STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24 Weeks in Genotype 1 or 3 and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablet for 12 weeks in Genotype 1 or 4 HCV-Infected Subjects with Renal Insufficiency
Name of Test Drugs:	Sofosbuvir, Ledipasvir/Sofosbuvir Fixed-Dose Combination
Study Number:	GS-US-334-0154 (Cohorts 1 & 2)
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Analysis Plan Version:	Version 1.0
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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
BUN	blood urea nitrogen
%CV / CV	(percent) coefficient of variation
CI	confidence interval
CrCl	creatinine clearance
CRF	case report form(s)
CSR	clinical study report
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FU	follow-up
HCV	hepatitis C virus
HLT	high-level term
IBW	ideal body weight
INR	International Normalized Ratio of prothrombin time
IL28B	IL28B gene
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
nadir	the lowest point
PK	pharmacokinetic
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	once daily
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SD	standard deviation
SOC	system organ class
SOF	sofosbuvir, GS-7977
SVR	sustained virologic response

TFL	tables, figures, and listings
TND	target not detected
ULN	upper limit of the normal range
ULOQ	upper limit of quantitation
VF	virologic failure
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in the summary and analysis of data for subjects in cohorts 1 and 2 from Study GS-US-334-0154. This SAP was based on the protocol amendment dated 23 April 2015. Related documents are the study protocol, study protocol amendments and electronic case report form (eCRF). Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

1.1.1. Primary Study Objectives

The primary objectives of this study are:

- To evaluate the safety of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks and LDV/SOF for 12 weeks as assessed by review of the accumulated safety data in each treatment arm
- To evaluate the efficacy of SOF 200 mg or 400 mg + RBV for 24 weeks and LDV/SOF for 12 weeks measured by the proportion of subjects with renal insufficiency who have achieved a sustained viral response 12 weeks after treatment discontinuation (SVR12) in each treatment arm
- To evaluate the steady state pharmacokinetics of SOF and its metabolites and LDV upon dosing SOF 200 mg or 400 mg or LDV/SOF in subjects with renal insufficiency

1.1.2. Secondary Study Objectives

The secondary objectives of this study are:

- To evaluate the proportion of subjects with renal insufficiency who attain SVR at 4 and 24 weeks after discontinuation of treatment (SVR4 and SVR24)
- To evaluate the kinetics of plasma HCV RNA during and after treatment discontinuation
- To evaluate the emergence of viral resistance to SOF and LDV during and after treatment discontinuation

1.1.3. Exploratory Study Objective

PPD

PPD

1.2. Study Design

1.2.1. Design Configuration, Subject Population and Treatment Cohorts

This is a multicenter, open label study that will evaluate the safety, tolerability, and antiviral efficacy of SOF with RBV or LDV/ SOF in chronic renal insufficiency and HCV infection subjects with genotype 1, 3 or genotype 4 HCV infection, including those with compensated cirrhosis.

This study will have 3 cohorts.

Approximately 35 subjects with severe renal insufficiency will be enrolled.

- Cohort 1: 10 subjects will receive SOF 200 mg QD + RBV 200 mg QD for 24 weeks.
- Cohort 2: Following review of safety, efficacy and PK data through posttreatment Week 4 of Cohort 1, 10 additional subjects will receive SOF 400 mg QD + RBV 200 mg QD for 24 weeks.
- Cohort 3: Following review of safety and available PK data through Week 12 of Cohort 2, 15 additional subjects will receive LDV/SOF QD for 12 weeks.

1.2.2. Study Duration

The total time to complete all study visits is approximately 54 weeks (Cohorts 1 and 2) or 42 weeks (Cohort 3) including the following periods:

- Up to 42-day (6-week) screening period
- An 24-week (Cohorts 1 and 2) or 12-week (Cohort 3) treatment period
- Up to 24-week posttreatment period

1.2.3. Schedule of Assessments

The schedule of assessments is provided as an appendix to the SAP (Appendix 2).

1.3. Sample Size and Power

Due to the exploratory nature of this study, no formal power or sample size calculations were performed to determine treatment group size. The total sample size of 35 is largely based on feasibility.

2. TYPE OF PLANNED ANALYSIS

2.1. DMC Analyses

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety, efficacy, and PK data for each cohort of the study before proceeding to the next. Specifically, all of the data through posttreatment week 4 from the SOF 200 mg group (Cohort 1) will be reviewed before screening, enrollment and dosing for the SOF 400 mg group (Cohort 2). A similar review and initiation process will occur between SOF 400 mg (Cohort 2) and LDV/SOF dose group (Cohort 3), with review of safety and PK data through Week 12 from Cohort 2 prior to initiating Cohort 3. The DMC will provide recommendations to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding the need for additional meetings or an alternative meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

2.2. Final Analysis for Cohorts 1 and 2

The final analysis for Cohorts 1 and 2 will be conducted when all subjects in Cohorts 1 and 2 have completed the 24 week posttreatment visit or have prematurely discontinued from study. The data will be finalized after all data queries are resolved for study visits through completion of the 24-week posttreatment visit. At the conclusion of data finalization for Cohorts 1 and 2, the final version of tables, figures and listings (TFLs) for Cohorts 1 and 2 will be generated.

2.3. Final Analysis for Cohorts 3

A separate SAP will be written to describe the analysis for data from Cohort 3.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

Analysis sets define which subjects are included in an analysis. A summary of the number and percentage of subjects in each analysis set will be provided by treatment cohort and in total as part of the subject disposition summary.

3.1.1. All Enrolled Subjects

All enrolled subjects are defined as subjects who were enrolled into the study.

3.1.2. Full Analysis Set

The full analysis set (FAS) includes subjects who were enrolled and received at least 1 dose of study drug. The study drugs for the Cohorts 1 and 2 in this study are SOF and RBV.

3.1.3. Safety Analysis Set

The safety analysis set includes subjects who received at least 1 dose of study drug.

3.1.4. PK Analysis Set

The PK analysis sets for SOF, its metabolites (GS-566500, GS-331007), and RBV will include all subjects who were enrolled, received at least one dose of study drug and for whom PK concentration data of interested analytes are available.

3.2. Subject Groups

Subjects will be grouped for analyses according to enrolled treatment cohort for efficacy analysis using the FAS. For safety analyses using the safety analysis set, subjects will be grouped according to their enrolled treatment cohort except when their actual treatment differs from enrolled treatment for the entire treatment duration. In this case, the subject is grouped based on actual treatment received.

3.3. Data Handling Conventions and Transformations

The COBAS® AmpliPrep/COBAS® TaqMan® HCV Test will be 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 HCV RNA value is within the linear range of the assay, 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."

For numerical HCV RNA data, values below LLOQ will be set to the LLOQ minus 1 (ie, 14 HCV RNA IU/mL, or 1.15 on the log10 scale). HCV RNA values returned as "target not detected" will also be set to 14 IU/mL.

For selected analyses, HCV RNA data (IU/mL) will be transformed to the logarithmic (base 10) scale ($\log_{10}$ IU/mL).

Total bilirubin values entered as < 0.2 mg/dL will be analyzed as 0.1 mg/dL; direct bilirubin values entered as < 0.1 mg/dL will be analyzed as 0.05 mg/dL. In general, other than the above 2 exceptions, laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation (ULOQ) will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (e.g., if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if it is < 0.2 mg/dL a value of 0.1 mg/dL will be assigned). In addition, laboratory data that are continuous in nature but are ≤ LLOQ or ≥ ULOQ will be imputed to the value of the lower or upper limit, respectively (e.g., if the result of a continuous laboratory test is ≤ 20, a value of 20 will be assigned)

PK concentration values below the limit of quantitation (BLQ) will be treated as zero for the determination of summary and order statistics. Individual values that are BLQ will be presented as "BLQ" in the concentration data listing. For the presentation of summary and order statistics, if at least 1 subject has a concentration value BLQ for the time point, then the minimum value will be displayed as "BLQ". If more than 25% of subjects have a concentration data value of BLQ for a given time point, then the minimum and the first quartile [Q1] will be displayed as "BLQ". If more than 50% of the subjects have a concentration data value of BLQ for a given time point, then the minimum and median values will be displayed as "BLQ". If more than 75% of the subjects have a concentration value of BLQ for a given time point, the minimum, Q1, median, and third quartile [Q3] values will be displayed as "BLQ". If all subjects have concentration data values BLQ for a given time point, then all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ".

Exposure parameters selected for statistical analysis will be natural log-transformed. Concentration values that are BLQ will be considered missing for any ratio or natural log-transformed statistical analyses.

3.4. Missing Data and Outliers

3.4.1. Missing Data

A missing data point for a given study visit may be due to any one of the following reasons:

- A visit occurred but data were not collected or were unusable
- A visit did not occur
- A subject permanently discontinued from the study before reaching the window

For analyses of categorical HCV RNA data, missing posttreatment HCV RNA data will have the missing data always imputed. Missing on-treatment HCV RNA data 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 TND", then the missing data point will be set to "< LLOQ TND". If a data point is missing and preceded and followed by values that are "< LLOQ detected", or preceded by "< LLOQ detected" and followed by "< LLOQ TND", or preceded by "< LLOQ TND" and followed by "< LLOQ detected", then the missing value will be set to "< LLOQ detected". In these situations the data point will be termed a bracketed success; otherwise, the data point will be termed a bracketed failure (ie, ≥ LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (ie, ≥ LLOQ detected) except for SVR24, which will be imputed according to SVR12 status. Success for SVR12 who have no further HCV RNA measurements collected will be counted as a success for SVR24 due to the high correlation between these 2 endpoints.

For the analyses of continuous HCV RNA efficacy data, when and only when a missing HCV RNA value is imputed as < LLOQ TND or < LLOQ detected according to the imputation rule described above, the corresponding continuous/numerical value will be imputed to LLOQ-1 IU/mL.

Except for the imputation rules described above, values for other missing data (including all safety data) will not be imputed.

3.4.2. Outliers

Outliers will be identified during data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes. All data will be included in the data analysis.

3.5. Visit Windows

3.5.1. Definition of Study Day 1, First/Last Dosing Date, and Baseline Value

The ***first dose date of individual study drug*** will be calculated separately for each study drug (ie, SOF, RBV) in a treatment cohort. **Study Day 1** is defined as **the first dose date of any study drug**, which is the minimum of the first dose dates of individual study drugs in a treatment cohort.

The ***last dose date of individual study drug*** will be calculated separately for each study drug in a treatment cohort. The last dose date for an individual study drug will be the end date on study drug administration CRF for the record where the "subject permanently discontinued" flag is 'Yes'. The ***last dose date of any study drug*** will be defined as the maximum of the last dosing dates of individual study drugs in a treatment cohort.

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).

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

3.5.2. Analysis Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purposes of data analysis, visit windows will be utilized when a single value at a visit is required for analysis.

Visit windows are defined for HCV RNA, vital signs, safety laboratory, and ECG. No analysis windows will be defined for echocardiogram data.

All available HCV RNA data will be included in efficacy analysis, unless a subject starts alternative HCV medication. HCV RNA data collected after starting alternative HCV medication will be excluded. Imputation for missing HCV RNA values are described in Section 3.4.1. For safety data, subjects who are permanently discontinued from study drug will be included in safety analyses up to the ***last dose date of any study drug*** + 30 days, unless otherwise specified. For interim DMC analyses, subjects still on study drug will have all available data included in the interim snapshot database included in analysis.

HCV RNA, vital signs, and safety laboratory data collected up to the ***last dose date of any study drug*** + 2 days are considered to be on-treatment data, and HCV RNA, vital signs and safety laboratory data collected after the ***last dose date of any study drug*** + 2 days are considered posttreatment data. On-treatment and posttreatment data will follow 2 different sets of visit windows.

On-treatment visit windows will be calculated from **Study Day 1** (ie, Study Day = collection date minus date of **Study Day 1**; +1 if result is ≥ 0) for HCV RNA, vital signs and other safety laboratory data as shown in Table 1.

Table 1. On-Treatment Visit Windows for Selected Tests

Visit ID	On-Treatment Visit Windows for HCV RNA, Vital Signs and Other Safety Labs
Baseline	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11
Week 2	12 ≤ Study Day ≤ 21
Week 4	22 ≤ Study Day ≤ 35
Week 6	36 ≤ Study Day ≤ 49
Week 8	50 ≤ Study Day ≤ 63
Week 10	64 ≤ Study Day ≤ 77
Week 12	78 ≤ Study Day ≤ 98
Week 16	99 ≤ Study Day ≤ 126
Week 20	127 ≤ Study Day ≤ 154
Week 24	155 ≤ Study Day ≤ 182

HCV RNA, vital sign, and safety laboratory data collected after the ***last dose date of any study drug*** + 2 days will be assigned to the posttreatment FU visit windows. Windows will be calculated from the ***last dose date of any study drug*** (ie, FU Day = collection date minus the ***last dose date of any study drug***) as shown in Table 2.

Table 2. Posttreatment Visit Windows for Selected Tests

FU Visit ID	Posttreatment Visit Windows for HCV RNA[a]	Posttreatment Visit Windows for ECG, Vital Signs and Other Safety Labs[b]
FU-4	21 ≤ FU Day ≤ 69	3 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	N/A
FU-24	147 ≤ FU Day ≤ 190	N/A

a SVR follow-up visit window (lower bound) must occur within 7, 14, and 21 days of target for SVR4, SVR12, and SVR24, respectively.
b Vital signs and safety labs will only be summarized for the 4-week follow-up visit (up to last dose date of any study drug + 30 days).

ECG data collected up to the last dose date of any study drug + 2 days are considered to be on-treatment data. The following visit windows shown in Table 3 will be used.

Table 3. On-Treatment Visit Windows for ECGs

Visit ID	On-Treatment Visit Windows for ECG Data
Baseline	Study Day ≤ 1
Week 4	2≤ Study Day ≤ 42
Week 8	43 ≤ Study Day ≤ 70
Week 12	71 ≤ Study Day ≤ 98
Week 16	99 ≤ Study Day ≤ 126
Week 20	127 ≤ Study Day ≤ 154
Week 24	155 ≤ Study Day ≤ 182

3.5.3. Selection of Data in the Event of Multiple Records in a 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. When a single value is needed, the following rules will be used:

- Select the record closest to the nominal day (ie, visit weeks x 7 days) for that visit except for HCV RNA posttreatment follow-up visits, for which the latest record in the analysis window should be selected.

- If there are 2 visits equidistant from the nominal day within the analysis window, take the latest.

- If there is more than 1 record on the selected day, take the average (for continuous data) or the worst (for categorical data). If there are 2 values on the same day, the second may be a retest because there was a problem with the first test (eg, specimen hemolyzed). In cases where the first test is cancelled, the retest value should be used.

- For ECG end of treatment value, select the last value on/prior to last dose date of any study drug +2.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment

The number and percentage of subjects enrolled and treated in each country and by each investigator within a country will be summarized by treatment cohort and overall. The denominator for this calculation will be the number of subjects in the safety analysis set.

4.2. Disposition of Subjects

A summary of subject disposition will be provided by treatment cohort and overall. This summary will present the number of subjects screened, subjects not enrolled, enrolled, in safety analysis set, in FAS, in PK analysis set, and the number and percentage of subjects meeting the following criteria:

- Completed study treatment
- Discontinued study treatment (with summary of reasons for not completing the study treatment)
- Completed the study
- Did not complete the study (with summary of reasons for not completing the study)

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

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

If a subject did not have any HCV RNA assessment beyond 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 Assessment and thereafter”. If a subject had the HCV FU-4 assessment but did not have any HCV RNA assessment beyond 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 Assessment and thereafter”.

The denominator for the percentages of subjects in each category will be the number of subjects in the safety analysis set.

No inferential statistics will be presented.

A data listing of date of informed consent, first dose date, last dose date of any study drug (study day), completed study treatment (yes/no), completed study (yes/no) and reasons for premature study treatment/study discontinuation will be provided. The last available observed nonmissing HCV RNA value prior to discontinuation and for up to 2 days after last dose will be included in this listing.

4.3. Extent of Exposure

4.3.1. Duration of Exposure to Study Drug

Duration of exposure to study regimen will be defined as (last dose date of any study drug – first dose date of any study drug + 1), regardless of temporary interruptions in study drug administration and will be expressed in weeks (recorded to 1 decimal place, eg, 10.1 weeks). Duration of exposure to individual study drug is defined as (last dose date of individual study drug – first dose date of individual study drug + 1 day), regardless of temporary interruptions in study drug administration. For subjects ongoing at the time of a DMC analysis, the last dosing date will be estimated based on the last available eCRF or laboratory date available in the snapshot database.

Duration of exposure to study regimen will be summarized using descriptive statistics (sample size, mean, standard deviation [SD], minimum, first quartile [Q1], median, third quartile [Q3], and maximum) and as the number of subjects exposed to study regimen through (ie, cumulative counts): Baseline (Day 1); Week 1 (Day 7); Week 2 (Day 14); Week 4 (Day 28); Week 6 (Day 42); Week 8 (Day 56); Week 10 (Day 70); Week 12 (Day 84); Week 16 (Day 112); Week 20 (Day 140); and Week 24 (Day 168).

Summaries will be provided by treatment cohort for the safety analysis set.

4.3.2. Exposure to RBV (mg)

Descriptive summary statistics will be provided for the daily dose of RBV administered by weeks (ie, first dose, and at Week 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24). The daily dose of RBV on study day 1, 8, 15, 29, 43, 57, 71, 85, 113, 141 and 165 will be summarized across all subjects who were on RBV on that day.

Descriptive summary statistics will be provided for the mean daily dose of RBV, with mean daily dose for each subject calculated by total RBV dose during study treatment divided by number of total RBV exposure days.

Summaries will be provided by treatment cohort for the safety analysis set.

4.3.3. Adherence to Study Drug

Adherence will be calculated separately for SOF (tablets) and RBV (tablets) as:

(Number of tablets taken) ÷ (Number of tablets prescribed for study drug at baseline) × 100%

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

4.3.3.1. Calculation of Number of Tablets Prescribed for Study Drug

For subjects who complete study drug or prematurely discontinue study drug for a reason other than virologic failure (ie, met virologic failure stopping criteria) number of tablets prescribed is displayed in Table 4.

Table 4. Number of Prescribed Tablets

	Cohort 1 (SOF 200mg +RBV 200 mg)	**Cohort 2 (SOF 400mg +RBV 200 mg)**
SOF tablet	2×168 (336) SOF 100 mg tablet	1×168 (168) SOF 400 mg tablet
RBV 200 mg tablet	1×168 (168)	1×168 (168)

- For Cohort 1, prescribed SOF (100 mg) would require 336 tablets for the 24-week treatment period (2 tablets/day ×168 days) and prescribed RBV (200 mg) would require 168 tablets for the 24-week treatment period (1 tablet/day × 168 days).

- For Cohort 2, prescribed SOF (400 mg) would require 168 tablets for the 24-week treatment period (1 tablets/day × 168 days) and prescribed RBV (200 mg) would require 168 tablets for the 24-week treatment period (1 tablet/day ×168 days).

Subjects who prematurely discontinue study drug for lack of efficacy (ie, virologic failure) will have prescribed medications calculated for the number of study days at the first date when virologic stopping criteria were met (ie, substitute number of days to virologic failure [date of first of 2 consecutive measurements or a last available value meeting criteria] for 168 days).

4.3.3.2. Calculation of Number of Tablets Taken

The number of tablets taken for SOF and RBV during the treatment period will be calculated as the sum of (number of tablets dispensed – number of tablets returned) at each distinct dispensing period across all bottles dispensed. For subjects who discontinue for virologic failure, bottles dispensed after the subject first met virologic failure criteria will not be included in calculations. 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 adherence to each study drug (sample size, mean, SD, minimum, Q1, median, Q3, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, $< 80\%$, ≥ 80 to $< 90\%$, $\geq 90\%$) will be provided by treatment cohort for the safety analysis set. Categorical displays will be presented for the number of subject who are at least 80% adherent to their drug regimen (ie, adherence is $\geq 80\%$ for each of the study drugs).

No inferential statistics will be provided.

4.4. Protocol Deviations

A summary of major protocol violations will be provided by the Clinical Operations group for subjects in the safety analysis set.

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

The following subject demographic and baseline characteristics will be summarized by treatment cohort and overall using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percent of subjects for categorical data. Variables to be summarized include the following:

- age (on date of first dose of any study drug) as a continuous variable
- sex at birth (male, female)
- race
- ethnicity (hispanic or latino, non-hispanic or latino)
- body weight and height
- body mass index as a continuous variable and for categories (< 30 kg/m^2, ≥ 30 kg/m^2)
- HCV genotype
- cirrhosis (presence, absence)
- IL28B (CC, CT, TT)
- baseline HCV RNA as a continuous variable and for categories ($<$ 6log10 IU/mL, $\geq$ 6log10 IU/mL)
- baseline ALT as a continuous variable and for categories ($\leq$1.5 x ULN, $>$ 1.5 x ULN)
- estimated glomerular filtration rate using the Cockcroft-Gault equation
- prior HCV treatment experience (treatment naïve, treatment experienced)
- prior HCV treatment response for treatment experienced subjects
- most recent HCV treatment regimen for treatment experienced subjects
- fibrotest score as a continuous variable and fibrotest stage as a categorical variable

Age is calculated as the integer of age in years at first dose of study regimen. eGFR will be calculated by the Cockcroft-Gault method using ideal body weight (IBW): $eGFR_{CG}$ (mL/min) = [(140 – age (yrs)) × IBW (kg) × (0.85 if female)] / (serum creatinine (mg/dL) × 72).

The summary of demographic data and baseline characteristics will be provided for the safety analysis set.

5.2. Medical History

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

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is SVR 12 weeks after treatment discontinuation (SVR12) defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after study drug cessation for the FAS. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Test will be used to determine HCV RNA results in this study.

The 2-sided 95% exact confidence interval (CI) based on Clopper-Pearson method will be provided for the SVR12 rate for each treatment cohort.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- The proportion of subjects who attain SVR at 4 and 24 weeks after treatment discontinuation, defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 4 and 24 weeks after stopping treatment (SVR 4 and SVR 24)
- The proportion of subjects with HCV RNA below LLOQ (ie, < 15 IU/mL) by study visit
- HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through end of treatment
- The proportion 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

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

For analyses of HCV RNA < LLOQ (ie, < 15 IU/mL) 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 categorical imputation rules described in Section 3.4.1. The 2-sided 95% exact confidence interval based on Clopper-Pearson method will be provided for the proportion within each treatment cohort. 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.

Graphs for the proportion 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 end of treatment (EOT). Imputation rules described in Section 3.4.1 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.

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. Point estimates and 95% Clopper-Pearson exact confidence intervals will be presented for the overall virologic failure.

A concordance table between SVR12 and SVR24 will be provided by treatment cohort.

In addition, the proportion of subjects with ALT normalization (defined as ALT > ULN at baseline and ALT ≤ ULN at each visit) will be presented by study visit. Tables for ALT normalization by visit will use similar methodology to the analyses of HCV RNA < LLOQ, but will use a missing = excluded analysis. Only those subjects with ALT greater than the ULN range at baseline (defined as the last ALT value collected prior to first dose of study drug) will be included in the analysis of ALT normalization.

7. SAFETY ANALYSES

Safety data will be summarized for subjects included in the safety analysis set. Summaries of safety data (treatment-emergent [TE] adverse events [AEs], TE maximum toxicity grades, changes from baseline in laboratory tests and vital signs parameters) will include all data collected on or after the first dose date of any study drug through the last dose date of any study drug plus 30 days for subjects who have stopped all study drugs, and all available data at the time of the database snapshot for subjects still on treatment at the time of a DMC interim analysis.

All safety data (except for laboratory tests with results that were cancelled by the lab) will be included in data listings based on the safety analysis set.

7.1. Adverse Events

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be attached to the clinical database.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator according to the Gilead Sciences, Inc. (Gilead) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities as specified in the clinical study 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 will be considered the least severe for the purposes of sorting for data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

The relationship of AE to study drug will be assessed by investigators as “Yes” or “No”.

Events for which the investigator did not record the relationship to study drug will be considered to be related to study drug for summary purposes. However, data listings will present the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those identified as serious in the clinical database. The clinical database will be reconciled with the SAE database from the Drug Safety and Public Health Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Treatment-emergent AEs are

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

7.1.5.2. Incomplete Dates

If the date of onset is incomplete, then the month and year (or year alone if month is not recorded) of onset determine whether the AE is treatment emergent. The event is treatment emergent if the month and year of onset (or year of onset) of the event meets both of the following criteria:

- The same as or after the month and year (or year) of the first dose of any study drug
- The same as or before the month and year (or year) of the 30th day after the date of the last dose of any study drug

7.1.6. Summaries of Adverse Events and Deaths

A brief summary of AEs will show, by treatment cohort, the number and percentage of subjects who (1) had any TE AE, (2) had any Grade 3 or 4 TE AE, (3) had any Grade 2, 3, or 4 TE AE, (4) had any TE treatment-related AE, (5) had any Grade 3 or 4 TE treatment-related AE, (6) had any Grade 2, 3 or 4 TE treatment-related AE, (7) had any TE SAE, (8) had any TE treatment-related SAE, (9) had any AE leading to permanent discontinuation from any study drug, (10) had any AE leading to permanent discontinuation from SOF, (11) had any AE leading to modification or interruption of any of the study drugs, (12) had any AE leading to interruption of SOF and (13) TE death during the study

Summaries (number and percentage of subjects) of adverse events (by SOC and PT) will be provided by treatment cohort using the safety analysis set as follows:

- All TE AEs
- Combined Grade 3 or 4 TE AEs
- Combined Grade 2, 3 or 4 TE AEs
- TE non-serious AEs occurring in at least 5% of subjects in any treatment cohort (this will be produced for ClinicalTrials.gov website)
- TE treatment-related AEs

- Combined Grade 3 or 4 TE treatment-related AEs
- Combined Grade 2, 3 or 4 TE treatment-related AEs
- TE SAEs
- TE treatment-related SAEs
- AEs leading to permanent discontinuation from any of the study drugs
- AEs leading to modification or interruption of any of the study drugs

Multiple events will be counted once only per subject in each summary. For data presentation, SOC will be ordered alphabetically, with PT sorted by decreasing total frequency within an SOC. For summaries by severity grade, the most severe event will be selected.

In addition to the presentation by SOC and preferred term, summaries will also be presented by preferred term only, ordered by decreasing total frequency for All TE AEs.

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

- All AEs
- SAEs
- Deaths
- AEs leading to permanent discontinuation of any of the study drugs
- Grade 3 or 4 AEs

7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the safety analysis set and will include data collected up to last dose of any study drug plus 30 days for subjects who have stopped all study drugs and all available data at the time of the database snapshot for subjects who are ongoing at the time of interim DMC analysis. Analysis will be based on values reported in conventional units. Laboratory results cancelled by the central laboratory will not be included in analysis.

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum and maximum) will be provided by treatment cohort for ALT, AST, total bilirubin, alkaline phosphatase, white blood cell (WBC) counts, neutrophils, lymphocytes, hemoglobin, platelets, reticulocytes, creatinine, INR, and creatinine clearance (calculated by the Cockcroft-Gault equation, using IBW) as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window

The mean, median, Q1, Q3, minimum and maximum will be displayed to reported number of digits, standard deviation to reported number of digits +1 for visits up to end of treatment. The posttreatment week 4 safety follow-up visit will be presented as an additional separate visit.

The number of subjects with hemoglobin < 10 g/dL and < 8.5 g/dL at any postbaseline visits (up to 30 days after the last dose of any study drug) will be summarized by treatment cohort.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assignment of toxicity grades to laboratory results for purposes of analysis as Grade 0, Grade 1 (mild) , Grade 2 (moderate), Grade 3 (severe) or Grade 4 (potentially life threatening). Grade 0 includes all values that do not meet criteria for an abnormality of at least Grade 1.

Some laboratory tests have laboratory toxicity criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline up to the last dose of any study drug plus 30 days for subjects who have stopped all study drugs or all available data in the database snapshot for subjects still on treatment at the time of a DMC interim analysis.

If the relevant baseline laboratory data are missing, then any abnormality of at least Grade 1 will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) of laboratory abnormalities using the Gilead Grading Scale will be provided by treatment cohort (subjects categorized according to most severe postbaseline abnormality grade):

- TE graded laboratory abnormalities
- TE Grade 3 or 4 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 any study drug) for the laboratory parameter of interest.

A listing of TE Grade 3 or Grade 4 laboratory abnormalities will be provided. This listing will include the complete laboratory test profile for each laboratory test with the graded result throughout the study.

All valid laboratory values will be listed. Values falling outside of the relevant reference range and/or meeting Gilead Grading Scale will be flagged, as appropriate, in the data listings.

7.3. Body Weight, Height, BMI and Vital Signs

Absolute value and change from baseline in vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP] and pulse) at each visit will be summarized for the safety analysis set using descriptive statistics by treatment cohort for each post baseline analysis window. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.5.3. No inferential statistics will be generated.

A listing of height (at screening), body weight, and BMI, and a listing of SBP, DBP, pulse, respiration and temperature will be provided.

7.4. Electrocardiogram (ECG) Results

Absolute value and change from baseline in PR interval, QRS interval, QT interval and QTcF at each visit will be summarized for the safety analysis set using descriptive statistics by treatment cohort for each post baseline analysis window. A listing of PR interval, QRS interval, QT interval, and QTcF will be provided.

A listing of overall assessment of ECG results including description regarding clinically significant abnormalities will be provided.

7.5. Echocardiogram Results

Absolute value and change from baseline in ejection fraction, fractional shortening, left ventricular end diastolic volume (LVEDV) and left ventricular internal dimension in diastole (LVIDd) at each visit will be summarized for the safety analysis set using descriptive statistics by

treatment cohort for each post baseline visit. A shift table of diastolic function score assessment at baseline versus each on-treatment visit will be presented by treatment cohort.

A listing of ejection fraction, fractional shortening, LVEDV, LVIDd and diastolic function score will be provided.

7.6. Concomitant Medications

Concomitant medications (ie, medications other than study drug that are taken while receiving study treatment) will be coded using the World Health Organization (WHO) Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant medications will be summarized (number and percentage of subjects) by treatment cohort, WHO drug class, and WHO generic name. Multiple drug use (by preferred name) will be counted once only per subject. The summary will be sorted alphabetically by drug class and then by decreasing total frequency within a class.

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

Summaries of concomitant medications will be provided for the safety analysis set. No inferential statistics will be generated.

A listing of all concomitant medications reported during the study will be provided.

7.7. Other Safety Measures

A data listing of cirrhosis determination will be provided.

A data listing will be provided for subjects who received dialysis during the study.

A data listing will be provided for subjects' prior HCV treatment and response.

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

8. PHARMACOKINETIC ANALYSES

Steady-state PK over dosing interval will be determined from intensive PK assessments at the Week 2 and Week 12 on-treatment visits.

Concentration of SOF (and its metabolites GS-566500 and GS-331007) and RBV in plasma will be determined using validated bioanalytical assays. The PK parameters for these analytes will be computed for all subjects with evaluable PK profiles. For each subject, the following PK parameters will be calculated, as appropriate:

Parameter	Description
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug in plasma
C_{max}	maximum observed concentration of drug in plasma
C_{tau}	observed drug concentration at the end of the dosing interval
$T_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the plasma concentration of drug versus time curve

PK parameters will be estimated by application of a nonlinear model using standard noncompartmental methods (WinNonlin® software v6.3). The linear up/log down trapezoidal rule will be used in conjunction with the appropriate noncompartmental model (usually input Model 200 for oral dosing), with input values for dose, time of dose, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible.

All predose sample times of less than time zero will be converted to zero. Samples below the limit of quantitation of the bioanalytical assays that occur prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data. The nominal time point for a key event or dosing interval (tau) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the pharmacokineticist on a profile-by-profile basis.

Accurate estimation of several PK parameters, such as λ_z and $T_{½}$, are dependent on the measured terminal elimination phase of the drug. The appropriateness of calculating these parameters will be assessed by the pharmacokineticist on a profile-by-profile basis.

Ten descriptive statistics (sample size, mean, SD, coefficient of variation [%CV], median, Q1, Q3, minimum, maximum, and geometric mean and its 95% CI) will be presented for PK concentration data and PK parameter data. For concentration values BLQ, the number of subjects with values of BLQ will be presented.

Plasma concentrations of SOF (and its metabolites GS-566500 and GS-331007) and RBV over time from the intensive PK assessments will be plotted in linear and semi-logarithmic scales as mean ± SD and as Q1, median, and Q3 by treatment cohort and visit.

9. SOFTWARE

SAS®, Version 9.2, SAS Institute Inc., Cary, NC, USA.

Phoenix® WinNonlin®, Version 6.2, Pharsight Corporation, Mountain View, CA, USA.

10. APPENDICES

Appendix 1. Tables, Figures, and Listings

Table Number	Title	Analysis Set
1	Subjects Enrolled and Treated by Country and Investigator	Safety Analysis Set
2	Subject Disposition	Screened Subjects
3	Reasons for Screen Failure	Screened Subjects
4	Demographics and Baseline Characteristics	Safety Analysis Set
5	Duration of Exposure to Study Regimen	Safety Analysis Set
6	Concomitant Medications	Safety Analysis Set
7	Adherence to Study Drug	Safety Analysis Set
8	Daily Dose of Ribavirin (mg) by Week	Safety Analysis Set
9	Summary of Mean Daily Dose of Ribavirin (mg)	Safety Analysis Set
10	SVR12	Full Analysis Set
11	Virologic Outcomes	Full Analysis Set
12	Concordance between SVR12 and SVR24	Full Analysis Set
13	SVR by Visit During Posttreatment Follow Up	Full Analysis Set
14	Proportion of Subjects with HCV RNA Less than LLOQ (15 IU/mL) While on Treatment by Visit	Full Analysis Set
15	HCV RNA (log10 IU/mL) and Change from Baseline by Visit Through End of Treatment	Full Analysis Set
16	Proportion of Subjects with ALT Normalization by Visit	Full Analysis Set with ALT>ULN at Baseline
17	Adverse Events: Brief Summary	Safety Analysis Set
18	All Treatment-Emergent Adverse Events	Safety Analysis Set
19	All Treatment-Emergent Adverse Events by Preferred Term	Safety Analysis Set
20	Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set
21	Grade 3 or 4 Treatment-Emergent Adverse Events	Safety Analysis Set
22	Grade 3 or 4 Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set
23	Grade 2, 3, or 4 Treatment-Emergent Adverse Events	Safety Analysis Set
24	Grade 2, 3, or 4 Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set
25	Adverse Events Leading to Permanent Discontinuation from Any Study Drug	Safety Analysis Set
26	Treatment-Emergent Serious Adverse Events	Safety Analysis Set
27	Treatment-Emergent Treatment-Related Serious Adverse Events	Safety Analysis Set
28	Treatment-Emergent Non-Serious AEs Occurring in At Least 5% of Subjects in Any Treatment Cohort	Safety Analysis Set
29	Adverse Events Leading to Modification or Interruption of Any Study Drug	Safety Analysis Set

Table Number	Title	Analysis Set
30.1	ALT (U/L) and Change from Baseline by Visit	Safety Analysis Set
30.2	AST (U/L) and Change from Baseline by Visit	Safety Analysis Set
30.3	Total Bilirubin (mg/dL) and Change from Baseline by Visit	Safety Analysis Set
30.4	Alkaline Phosphatase (U/L) and Change from Baseline by Visit	Safety Analysis Set
30.5	Hemoglobin (g/dL) and Change from Baseline by Visit	Safety Analysis Set
30.6	Subjects with Postbaseline Hemoglobin < 10 g/dL and < 8.5 g/dL	Safety Analysis Set
30.7	Reticulocytes (x10^3 /uL) and Change from Baseline by Visit	Safety Analysis Set
30.8	WBC (x10^3 /uL) and Change from Baseline by Visit	Safety Analysis Set
30.9	Neutrophils (x10^3 /uL) and Change from Baseline by Visit	Safety Analysis Set
30.10	Lymphocytes (x10^3 /uL) and Change from Baseline by Visit	Safety Analysis Set
30.11	Platelets (x10^3 /uL) and Change from Baseline by Visit	Safety Analysis Set
30.12	INR and Change from Baseline by Visit	Safety Analysis Set
30.13	Creatinine (mg/dL) and Change from Baseline by Visit	Safety Analysis Set
30.14	Estimated Glomerular Filtration Rate by Cockcroft-Gault (mL/min) and Change from Baseline by Visit	Safety Analysis Set
31	Treatment-Emergent Graded Laboratory Abnormalities	Safety Analysis Set
32	Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set
33.1	Systolic Blood Pressure (mmHg) and Change from Baseline by Visit	Safety Analysis Set
33.2	Diastolic Blood Pressure (mmHg) and Change from Baseline by Visit	Safety Analysis Set
33.3	Pulse (bpm) and Change from Baseline by Visit	Safety Analysis Set
34.1	PR Interval (ms) and Change from Baseline by Visit	Safety Analysis Set
34.2	QRS Interval (ms) and Change from Baseline by Visit	Safety Analysis Set
34.3	QT Interval (ms) and Change from Baseline by Visit	Safety Analysis Set
34.4	QTcF (ms) and Change from Baseline by Visit	Safety Analysis Set
34.5	Summary of On-Treatment ECG Abnormality	Safety Analysis Set
35.1	Echocardiogram: Ejection Fraction (%) and Change from Baseline by Visit	Safety Analysis Set
35.2	Echocardiogram: Fractional Shortening (%) and Change from Baseline by Visit	Safety Analysis Set
35.3	Echocardiogram: LVEDV (mL) and Change from Baseline by Visit	Safety Analysis Set
35.4	Echocardiogram: LVIDd (cm) and Change from Baseline by Visit	Safety Analysis Set
35.5	Echocardiogram: Shift Table of Baseline versus On-Treatment Diastolic Function Score Assessment by Visit	Safety Analysis Set
36.1	Individual Data and Summary Statistics of Plasma Intensive Concentration (ng/mL) at Protocol-Specified Sampling Times by Visit	SOF PK Analysis Set
36.2	Individual Data and Summary Statistics of Plasma Intensive Concentration (ng/mL) at Protocol-Specified Sampling Times by Visit	GS-566500 PK Analysis Set

Table Number	Title	Analysis Set
36.3	Individual Data and Summary Statistics of Plasma Intensive Concentration (ng/mL) at Protocol-Specified Sampling Times by Visit	GS-331007 PK Analysis Set
36.4	Individual Data and Summary Statistics of Plasma Intensive Concentration (ng/mL) at Protocol-Specified Sampling Times by Visit	RBV PK Analysis Set
36.5	Individual Data and Summary Statistics of Plasma Intensive Concentration (ng/mL) at Protocol-Specified Sampling Times by Visit - With Specified Sampling Data Removed	RBV PK Analysis Set
37.1	Individual Data and Summary Statistics of Plasma Trough Concentration (ng/mL) by Visit	SOF PK Analysis Set
37.2	Individual Data and Summary Statistics of Plasma Trough Concentration (ng/mL) by Visit	GS-566500 PK Analysis Set
37.3	Individual Data and Summary Statistics of Plasma Trough Concentration (ng/mL) by Visit	GS-331007 PK Analysis Set
37.4	Individual Data and Summary Statistics of Plasma Trough Concentration (ng/mL) by Visit	RBV PK Analysis Set
37.5	Individual Data and Summary Statistics of Plasma Trough Concentration (ng/mL) by Visit –With Specified Sampling Data Removed	RBV PK Analysis Set
38.1	Individual Estimate and Summary Statistics for Pharmacokinetic Parameters by Visit	SOF PK Analysis Set
38.2	Individual Estimate and Summary Statistics for Pharmacokinetic Parameters by Visit	GS-566500 PK Analysis Set
38.3	Individual Estimate and Summary Statistics for Pharmacokinetic Parameters by Visit	GS-331007 PK Analysis Set
38.4	Individual Estimate and Summary Statistics for Pharmacokinetic Parameters by Visit	RBV PK Analysis Set
38.5	Individual Estimate and Summary Statistics for Pharmacokinetic Parameters by Visit –With Specified Sampling Data Removed	RBV PK Analysis Set

Figure Number	Title	Analysis Set
1	Subject Disposition	Safety Analysis Set
2	Proportion of Subjects with HCV RNA < LLOQ While on Treatment by Visit	Full Analysis Set
2.1	Proportion of Subjects with SVR (HCV RNA < LLOQ) by Posttreatment Visit	Full Analysis Set
3.1	Mean (SD) Plasma Concentration - Time (0 hour - 12 hours) Profiles by Visit	SOF PK Analysis Set
3.2	Mean (SD) Plasma Concentration - Time (0 hour - 12 hours) Profiles by Visit	GS-566500 PK Analysis Set
3.3	Mean (SD) Plasma Concentration - Time (0 hour - 12 hours) Profiles by Visit	GS-331007 PK Analysis Set
3.4	Mean (SD) Plasma Concentration - Time (0 hour - 12 hours) Profiles by Visit	RBV PK Analysis Set
3.5	Median (Q1, Q3) Plasma Concentration - Time (0 hour - 12 hours) Profiles by Visit	SOF PK Analysis Set
3.6	Median (Q1, Q3) Plasma Concentration - Time (0 hour - 12 hours) Profiles by Visit	GS-566500 PK Analysis Set
3.7	Median (Q1, Q3) Plasma Concentration - Time (0 hour - 12 hours) Profiles by Visit	GS-331007 PK Analysis Set
3.8	Median (Q1, Q3) Plasma Concentration - Time (0 hour - 12 hours) Profiles by Visit	RBV PK Analysis Set

Listing Number	Title	Analysis Set
1	Inclusion and Exclusion Criteria	Subjects Not Treated
2	Subjects Enrolled and Treated Who Did Not Meet Eligibility Criteria	Safety Analysis Set
3	Subject Disposition	Safety Analysis Set
4	Subject Demographics and Baseline Characteristics	Safety Analysis Set
5	Cirrhosis Determination	Safety Analysis Set
6	Medical History	Safety Analysis Set
7	Study Drug Administration	Safety Analysis Set
8	Study Drug Accountability and Adherence	Safety Analysis Set
9	Prior and Concomitant Medications	Safety Analysis Set
10	HCV RNA (log10 IU/mL) and Change from Baseline	Safety Analysis Set
11	Subjects with Virologic Failure	Safety Analysis Set
12	Subjects with 'Other' Virologic Outcome	Safety Analysis Set
13	Subjects with Postbaseline Hemoglobin < 10 g/dL and <8.5 g/dL	Safety Analysis Set
14	All Adverse Events	Safety Analysis Set
15	Grade 3 or 4 Adverse Events	Safety Analysis Set
16	Serious Adverse Events	Safety Analysis Set
17	Adverse Events Leading to Premature Discontinuation from Any Study Drug	Safety Analysis Set
18	Deaths	Safety Analysis Set
19	Central Laboratory (Covance) Reference Ranges	Safety Analysis Set
20	Subjects with Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set
21	Screen Labs: HBsAg, Anti-HIV Ab, Anti-HCV Ab, HbA1c, and Serum Beta hCG	Safety Analysis Set
22	Hematology: Hematocrit, Hemoglobin, Reticulocyte Count, MCV, RBC, WBC, and Platelets	Safety Analysis Set
23	Hematology: WBC, Neutrophils, and Lymphocytes	Safety Analysis Set
24	Hematology: Eosinophils, Basophils, and Monocytes	Safety Analysis Set
25	Chemistry: Sodium, Potassium, Serum Creatinine, Estimated GFR (Cockcroft-Gault), and Glucose	Safety Analysis Set
26	Chemistry: AST, ALT, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, GGT, and Albumin	Safety Analysis Set
27	Coagulation and Other Laboratory Tests: INR, APTT, and TSH	Safety Analysis Set
28	Vital Signs	Safety Analysis Set
29	Height, Weight, and BMI	Safety Analysis Set
30	Overall Assessment of Electrocardiogram Results	Safety Analysis Set
30.1	Electrocardiogram measurements	Safety Analysis Set

Listing Number	Title	Analysis Set
31	Echocardiogram Results	Safety Analysis Set
32	Echocardiogram: Ejection Fraction and LVEDV	Safety Analysis Set
33	Dialysis	Safety Analysis Set
34	Pregnancy	Safety Analysis Set
35	Prior HCV Treatment and Response	Safety Analysis Set
36	Plasma PK Sampling Details and PK Concentrations	PK Analysis Set

Appendix 2. Schedule of Assesments for Cohorts 1 and 2

Study Procedure	Screen[a]	Day 1[b]	Treatment Visits[i]										Post-Treatment Visits[j]			ET[c]
			Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 4	Week 12	Week 24	
Written Informed Consent	X															
Medical History	X															
HCV RNA Genotype	X															
IL28B Genotyping	X															
HbA1c	X															
HCV, HBV, HIV Serology	X															
TSH	X															
Physical Exam, including Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X			X		X		X	X	X	X	X	X	X	X
Echocardiogram	X								X			X				
Height	X															
Weight	X															
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Screen[a]	Day 1[b]	Treatment Visits[i]										Post-Treatment Visits[j]			ET[c]
			Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 4	Week 12	Week 24	
Coagulation (PT, PTT, and INR)	X	X							X				X			X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV RNA Viral Load	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV RNA Sequencing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[e]	X	X			X		X		X	X	X	X	X	X	X	X
Creatinine Clearance	X															
Optional Pharmacogenetic Sample[k]		X														
Intensive PK				X[f]					X[f]							
Trough PK Sample[g]			X		X	X	X	X		X	X	X				X
Archive Plasma Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration		X	Weeks 1-24													

Study Procedure	Screen[a]	Day 1[b]	Treatment Visits[i]										Post-Treatment Visits[j]			ET[c]
			Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 4	Week 12	Week 24	
Review Dosing Diary/Perform Accountability[h]			X	X	X	X	X	X	X	X	X	X				
AEs/ Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X			X

a Screening evaluations must be completed within 42 days prior to Day 1.

b Day 1 tests and procedures must be completed prior to administration of the first dose of study drugs

c Within 72 hours of permanently discontinuing study drug.

d Full PE at Day 1 and ET visits only; symptom-directed PE at all other timepoints. Vital signs include blood pressure, pulse, respiration rate, and temperature

e Females of childbearing potential only. To confirm eligibility at Day 1, a urine pregnancy test may be collected for subjects able to pass urine. For subjects unable to pass urine, a serum pregnancy test at Day 1 must be performed at a local lab prior to dosing to confirm eligibility along with sample collected and send to central lab. During post-treatment of the study, serum or urine pregnancy testing will occur every month during non-clinic post treatment visits. The subject will be contacted by telephone to confirm that pregnancy testing has been performed post-treatment during non-clinic visits.

f Intensive plasma PK evaluations will be assessed at the following timepoints: 0 (predose -5 minutes), 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose.

g Trough plasma PK samples will be drawn prior to dosing.

h Dosing Diaries will be completed for all non-observed doses and will be reviewed at every visit. Unused study drug will be returned to perform study drug accountability in the original container at each visit following Day 1 for study drug compliance assessment.

i A window of ± 2 days is allowed for the treatment visits on weeks 1, 2, and 12. A window of ± 4 days is allowed for the treatment visits weeks, 4-10, and 16-24. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

j A window of ± 7 days is allowed for the post treatment visits.

k The sample should be collected on Day 1 prior to dosing, but may be collected at any time during the study or at a separate post-study visit, if necessary.

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