STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Ledipasvir/Sofosbuvir in Subjects with Genotype 1, 4, 5 and 6 Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease
Name of Test Drug:	ledipasvir/sofosbuvir (LDV/SOF)
Study Number:	GS-US-337-4063
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Analysis Plan Author:	PPD

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LIST OF IN-TEXT-TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (also SGPT)
APRI	AST:platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
BPM	beats per minute
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
DAA	direct acting antiviral
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ESRD	End Stage Renal Disease
FAS	full analysis set
FDC	fixed-dose combination
FU	follow-up
GT	genotype
HCV	hepatitis C virus
HLGT	high level group term
HLT	high level term
HRQoL	health related quality of life
INR	international normalized ratio of prothrombin time
IWRS	interactive web response system
LDV	ledipasvir
LLOQ	lower limit of quantitation
LLT	lower level term
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
Peg-IFN	pegylated interferon
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan

SD	standard deviation
SOC	system organ class
SOF	sofosbuvir (Sovaldi®)
SVR	sustained virologic response
SVRx	sustained virologic response x weeks after stopping study drug
TE	treatment-emergent
TFLs	tables, figures, and listings
TND	target not detected
ULN	upper limit of normal
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 tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-337-4063. This SAP is based on the amended study protocol dated 02 March 2017 and the electronic case report form (eCRF). The SAP will be finalized prior to database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are:

- To evaluate the antiviral efficacy of treatment with ledipasvir/sofosbuvir (LDV/SOF) for 8, 12, or 24 weeks in subjects with chronic hepatitis C virus (HCV) infection who are on dialysis for End Stage Renal Disease (ESRD), 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 each treatment regimen

The secondary objectives of this study are:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of each study treatment regimen (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to LDV and SOF during treatment and after cessation of treatment
- To evaluate the steady-state pharmacokinetics of LDV and SOF and its metabolites in subjects who are on dialysis for (ESRD)

The exploratory objectives of this study are:

1.2. Study Design

This is a multicenter, open-label Phase 2 study that will evaluate the safety, tolerability, and antiviral efficacy of LDV/SOF in subjects on dialysis for ESRD with genotype 1, 4, 5, or 6 HCV infection.

Approximately 100 subjects with genotype 1, 4, 5, or 6 HCV infection will be enrolled to 1 of 3 groups and will receive treatment with LDV/SOF for 8, 12, or 24 weeks. The treatment group to which subjects are assigned will be determined by genotype, the absence or presence of cirrhosis and whether the subject is treatment naïve or treatment experienced.

Group 1: Treatment naïve genotype 1 subjects without cirrhosis will be treated with LDV/SOF for 8 weeks

Group 2: Treatment experienced genotype 1 subjects and treatment naïve or treatment experienced genotype 4, 5, and 6 subjects without cirrhosis will be treated with LDV/SOF for 12 weeks

Group 3: Subjects with compensated cirrhosis will be treated with LDV/SOF for 24 weeks

The total time to complete all study visits is approximately 52 weeks (42 weeks for those requiring extension of the Screening period):

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

The schedule of assessments is provided as an appendix to the SAP (Appendix 1).

1.3. Sample Size and Power

With a sample size of 100 subjects, a 2-sided 95% exact confidence interval will extend at the most 20% in length.

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 data in order to protect subject welfare and preserve study integrity. The DMC will recommend to the sponsor 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 whether the study should continue with modifications.

Reviews will be conducted after the first 12 subjects have completed 12 weeks of treatment, or early termination. After the initial meeting, safety reviews will be conducted at approximately 3 month intervals during the trial until the last enrolled subject completes study treatment. These safety reviews will alternate between the following:

- A review by the DMC chair of all SAEs and deaths
- A review of safety data by the DMC meeting as specified in the DMC charter.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

2.2. Interim Analysis

2.2.1. Posttreatment Week 4 Analysis

A posttreatment Week 4 analysis will be conducted for administrative purposes after all subjects complete the posttreatment Week 4 visit or prematurely discontinue from study. All safety and efficacy data through the posttreatment Week 4 visit will be included. The results will be restricted to a limited group of individuals within Gilead. There will be no changes to the study design, study conduct, or the sample size as a result of this administrative analysis.

2.2.2. Posttreatment Week 12 Analysis

The analysis for the primary efficacy endpoint SVR12 will be conducted when all subjects have completed the posttreatment Week 12 visit or have prematurely discontinued from study. All the safety and efficacy data through the Posttreatment Week 12 visit will be cleaned, finalized and included for the analysis.

2.3. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

3.1. Analysis Sets

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

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all subjects enrolled in the study after screening. Subjects are grouped within the All Enrolled Analysis Set by treatment group to which they were enrolled.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes subjects who are enrolled into the study and received at least 1 dose of study drug. Subjects are grouped within the FAS by genotype and treatment group to which they were enrolled.

This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who received at least 1 dose of study drug. Subjects are grouped within the Safety Analysis Set according to the treatment they actually received.

This is the primary analysis set for safety analyses.

3.1.4. Pharmacokinetic (PK) Analysis Set

The PK Analysis Set includes all subjects who took at least 1 dose of the study drug and have at least 1 nonmissing postdose concentration value for the corresponding analyte in plasma. The analytes of interest may include LDV and SOF (and its metabolites GS-566500 and GS-331007).

3.1.4.1. Intensitive PK Substudy Analysis Set

CCI [redacted]

CCI [redacted]

3.1.4.2. CCI [redacted]

CCI [redacted]

3.2. Subject Grouping

For analyses based on the All Enrolled Analysis Set, FAS, or demographic and baseline characteristics tables, subjects will be grouped according to the HCV genotype and treatment group. Unless otherwise specified, groups by genotype including GT1a, GT1b, GT1 Other, GT1 total, GT4, GT5, and GT6, Indeterminate, and Total.

For analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received is defined as the enrolled treatment except for subjects who received treatment that differs from the enrolled treatment for the entire treatment duration. In this case, the actual treatment received is defined as the treatment received for the entire treatment duration.

3.3. Examination of Subject Subsets

Subject subsets within each genotype will also be explored by baseline characteristics for the primary efficacy endpoint, SVR12. The baseline characteristics include the following:

- age (< 65 years, ≥ 65 years)
- sex (male, female)
- cirrhosis (presence, absence)
- prior HCV treatment experience (treatment naive, treatment experienced)
- prior HCV treatment for treatment experienced subjects [DAA Naive (Peg-IFN + RBV, Other)]
- HCV genotype
- baseline HCV RNA (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- baseline body mass index (BMI) (< 30 kg/m^2, ≥ 30 kg/m^2)
- baseline alanine aminotransferase (ALT) (≤ 1.5 × upper limit of normal (ULN), > 1.5 × ULN)

- IL28B (CC, non-CC; with non-CC further broken down to CT, TT)
- type of current dialysis (Hemodialysis, Peritoneal Dialysis)
- adherence to study regimen (< 80%, ≥ 80%)

3.4. Missing Data and Outliers

3.4.1. Missing Data

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

For missing last dosing date of study drug, imputation rules are described in Section 3.6.1. The handling of missing or incomplete dates for adverse event (AE) onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4

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

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

For the analyses of continuous HCV RNA efficacy data, when and only when a missing HCV RNA value is imputed as < LLOQ TND or < LLOQ detected according to the imputation rule described above, the corresponding continuous value will be imputed to LLOQ − 1 IU/mL. No other imputation will be performed for continuous HCV RNA data.

For health-related quality of life data including SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C, missing data at on-treatment visits, and posttreatment follow-up Week 12 (FU-

12) visit will not be imputed. For SF-36, if there are multiple responses to an item, the response will be set to missing.

3.4.2. Outliers

Outliers will be identified during data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.5. Data Handling Conventions and Transformations

By-subject listings will be presented for all subjects in the Safety Analysis Set and sorted by subject ID number, visit date, and time (if applicable) unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within subject.

Age (in years) on the date of the first dose of study drug and sex at birth will be used for analyses and presentation in listings.

If a subject was not dosed with study drug at all, then the date the informed consent was signed will be used instead of the first dose date of study drug.

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

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

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

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

COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 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, then the result will be reported as the "<< numeric value>> IU/mL." This result will be referred to in this document as the numeric result or as "≥ LLOQ detected" for categorical result.

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

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

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

For numerical HCV RNA data, values below LLOQ will be set to the LLOQ − 1 IU/mL (ie, 14 HCV RNA IU/mL). HCV RNA values returned as "No HCV RNA 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).

Natural logarithm-transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the lower limit of quantitation (LLOQ) at postbaseline time points.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

3.6. Visit Windows

3.6.1. 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 will be the end date on study drug administration eCRF for the record where the "subject permanently discontinued" flag is 'Y'. The last dose date will be defined as the maximum of the last dose dates of the study drugs. If there are subjects for whom the date of last study drug is unknown due to the reason that the subject was lost to follow-up and not able to be contacted, the date of last dose will be estimated using the maximum of nonmissing study drug start or stop dates, visit dates, and laboratory collection dates (posttreatment visits and unscheduled visits are not included).

3.6.2. Analysis Windows

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

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

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

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

Nominal Visit	Nominal Day (Lower Limit, Upper Limit) 8-Week Groups	Nominal Day (Lower Limit, Upper Limit) 12-Week Groups	Nominal Day (Lower Limit, Upper Limit) 24-Week Groups
Baseline	1 (none, 1)	1 (none, 1)	1 (none, 1)
Week 2	14 (12, 21)	14 (12, 21)	14 (12, 21)
Week 4	28 (22, 35)	28 (22, 35)	28 (22, 35)
Week 6	42 (36, 49)	42 (36, 49)	42 (36, 49)
Week 8	56 (50, ≥ 57)	56 (50, 70)	56 (50, 70)
Week 12	NA	84 (71, ≥ 85)	84 (71, 98)
Week 16	NA	NA	112 (99, 126)
Week 20	NA	NA	140 (127, 154)
Week 24	NA	NA	168 (155, >=168)

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

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

Nominal FU [a] Visit	HCV RNA			Vital Signs and Safety Laboratory Data [b]		
	Nominal FU Day	Lower Limit	Upper Limit	Nominal FU Day	Lower Limit	Upper Limit
FU-4	28	21	69	28	4	30
FU-12	84	70	146	NA	NA	NA
FU-24	168	147	210	NA	NA	NA

a. FU-x visit = posttreatment Week-x follow-up visit.
b. Vital signs and safety labs will only be summarized for the FU-4 visit (up to 30 days after last dose).

3.6.3. Selection of Data in the Event of Multiple Records in an Analysis Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

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

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, average (arithmetic mean) will be used for the baseline value.
- For postbaseline visits:
  - The record closest to the nominal day for that visit will be selected except for HCV RNA posttreatment follow-up visits, for which the latest record in the analysis window will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

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

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided for each country 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 treatment group. This summary will present the number of subjects screened, the number of subjects not enrolled, the number of subjects enrolled, the number of subjects enrolled but never treated, 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 of study

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

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

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

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 by a flowchart.

The following by-subject listings will be provided by subject ID number in ascending order to support the above summary tables:

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

4.2. Extent of Exposure

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

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dose date minus first dose date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.8 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), Week 16 (Day 112), Week 20 (Day 140), and Week 24 (Day 168). A 3-day window is applied to the last planned on-treatment visit to match with the protocol-specified visit window, i.e. number of subjects exposed through Week 8 will be calculated as the number of subjects who were exposed to study drug for at least 53 days. Number of subjects exposed through week 12 will be calculated as the number of subjects who were exposed to study drug for at least 81 days. Number of subjects exposed through week 24 will be calculated as the number of subjects who were exposed to study drug for at least 165 days.

4.2.2. Adherence to Study Drug

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

$$\text{Total Number of Doses Administered} = \left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets returned}\right)$$

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

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

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

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

In this study, the total amount of LDV/SOF prescribed for 8 weeks would require 56 tablets, for 12 weeks would require 84 tablets, and for 24 weeks would require 168 tablets.

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

Descriptive statistics for the level of adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) with the number and percentage of subjects belonging to adherence categories (eg, {< 80%, ≥ 80 to < 90%, ≥ 90%}) will be provided by treatment group for the Safety Analysis Set. Categorical displays also will be provided for the number of subjects who are at least 80% adherent to their drug regimen (ie, adherence is ≥ 80% for the study drugs).

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 DATA

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by genotype and using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for age and BMI (kg/m^2), and using the numbers and percentages of subjects for age categories (< 65 years, ≥ 65 years), BMI categories (< 30 kg/m^2, ≥ 30 kg/m^2), sex, race, and ethnicity. Age is calculated in years at the date of initial study drug administration. If a subject did not receive study drug after enrollment, the subject's age will be calculated from the date that the subject signed the informed consent form. The summary of demographic data will be provided for the Safety Analysis Set by HCV genotype and treatment group.

A by-subject demographic listing, which includes first dose date, will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- HCV genotype and subtypes
- IL28B (CC, Non-CC (including CT, and TT))
- baseline HCV RNA as a continuous variable and as categories (< 800,000 IU/mL, ≥800,000 IU/mL)
- baseline ALT as a continuous variable and for categories (≤ 1.5 × ULN, > 1.5 × ULN)
- prior HCV treatment experience (treatment naïve, treatment experienced)
- cirrhosis (presence, absence, missing)
- renal transplant (yes, no)
- prior HCV treatment for treatment experienced subjects [DAA Naive (Peg-IFN + RBV, Other]
- prior HCV treatment response (non-responder, relapse/breakthrough, early treatment discontinuation, and unknown) for treatment experienced subjects
- type of current dialysis (Hemodialysis, Peritoneal Dialysis)

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

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

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

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 the treatment duration, and the prior HCV treatment response.

5.3. Medical History

Medical history collected at screening will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized by system organ class (SOC), preferred term (PT), treatment group, and overall. Subjects who report 2 or more medical history items that are coded to the same SOC and/or PT will be counted only once by the unique coded term in the summary. The summary will be provided for the Safety Analysis Set. No inferential statistics will be generated.

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).

A by-subject listing of renal transplant will be provided by subject ID number.

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 for this assay is 15 IU/mL.

6.1.2. Primary Analysis of the Primary Efficacy Endpoint

The SVR12 rate in each of genotype will be calculated along with 2-sided 95% exact CI based on Clopper-Pearson method {Clopper 1934}.

6.1.3. Subgroup Analysis of the Primary Efficacy Endpoint

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

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

Secondary efficacy endpoints include the following:

- The percentage of subjects with HCV RNA < LLOQ at 4 and 24 weeks after discontinuation of treatment (SVR4 and SVR24)
- The percentage of subjects with HCV RNA < LLOQ while on treatment by study visit
- HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through end of treatment (EOT)
- The percentage of subjects with virologic failure as the following:
  - On-treatment virologic failure
    - HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ, while on treatment, confirmed with 2 consecutive values (note, second confirmation value can

be posttreatment), or last available on-treatment measurement with no subsequent follow up values (ie, breakthrough)

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

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

— Relapse

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

- The steady-state pharmacokinetics of LDV and SOF and its metabolites in subjects who are on dialysis for End Stage Renal Disease (ESRD)

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

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

For analyses of HCV RNA < LLOQ by visit while on treatment and during the posttreatment (SVR) follow-up period, subjects will be assigned a value at each visit based on the analysis visit windows specified in Section 3.6.2. Missing values will be imputed based on the categorical imputation rules described in Section 3.4.1. The 2-sided 95% exact CI based on Clopper-Pearson method will be provided for the percentage of subjects with HCV RNA < LLOQ at each visit within each 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.

Graphs for the percentage of subjects with HCV RNA < LLOQ over time during treatment will be displayed by genotype.

Summary statistics will be presented for absolute values and change from baseline in HCV RNA (log_{10} IU/mL), by genotype and by visit through 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. Plots of the mean ± SD and median (Q1, Q3) of absolute values and changes from baseline in HCV RNA through EOT will be presented.

For the SVR12 endpoint analysis, a summary table of the number and percentage of subjects with SVR12, virologic failure, 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/no). Subjects who do not achieve SVR12 and do not meet criteria for virologic failure will be categorized as "Other." The denominator for relapse will be the number of subjects who had HCV RNA < LLOQ on their last observed on-treatment HCV RNA measurement; otherwise, the denominator will be the number of subjects in the FAS.

A concordance table between SVR12 and SVR24 will be provided for each genotype. Subjects with both observed SVR12 and observed SVR24 data will be included for this analysis.

Drug resistant substitutions will be analyzed and reported based on change from baseline sequence and/or change from HCV genotype reference strain as part of the Virology Study Report.

6.3. Exploratory Efficacy Endpoints

CCI [redacted]

CCI [redacted]

6.4. Changes From Protocol-Specified Efficacy Analyses

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

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

The primary safety endpoint is any AE that led to permanent discontinuation of study drug.

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

Serious adverse events will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

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

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

7.1.5.2. Incomplete Dates

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

7.1.6. Summaries of Adverse Events and Deaths

A brief high-level summary of TEAEs will be provided by the number and percentage of subjects who had the following: any AE, any AE of Grade 3 or above, any AE of Grade 2 or above, any treatment-related AE, any treatment-related AE of Grade 3 or above, any treatment-related AE of Grade 2 or above, any SAE, any treatment-related SAE, and any AE that led to premature discontinuation of LDV/SOF, and any AE that led to interruption of LDV/SOF. 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 LDV/SOF
- Adverse Events Leading to Interruption of LDV/SOF

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 LDV/SOF
- AEs leading to interruption of LDV/SOF

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 LDV/SOF
- AEs leading to interruption of LDV/SOF
- AE with changes other than resolution dates between the SVR12 and SVR24 analyses (provided only at the final analysis)

All deaths (including those that are treatment emergent and those that are not treatment emergent) observed during the study will also be summarized.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the safety analysis set and will include data collected up to last dose of any 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, serum chemistry, coagulation, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided for ALT, aspartate aminotransferase (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 each postbaseline visit
- Change from baseline at each postbaseline visit

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

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

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.3 (Selection of Data in the Event of Multiple Records in a Window).

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.

7.2.2. Graded Laboratory Values

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

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

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

7.2.2.2. Summaries of Laboratory Abnormalities

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

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

- Graded laboratory abnormalities
- Grade 3 or above laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after last dose of study drug for the laboratory parameter of interest.

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

7.3. Body Weight, Height, and Vital Signs

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

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.3 (Selection of Data in the Event of Multiple Records in a Window). No inferential statistics will be generated.

A by-subject listing of vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min], respiration [breaths/min], and body temperature [°C]) will be provided by subject ID number and visit in chronological order. In the same manner, a by-subject listing of body weight, height, and BMI will be provided separately.

7.4. 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 prior to the initial study drug dosing date.
- Concomitant medications: any medications initially taken on or after the initial study drug dosing date and within the study drug's treatment period (including study drug's therapeutic reach).
- Prior and concomitant medications: any medications taken both prior to and on or after the initial study drug dosing date and within the study drug's treatment period (including study drug's therapeutic reach); or any medications taken prior to the baseline visit date with a stop date of "continuing".

Concomitant medications will be summarized by preferred name 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 preferred 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 initial study drug dosing date or start date that is after the last study drug dosing date will be excluded from a concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the initial study drug dosing date will be excluded from the concomitant medication summary. If a partial start date is entered, then any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing dates will be included in the concomitant medication summary. Summaries will be based on the Safety Analysis Set. No inferential statistics will be generated.

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

7.5. Electrocardiogram Results

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

7.6. Other Safety Measures

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

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

Plasma concentrations of SOF (and its metabolites GS-566500 and GS-331007) and LDV in plasma will be determined using validated bioanalytical assays.

Population PK models for SOF, GS-331007 and LDV, previously developed for the Phase 2/3 LDV/SOF US NDA population analyses, will be applied to the data from all PK samples collected in this study. Details of the population PK analysis will be provided in a separate population PK analysis plan.

The systemic concentration of study drug prior to and immediately following hemodialysis will also be summarized using descriptive summary statistics (sample size, mean, SD, coefficient of variation [%CV], median, Q1, Q3, minimum, maximum). For concentration values BLQ, the number of subjects with values of BLQ will be presented.

CCI

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9. REFERENCES

Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Dec. Biometrika 1934;26 (4):pp. 404-13.

10. SOFTWARE

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

WinNonlin® Phoenix® software v6.3 (Pharsight Corporation, Mountain View, CA).

11. SAP REVISION

12. APPENDICES

Appendix 1 Schedule of Assessments

Appendix 1 Schedule of Assessments

Appendix Table 1. Screening/Baseline/ On-Treatment and Post Treatment Study Visits for Group 1

			On-treatment Study Week (± 3 days)				Post treatment Study Week (± 5 days)[i]		
	Screen	**Baseline/Day 1[a]**	**2**	**4**	**6**	**8/ET**	**4**	**12**	**24**
Informed Consent	X								
Determine Eligibility	X	X							
Medical History	X								
Physical Examination	X	X				X	X	X	X
Height	X								
Weight	X	X				X			
Vital Signs	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X				X			
AEs /SAE[b]	X	X	X	X	X	X	X	X[b]	X[b]
Concomitant Medications	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling	X	X		X		X	X		
Health Related Quality of Life[c]		X				X		X	
Review of Study Medication Compliance			X	X	X	X			
Study Drug Dispensing[d]		X		X					
Laboratory Assessments									
Hematology, Chemistry	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X				X			
HCV RNA	X	X	X	X	X	X	X	X	X

	Screen	Baseline/Day 1[a]	On-treatment Study Week (± 3 days)				Post treatment Study Week (± 5 days)[i]		
			2	4	6	8/ET	4	12	24
Viral Sequencing/Phenotyping[e]		X	X	X	X	X	X	X	X
Sparse PK			X	X	X	X			
Intensive PK [g,h]					X[h]	X[h]			
Hemodialysis PK [g,i]					X[i]	X[i]			
Serum β-hCG Pregnancy Test[j]	X	X		X		X	X		
Serum Drug Screen	X								
HCV & IL28B Genotyping	X								
HCV, HIV, HBV Serology	X								
HBV DNA[k]		X		X		X	X	X	X
HbA1c	X								
Fibrotest ®	X								
Archive Sample[f]		X				X			
Pharmacogenomic Sample[f]		X							
CD4 Cell Count [l]	X	X		X		X	X		
HIV-1 RNA[l]	X	X		X		X	X		

a Baseline/Day 1 assessments must be performed prior to dosing
b Only SAEs will be collected at post-treatment Weeks 12 and 24.
c Health Related Quality of Life (HRQoL) Surveys (e.g., SF-36, CLDQ-HCV, FACIT-F and WPAI) will be conducted for all subjects where the surveys are available at Day 1, Week 8, ET (if applicable), and posttreatment Week 12.
d The IWRS will provide direction on the specifics of each subject's study drug dispensing
e. Plasma samples will be collected for possible viral resistance testing and other virology studies
f Subjects may opt out of archive/pharmacogenomics sample collection.
g Only for subjects who have provided consent for this sample and testing.
h Intensive PK evaluations will be assessed at the following timepoints: 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6 ,8, 10, and 12 hours post dose once either on Week 6 or 8, per investigator discretion.

i Hemodialysis PK blood samples will be collected at one hemodialysis session between Week 6 and Week 12, inclusive (as appropriate based on treatment group), evaluations will include: 1. A single blood sample will be collected within 10 minutes before hemodialysis initiates. 2. During hemodialysis, a single sample will be collected from both the arterial and venous sides of the dialyzer within 1 hour of hemodialysis concluding. 3. Finally, a single blood sample will be collected within 10 minutes after hemodialysis concludes.

j For females of child bearing potential only

k. Only for subjects who are HBcAb+ at Screening

l For HIV/HCV co-infected subjects only.

Appendix Table 2. Screening/Baseline/ On-Treatment and Post Treatment Study Visits for Group 2

			On-treatment Study Week (± 3 days)					Post treatment Study Week (± 5 days)[i]		
	Screen	Baseline/Day 1[a]	2	4	6	8	12/ET	4	12	24
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X					X	X	X	X
Height	X									
Weight	X	X					X			
Vital Signs	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X					X			
AEs /SAE[b]	X	X	X	X	X	X	X	X	X[b]	X[b]
Concomitant Medications	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling	X	X		X		X	X	X		
Health Related Quality of Life[c]		X					X		X	
Review of Study Medication Compliance			X	X	X	X	X			
Study Drug Dispensing[d]		X		X		X				
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X					X			
HCV RNA	X	X	X	X	X	X	X	X	X	X
Viral Sequencing/Phenotyping[e]		X	X	X	X	X	X	X	X	X

	Screen	Baseline/Day 1[a]	On-treatment Study Week (± 3 days)					Post treatment Study Week (± 5 days)[i]		
			2	4	6	8	12/ET	4	12	24
Sparse PK			X	X	X	X	X			
Intensive PK [g,h]					X[h]	X[h]	X[h]			
Hemodialysis PK [g,i]					X[i]	X[i]	X[i]			
Serum β-hCG Pregnancy Test[j]	X	X		X		X	X	X		
Serum Drug Screen	X									
HCV & IL28B Genotyping	X									
HCV, HIV, HBV Serology	X									
HBV DNA[k]		X		X		X	X	X	X	X
HbA1c	X									
Fibrotest ®	X									
Archive Sample[f]		X					X			
Pharmacogenomic Sample[f]		X								
CD4 Cell Count [l]	X	X		X		X	X	X		
HIV-1 RNA[l]	X	X		X		X	X	X		

a Baseline/Day 1 assessments must be performed prior to dosing
b Only SAEs will be collected at post-treatment Weeks 12 and 24.
c Health Related Quality of Life (HRQoL) Surveys (e.g., SF-36, CLDQ-HCV, FACIT-F and WPAI) will be conducted for all subjects where the surveys are available at Day 1, Week 8, ET (if applicable), and posttreatment Week 12.
d The IWRS will provide direction on the specifics of each subject's study drug dispensing
e. Plasma samples will be collected for possible viral resistance testing and other virology studies
f Subjects may opt out of archive/pharmacogenomics sample collection.
g Only for subjects who have provided consent for this sample and testing.
h` Intensive PK evaluations will be assessed at the following timepoints: 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6 ,8, 10, and 12 hours post dose once either on Week 6 or 8, per investigator discretion.

i Hemodialysis PK blood samples will be collected at one hemodialysis session between Week 6 and Week 12, inclusive (as appropriate based on treatment group), evaluations will include: 1. A single blood sample will be collected within 10 minutes before hemodialysis initiates. 2. During hemodialysis, a single sample will be collected from both the arterial and venous sides of the dialyzer within 1 hour of hemodialysis concluding. 3. Finally, a single blood sample will be collected within 10 minutes after hemodialysis concludes.

j For females of child bearing potential only

k. Only for subjects who are HBcAb+ at Screening

l For HIV/HCV co-infected subjects only.

Appendix Table 3. Screening/Baseline/ On-Treatment and Post Treatment Study Visits for Group 3

			On-Treatment Week (±3 Days)								Post-Treatment Week (±5 Days)		
	Screen	Baseline/Day1[a]	2	4	6	8	12	16	20	24/ET	4	12	24
Informed Consent	X												
Determine Eligibility	X	X											
Medical History	X												
Physical Examination	X	X								X	X	X	X
Height	X												
Weight	X	X								X			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X								X			
AEs/SAE[b]	X	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling	X	X		X		X	X	X	X	X	X		
Health-Related Quality of Life[c]		X								X		X	
Review of Study Medication Compliance			X	X	X	X	X	X	X	X			
Study Drug Dispensing[d]		X		X		X	X	X	X				
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X								X			
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral Sequencing/		X	X	X	X	X	X	X	X	X	X	X	X

	Screen	Baseline/Day1[a]	On-Treatment Week (±3 Days)								Post-Treatment Week (±5 Days)		
			2	4	6	8	12	16	20	24/ET	4	12	24
Phenotyping[e]													
Sparse PK			X	X	X	X	X	X	X	X			
Intensive PK [g, h]					X[h]	X[h]	X[h]						
Hemodialysis PK[g, i]					X[i]	X[i]	X[i]						
Serum β-hCG Pregnancy Test[j]	X	X		X		X	X	X	X	X	X		
Serum Drug Screen	X												
HCV & IL28B Genotyping	X												
HCV, HIV, HBV Serology	X												
HBV DNA[k]		X		X		X	X	X	X	X	X	X	X
HbA1c	X												
Fibrotest®	X												
Archive Sample[f]		X								X			
Pharmacogenomic Sample[f]		X											
CD4 Cell Count[l]	X	X		X		X	X	X	X	X	X		
HIV-1 RNA[l]	X	X		X		X	X	X	X	X	X		

a Baseline/Day 1 assessments must be performed prior to dosing
b Only SAEs will be collected at post-treatment Weeks 12 and 24.
c Health Related Quality of Life (HRQoL) Surveys (e.g., SF-36, CLDQ-HCV, FACIT-F and WPAI) will be conducted for all subjects where the surveys are available at Day 1, Week 24, ET (if applicable), and posttreatment Week 12.
d The IWRS will provide direction on the specifics of each subject's study drug dispensing
e Plasma samples will be collected for possible viral resistance testing and other virology studies
f Subjects may opt out of archive/pharmacogenomics sample collection.

g Only for subjects who have provided consent for this sample and testing.
h Intensive PK evaluations will be assessed at the following timepoints: 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6 ,8, 10, and 12 hours post dose once either on Week 6 8, or 12 per investigator discretion.
i Hemodialysis PK blood samples will be collected at one hemodialysis session between Week 6 and Week 12, inclusive (as appropriate based on treatment regimen), evaluations will include: 1. A single blood sample will be collected within 10 minutes before hemodialysis initiates. 2. During hemodialysis, a single sample will be collected from both the arterial and venous sides of the dialyzer within 1 hour of hemodialysis concluding. 3. Finally a single blood sample will be collected within 10 minutes after hemodialysis concludes.
j For females of child bearing potential
k. Only for subjects who are HBcAb+ at Screening
l For HIV/HCV co-infected subjects only.