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.

7.2.6. 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, and any AE that led to premature discontinuation of SOF/VEL, and any AE that led to interruption of SOF/VEL. 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
- AEs leading to premature discontinuation of SOF/VEL
- AEs leading to interruption of SOF/VEL
- Deaths

Multiple events will be counted once only per subject in each summary. Adverse events will be summarized and listed 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 also be summarized by PT only, in order of descending incidence for:

- All AEs
- 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 SOF/VEL
- AEs leading to interruption of SOF/VEL

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

- All AEs
- AEs of Grade 3 or above
- SAEs
- Deaths
- AEs leading to premature discontinuation of SOF/VEL
- AEs leading to interruption of SOF/VEL

7.3. 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 last dose of study drug plus 30 days for subjects who have permanently discontinued study drug. 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 and serum chemistry 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.

7.3.1. 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, white blood cell (WBC) counts, neutrophils, lymphocytes, hemoglobin, platelets, reticulocytes, and international normalized ratio (INR) as follows:

- Baseline values
- Values at Week 12 and FU-4
- Change from baseline at Week 12 and FU-4

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 and the SD will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

7.3.2. Graded Laboratory Values

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

7.3.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug. If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 will be considered treatment emergent.

7.3.2.2. Summaries of Laboratory Abnormalities

Categorical laboratory data 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 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.

7.4. Body Weight, Height, and Vital Signs

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, concomitant, or both using the following definitions:

- Prior medications: any medications taken and stopped prior to or on the date of first study drug administration
- Concomitant medications: any medications taken after the date of first study drug administration and up to the last dosing date of study drug. Prior and concomitant medications: any medications taken both prior to and on or after the initial study drug dosing date and within the treatment period (including the therapeutic reach of a study), or any medications taken prior to the baseline visit date with a stop date of "continuing"

Concomitant medications will be summarized by generic name of the drug using the number and percentage of subjects. 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 generic names. For drugs with the same frequency, sorting will be done alphabetically.

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 a start date that is after the date of the last dose of study drug will be excluded from a concomitant medication summary. If a partial stop date is entered on the eCRF, 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, then 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. Summaries will be based on the Safety Analysis Set. No inferential statistics will be generated.

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

7.6. Other Safety Measures

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

7.7. Changes From Protocol-Specified Safety Analyses

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

8. 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.

Weins BL, Lystig TC, Berry SM. Recent Statistical Contributions to Medical Device Development. Therapeutic Innovation & Regulatory Science 2013:1-8.

Yu ML, Chuang WL. Treatment of chronic hepatitis C in Asia: when East meets West. J Gastroenterol Hepatol. 2009;24 (3):336-45.

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. Schedule of Assessments

Appendix Table 1. Screening, On-Treatment Visits

	Screening[2] (Day -28 to Day 0)	Baseline/Day 1	On-treatment Study Week (± 3 days)			Post-treatment Study Week (± 5 days)	
			Week 4	Week 8	End of Treatment Week 12 or ET[1]	Week 4	Week 12
Written Informed Consent	X						
Medical History	X	X					
Symptom-Directed Physical and Vital Signs if indicated	X	X			X	X	
AEs and Concomitant Medications	X[3]	X			X	X	
Review of Study Medication Compliance					X		
Hematology, Chemistry, Coagulation	X	X			X	X	
HCV RNA	X	X			X		X
HCV Genotyping	X						
HIV testing, HCV and HBV Serology	X						
Archive Sample		X			X		X
Cirrhosis determination	X						
Urine Pregnancy Testing[4]	X	X			X	X	
Study Medication Dispensation		X	X	X			

1 ET = Early Termination
2 The screening window can be extended to 42 days prior to Day 1 for extenuating circumstances with sponsor approval
3 Concomitant medications and AE related to Screening Procedures only
4 Females of child-bearing potential only