STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir, With or Without Ribavirin, in HCV Infected Subjects Who Have Failed Prior Treatment With Sofosbuvir-based Therapies
Name of Test Drug:	Ledipasvir/Sofosbuvir (Harvoni) Fixed-Dose Combination
Study Number:	GS-US-337-1746
Protocol Version/Date:	Amendment 2: 23 July 2015
Analysis Type:	SVR12 and Final Analysis
Analysis Plan Version:	Version 1
Analysis Plan Date:	28 March 2017
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
APRI	AST platelet ratio index
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BMI	body mass index
BPM	beats per minute
CI	confidence interval
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FAS	full analysis set
FDC	fixed dose combination
FU	follow-up
GSI	Gilead Sciences, Inc.
HCV	hepatitis C virus
HLGT	high level group term
HLT	high level term
ID	identification
IWRS	Interactive Web Response System
LLT	lower level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
INR	international normalized ratio
NI	non-inferiority
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
RAV	resistance-associated variants
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error

SOC	system organ class
SOF	sofosbuvir (Sovaldi®)
SVR	sustained virologic response
SVRx	sustained virologic response x weeks after stopping study drug
TE	treatment-emergent
TFLs	tables, figures, and listings
TND	target not detected
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in the tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-337-1746. The SAP is based on the study protocol amendment 2 dated 23 July 2015 and the electronic case report form (eCRF). However, the study was early terminated after 87 subjects were enrolled due to lack of feasibility of enrolling originally planned 430 subjects. Statistical analysis methods also changed corresponding to the sample size change. Detailed changes are documented in Section 6.4.

Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the efficacy of treatment with ledipasvir/sofosbuvir fixed-dose combination (LDV/SOF FDC) for 12 or 24 weeks, with or without ribavirin (RBV), as measured by the proportion of subjects with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)

- To evaluate the safety and tolerability of LDV/SOF FDC with or without RBV for 12 or 24 weeks, as assessed by review of the accumulated safety data

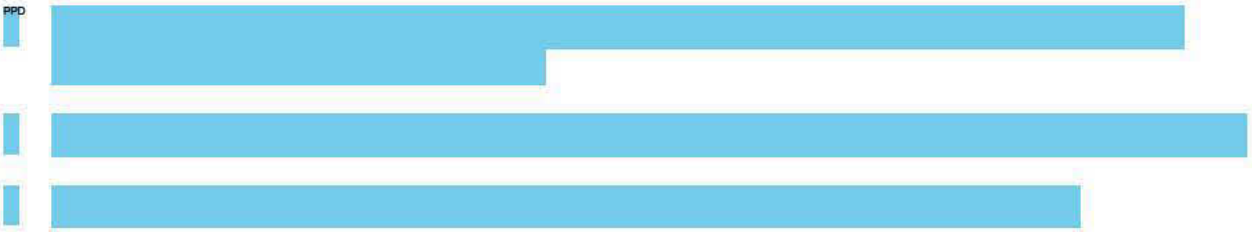
The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)

- To determine the proportion of subjects with virologic failure

- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation among subjects with virologic failure

The exploratory objectives of this study are as follows:



1.2. Study Design

This is a Phase 3b, multicenter, open label study in adult male and female subjects with chronic genotype (GT) 1 or 4 hepatitis C virus (HCV) infection and who have failed prior SOF-based HCV therapy, including in combination with simeprevir (SMV) ± RBV or with RBV ± pegylated inferferon (PEG).

Approximately 50% of subjects enrolled may have had prior treatment with SOF + SMV ± RBV. Approximately 5% of subjects may be infected with GT 4 HCV.

Approximately 430 subjects are planned to enroll into 2 cohorts:

- **Cohort 1**: subjects without cirrhosis (n=180) will be randomized in a 1:1 ratio into Group 1 and 2:

  Group 1: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily for 12 weeks

  Group 2: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily and RBV at a total daily oral dose of 1000-1200 mg divided twice a day (BID) for 12 weeks

- **Cohort 2**: subjects with compensated cirrhosis (n=250) will be randomized in a 1:1 ratio into Groups 3 and 4:

  Group 3: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily and RBV at a total daily oral dose of 1000-1200 mg divided BID for 12 weeks.

  Group 4: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily for 24 weeks

Randomization will be stratified by genotype 1 or 4, and by prior SOF therapy in combination with SMV or without SMV

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

The total time to complete all study visits is up to approximately 42 or 54 weeks (group 4 only) including the following periods:

- Up to 42-day (6-week) screening period
- A 12-week treatment period for Groups 1 - 3, and 24-week treatment period for Group 4
- Up to 24-week posttreatment period

The study was early terminated after 87 subjects were enrolled due to lack of feasibility of enrolling originally planned 430 subjects.

1.3. Sample Size and Power

Cohort 1: For the non-inferiority comparison of SVR12 in the noncirrhotic cohort (group 1 vs. 2) with a 10% non-inferiority margin, a sample size of 90 subjects per treatment group will provide at least 90% power to establish non-inferiority at 1-sided 0.025 level, assuming the SVR12 rates are 98% for both groups.

Cohort 2: For the non-inferiority comparison of SVR12 in the compensated cirrhotic cohort (group 3 vs. 4) with a 10% non-inferiority margin, a sample size of 125 subjects per treatment group will provide at least 90% power to establish non-inferiority at 1-sided 0.025 level, assuming the SVR12 rates are 95% for both groups.

However, the study was early terminated after 87 subjects were enrolled due to lack of feasibility of enrolling originally planned 430 subjects.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee

This study does not have a data monitoring committee.

2.2. Interim Analysis

2.2.1. Posttreatment Week 12 Analysis

The analysis for the primary endpoint SVR12 will be conducted after all subjects complete the Posttreatment Week 12 visit or prematurely discontinue 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.

Analyses on efficacy will be presented by each treatment group and total for each cohort and overall, while on other analyses, like safety analyses, demographics and baseline characteristics will be presented by each treatment group for each cohort and overall.

3.1. Analysis Sets

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

3.1.1. All Randomized/Enrolled Analysis Set

The All Randomized/Enrolled Analysis Set includes all subjects who were randomized or enrolled in the study. Subjects are grouped within the All Randomized/Enrolled Analysis Set according to the treatment they actually received.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled subjects who took at least 1 dose of study drug. The study drugs in this study are LDV/SOF FDC, with or without RBV. The difference between the FAS definition provided in the protocol and this SAP is documented in Section 6.4.

3.1.2.1. Full Analysis Set by Randomized Treatment

Subjects are grouped according to the treatment they were randomized. This is the primary analysis set for efficacy analyses.

3.1.2.2. Full Analysis Set by Actual Treatment

Subjects are grouped according to their cirrhotic status and the treatment/duration they actually received. This is applied for key efficacy analyses.

3.1.3. Safety Analysis Set

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

This is the primary analysis set for safety analyses.

3.2. Subject Grouping

For analyses based on the All Randomized/Enrolled Analysis Set or FAS by Randomized Treatment, subjects will be grouped according to the treatment to which they were randomized. For analyses based on other analysis sets, such as the Safety Analysis Set and FAS by actual treatment, subjects will be grouped according to the actual treatment received. The actual treatment received is defined as the randomized treatment except for subjects who received treatment that differs from the randomized treatment for the entire treatment duration. In this case, the actual treatment received is defined as the treatment received for the entire treatment duration.

Randomized Treatment groups will be:

1. Cohort 1 subjects received LDV/SOF 12 week
2. Cohort 1 subjects received LDV/SOF + RBV 12 weeks
3. Cohort 2 subjects received LDV/SOF + RBV 12 week
4. Cohort 2 subjects received LDV/SOF 24 weeks

Due to randomization errors, cirrhotic subjects might be included in cohort 1 and non-cirrhotic subjects might be included in cohort 2 for some efficacy analyses by randomized treatment group.

Actual Treatment groups will be:

1. Cohort 1 Non-cirrhotic subjects received LDV/SOF 12 week
2. Cohort 1 Non-cirrhotic subjects received LDV/SOF + RBV 12 weeks
3. Cohort 2 Cirrhotic subjects received LDV/SOF + RBV 12 week
4. Cohort 2 Cirrhotic subjects received LDV/SOF 24 weeks

3.3. Strata and Covariates

Approximately 430 subjects will be enrolled into 2 cohorts. In each cohort, subjects will be randomized at a 1:1 ratio into two treatment groups (Non-cirrhotic subjects for cohort 1 and Cirrhotic subjects for cohort 2) via the interactive web response system (IWRS) using a stratified randomization schedule.

Stratification will be based on the following variables:

- HCV genotype 1 or 4
- Prior SOF therapy in combination with SMV or without SMV

If there are discrepancies in stratification factor values between the IWRS and the clinical database, the values recorded in the clinical database will be used for analyses and a listing is provided to document those discrepancies.

3.4. Examination of Subject Subsets

Subsetting of subjects based on randomization stratification factors will be explored for subgroup analyses. If there are discrepancies in stratification factor values between the IWRS and the clinical database, the values recorded in the clinical database will be used for analyses.

The subject subsets will be explored for the primary efficacy endpoint, SVR12 and Virologic Outcomes using both FAS populations. The presumed prognostic baseline characteristics include the following:

- age (< 65 years, ≥ 65 years)
- sex (male, female)
- race (white, black, other)
- ethnicity (Hispanic or Latino, not Hispanic or Latino)
- baseline BMI (< 30 kg/m^2, ≥ 30 kg/m^2)
- baseline RAVs (yes, no, not-determined)
- baseline albumin (<=3.5 g/dL, >3.5 g/dL)
- baseline platelets (<=75,000/µL, 75,000 - <=100,000/µL, >100,000/µL)
- HCV subgenotype (1, 4; with 1 further broken down to 1a, 1b, No confirmed subtype)
- cirrhosis (presence, absence, missing if any)

- IL28B (CC, non-CC; with non-CC further broken down to CT, TT)
- baseline HCV RNA (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- prior HCV treatment experience (treatment naive, treatment expreienced)
- the most recent HCV treatment combinations (SOF + SMV, SOF + SMV + RBV, SOF + RBV, SOF + PEG + RBV)
- number of prior HCV treatment regimens (1, 2, or 3 or more)
- completed study treatment, discontinued study treatment
- adherence to study regimen (< 80%, ≥ 80%)
- adherence to LDV/SOF (< 80%, ≥ 80%)
- adherence to RBV (Group 2 and 3 only) (< 80%, ≥ 80%)

3.5. Multiple Comparisons

No multiplicity adjustment will be made for testing since the statistical comparisons performed are for exploratory purpose only between group 1 vs group 2, and between group 3 vs group 4 due to small sample size actually enrolled.

3.6. Missing Data and Outliers

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

3.6.1. Missing Data

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

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 an HCV RNA data point is missing and is preceded and followed in time by values that are "< LLOQ target not detected (TND)," then the missing data point will be set to "< LLOQ TND."

If a data point is missing and preceded and followed by values that are "< LLOQ detected," or preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected," then the missing value will be set to "< LLOQ detected." In these situations the data point will be termed a bracketed success; otherwise, the data point will be termed a bracketed failure (ie, ≥ LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (ie, ≥ LLOQ detected) 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 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, posttreatment follow-up Week 4 (FU-4) visit, and posttreatment follow-up Week 12 (FU-12) visit will not be imputed. Last posttreatment observation carried forward will be used for imputation of missing data at posttreatment follow-up Week 24 visit.

3.6.2. Missing Date

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

For some countries, only birth year is collected on the eCRF. In those cases, "01 January" will be used for the unknown birth day and month for the purpose of age calculation, unless age is captured on the CRF.

3.6.3. 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.

3.7. Data Handling Conventions and Transformations

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

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

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

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

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

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

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

The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0 was used to determine HCV RNA results in this study. The lower limit of quantitation (LLOQ) of the assay is 15 IU/mL.

When the calculated HCV RNA IU/mL is within the linear range of the assay, then the result will be report 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 "target not detected" will also be set to LLOQ – 1 IU/mL.

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (eg, log10 scale) or nonparametric analysis methods may be used, as appropriate.

3.8. Visit Windows

3.8.1. Definition of Study Day

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

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

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

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

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

3.8.2. Analysis Windows

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

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

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

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

	Cohort 1: Subjects Without Cirrhosis					
	Group 1 (LDV/SOF 12 Weeks)			Group 2 (LDV/SOF+RBV 12 Weeks)		
Nominal Visit	Nominal Day	Lower Limit	Upper Limit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1	1	(none)	1
Week 1	7	2	11	7	2	11
Week 2	14	12	21	14	12	21
Week 4	28	22	42	28	22	42
Week 8	56	43	70	56	43	70
Week 12	84	71	≥ 85	84	71	≥ 85

	Cohort 2: Subjects With Cirrhosis					
	Group 3 (LDV/SOF+RBV 12 Weeks)			Group 4 (LDV/SOF 24 Weeks)		
Nominal Visit	Nominal Day	Lower Limit	Upper Limit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1	1	(none)	1
Week 1	7	2	11	7	2	11
Week 2	14	12	21	14	12	21
Week 4	28	22	42	28	22	42
Week 8	56	43	70	56	43	70
Week 12	84	71	≥ 85	84	71	98
Week 16	NA			112	99	126
Week 20	NA			140	127	154
Week 24	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) visit. Visit windows will be calculated from the last dose date (ie, FU Day = collection date minus the last dose date) as shown in Table 3-2.

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

	HCV RNA			Vital Signs and Safety Laboratory Data[b]		
Nominal FU[a] Visit	Nominal FU Day	Lower Limit	Upper Limit	Nominal FU Day	Lower Limit	Upper Limit
FU-4	28	21	69	28	4	30
FU-12	84	70	146	84	31	146
FU-24	168	147	210	168	147	210

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), the time windows after FU-4 was for listing purpose only.

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

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

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

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

- For postbaseline visits:

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

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

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

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

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided for each country and investigator within a country by treatment group for each cohort and overall. 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 treatment group for each cohort and overall. This summary will present the number of subjects screened, the number of subjects Randomized/enrolled and the number of subjects in each of the categories listed below.

- Subjects Randomized but Never Treated
- Subjects in Safety Analysis Set
- Subject in Full Analysis Set by Randomized Treatment
- Subject in Full Analysis Set by Actual Treatment
- Subject in Completed study treatment
- Subject in did not complete study treatment with reasons for premature discontinuation of study treatment
- Subject in completed the study
- Subject in did not complete the study with reason for premature discontinuation of study

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

- Who had no HCV posttreatment Week 4 assessment and thereafter (No HCV FU-4 and thereafter)
- Who had HCV posttreatment Week 4 assessment but no HCV posttreatment Week 12 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 randomized, 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 identification (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, 4.5 weeks).

The total duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and using the number of subjects (ie, cumulative counts) and percentage of subjects exposed through the following time periods: baseline (Day 1), Week 1 (Day 7), Week 2 (Day 14), Week 4 (Day 28), Week 10 (Day 70), Week 12 (Day 84), and Week 16 (Day 112), Week 20 (Day 140), and Week 24 (Day 168), with Week 16 to Week 24 for group 4 only. A 3-day window is applied to the last planned on-treatment visit to match with the protocol-specified visit window, ie, Groups 1 -3 subjects will have number of subjects exposed through week 12 calculated as the number of subjects who were exposed study drug for at least 81 days. Similarly, Group 4 subjects will have number of subjects exposed through week 24 calculated as the number of subjects who were exposed study drug for at least 165 days. Summaries will be provided by treatment group for each cohort and overall for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

The presumed total number of tablets administered to a subject will be determined by the data collected on the drug accountability 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/±RBV (90/400 mg, ±RBV total 1000-1200mg divided BID if prescribed) prescribed for 12 weeks or 24 weeks (for group 4), total number of tablets needed for LDV/SOF and RBV is as specified in Table 4-1.

Table 4-1. LDV/SOF and RBV tablets needed for each group

	Cohort 1		Cohort 2	
	Group 1 LDV/SOF 12 Weeks	**Group 2 LDV/SOF+RBV 12 Weeks**	**Group 3 LDV/SOF+RBV 12 Weeks**	**Group 1 LDV/SOF 24 Weeks**
LDV/SOF Tablets	84	84	84	168
RBV Tablets	NA	5x84 (420) for baseline weight < 75 kg 6x84 (504) for baseline weight >=75 kg	5x84 (420) for baseline weight < 75 kg 6x84 (504) for baseline weight >=75 kg	NA

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

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

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

5. BASELINE CHARACTERISTICS

5.1. Demographics

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

A by-subject demographic listing, which includes the date the informed consent was signed, will be provided by subject ID number in ascending order.

5.2. Baseline Characteristics

Baseline data is defined as data collected on Day 1 predose or last available data collection in the screening period, if not collected on Day 1. Summarization on baseline characteristics will be also performed on the Safety Analysis Set and on FAS by randomized treatment. Baseline characteristics include:

- Body mass index (BMI; in kg/m^2) as a continuous variable and as categories (< 30 kg/m^2, ≥ 30 kg/m^2)
- HCV subgenotype (1 and further specified if coded as 1a , 1b or No confirmed subtype; 4, others if collected)
- IL28B (CC, Non-CC, further specify Non-CC with CT, TT)
- baseline HCV RNA (log10 IU/mL) as a continuous variable and as categories (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- Baseline RAVs (yes, no, not-determined)
- Baseline albumin (<=3.5 g/dL, >3.5 g/dL)
- baseline platelets (<=75,000/μL, 75,000 -<= 100,000/μL, >100,000/μL)
- Prior HCV treatment experience (treatment naïve, treatment experienced) as categorical variable. For treatment experienced subjects, summarizations on the most recent HCV treatment combinations (SOF + SMV, SOF + SMV + RBV, SOF + RBV, SOF + PEG + RBV), and on prior HCV treatment response (Non-Responder, Relapse/Breakthrough, Other with specific reasons) will be provided.

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

These baseline characteristics will be summarized 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.

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 and prior HCV treatment and response will be provided for all subjects at screening.

5.3. Baseline Fibrosis Stage

The baseline fibrosis stage is determined using liver biopsy results. Once the liver biopsy results are not available, the Fibrotest results are used instead, with the cut off values of 0.21, 0.31, 0.58, and 0.72 for F0, F1, F2, F3, and F4 respectively.

The baseline fibrosis stage will be summarized as categorical variable. Summarization will be performed on the Safety Analysis Set and on FAS by randomized treatment. The 2-sided 95% exact CI of the proportion based on Clopper-Pearson method will be provided {Clopper 1934}.

A by-subject listing of the baseline fibrosis stage will be provided by subject ID number in ascending order.

5.4. Medical History

Medical history collected at screening will be coded using the most recent available Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized by system organ class (SOC), preferred term (PT), treatment group for each cohort, 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).

6. EFFICACY ANALYSES

All the efficacy analyses are conducted on FAS by randomized treatment and on FAS by actual treatment, unless specified otherwise.

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is SVR12 defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after discontinuation of the study drug in the FAS. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0 will be used to measure HCV RNA. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay, or other alternative assay decided by Gilead.

6.1.2. Summary for the Primary Efficacy Endpoint

The primary efficacy endpoint is SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of therapy). The primary analysis will be performed after all enrolled subjects have been followed through 12 weeks posttreatment or discontinued from study.

In the primary efficacy analysis, the SVR12 rate will be summarized by FAS by randomized treatment and by FAS by actual treatment, the 2-sided 95% exact CI of SVR12 based on Clopper-Pearson method will be provided {Clopper 1934}.

In Cohort 1, a non-inferiority test of SVR12 rates will be performed comparing Group 1 and 2. A non-inferiority margin of 10% will be applied. Non-inferiority will be established if the lower bound of the 2-sided 95% confidence interval (CI) of the difference in SVR12 (Group 1 - Group 2) is greater than -10%. The CI will be constructed using stratum-adjusted Mantel-Haenszel (MH) proportions, stratified by the randomization stratification factors (i.e., genotype 1or 4; prior SOF therapy in combination with SMV or without SMV).

A similar non-inferiority tests of SVR12 rates will be performed comparing Group 3 and 4 in Cohort 2. The NI margin of 10% is chosen primarily based on clinical judgment. The statistical justification of a NI margin is based on a two-step process in which: 1) we estimate the treatment benefit of the control regimens (LDV/SOF + RBV for 12 weeks for cohort 1; LDV/SOF for 24 weeks for cohort 2) and the historical control (M1), and 2) we define a margin which preserve some fraction of the treatment benefit characterized in Step 1 above (M2).

The M1 and M2 in the current study design as follows:

- M1 = the smallest treatment benefit of the control regimens over the historical control
- M2 = 50% of M1

Based on the Phase 2 ELECTRON-2, GS-US-337-1118, and SYNERGY data, the SVR12 rates for LDV/SOF + RBV for 12 weeks are summarized below:

Table 6-1. Summary of SVR12 Rates in Phase 2 Studies

Study	SVR12 Rates			
	LDV/SOF 12 Weeks		LDV/SOF + RBV 12 Weeks	
Electron-2			n/a	Without cirrhosis: 100% (19/19)
GS-US-337-1118			With cirrhosis: 100% (14/14)	Without cirrhosis: 100% (36/36)
SYNERGY	Advanced liver disease (Knodell score 3, 4) 100% (7/7)	Other (Knodell score 0, 1) 100% (7/7)		
Overall	100% (7/7) 95% CI: (59%, 100%)	100% (7/7) 95% CI: (59%, 100%)	100% (14/14) 95% CI: (77%, 100%)	100% (55/55) 95% CI: (94%, 100%)

The smallest treatment benefit of LDV/SOF 12 weeks and LDV/SOF + RBV 12 weeks are 59% and 77%, respectively (the smaller lower bound of the two 95% CIs).

Note: SVR12 rate of LDV/SOF for 24 weeks is assumed to be at least as high as that of LDV/SOF for 12 weeks.

Since there is no approved standard of care in this patient population, a spontaneous SVR12 rate of at most 5% is assumed as the historical control rate. Using the smallest treatment benefit for the control regimens (ie, the smaller of 59% and 77%) and the highest spontaneous SVR12 rate of the historical control, M1=59%-5%=54%. Based on these conservative estimates, a 10% NI margin would retain at least ensure at least 81.5% of the treatment benefit of LDV/SOF + RBV for 12 weeks or LDV/SOF for 24 weeks over the historical control.

However, due to the actual sample size for this study is much smaller than the originally planned sample size, the tests are for exploratory purpose only and the interpretation needs to be cautious since the actual sample size does not have enough power for the test.

6.1.3. Subgroup Analysis of the Primary Efficacy Endpoint

Point estimates and 95% exact confidence intervals (CIs) of the SVR12 rates based on Clopper-Pearson method will be displayed {20839} on FAS by randomized treatment and FAS by actual treatment for each subgroup. Subgroups are outlined in Section 3.4. Subgroup factors used for randomization will be summarized separately.

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 dose reduction and modification are also explored.

Forest plot of SVR12 by Subgroup and treatment groups for each cohort will be provided. No statistical comparisons are performed for the subgroup analyses.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The following secondary antiviral efficacy endpoints will be analyzed:

- The proportion of subjects with HCV RNA < LLOQ (ie, < 15 IU/mL) at 4 , 12 and 24 weeks after discontinuation of therapy (SVR 4, SVR12 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 Antiviral Efficacy Endpoints

The point estimates of SVR4, SVR12, SVR24 rates and their 2-sided 95% exact confidence intervals (CIs) based on Clopper-Pearson method will be provided as applicable {Clopper 1934}, on FAS by randomized treatment and FAS by actual treatment.

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 3.6. The 2-sided 95% exact confidence interval based on Clopper-Pearson method will be provided for the proportion. 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 on treatment and during the posttreatment follow-up period 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 3.6 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 end of treatment will be presented.

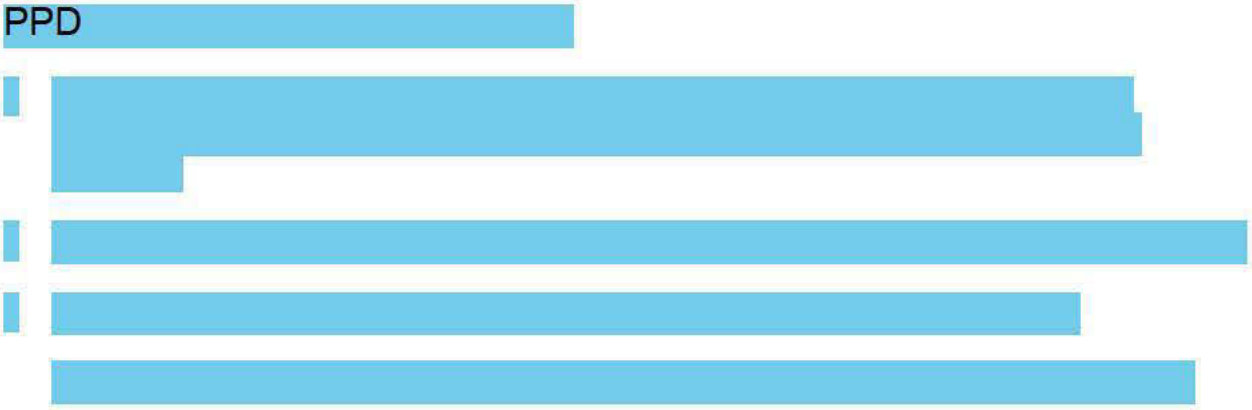
For the SVR12 endpoint analysis, a summary table of the number and percentage of subjects with SVR12, virologic failure (VF), and Other will be created. All subjects who achieve SVR12 will be categorized as SVR12. Virologic failure will be descriptively summarized as "on-treatment virologic failure"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

A concordance table between SVR12 and SVR24 will be provided by treatment group for each cohort and overall. Subjects with both observed SVR12 and observed SVR24 data will be included for this analysis.

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints

PPD



6.3.2. Analysis Methods for Exploratory Efficacy Endpoints

6.4. Changes From Protocol-Specified Efficacy Analyses

6.4.1. Change on FAS definition

The protocol defined FAS as all randomized subjects who took at least 1 dose of study drug. Subjects are grouped according to the treatment they were randomized.

Due to randomization errors, two new FAS populations are defined and used for efficacy analyses:

Full Analysis Set by Randomized Treatment: this is the same as the FAS definition in the protocol. One cirrhotic patient (subject ID = PPD wrongly randomized into group 1 (SOF/LDV 12 weeks) was extended to 24 week treatment for ethnical reasons.

Full Analysis Set by Actual Treatment: this FAS population is defined based on the Cirrhotic status of the subject and the treatment/duration the subject actually received. For example, the subject PPD (in the group 1 for Full Analysis Set by Randomized Treatment) is in group 4 for analysis since his status is cirrhotic and received 24 week SOF/LDV.

Four subjects dosed were randomized wrongly or took wrong drug. The details and decisions for those subjects are as follows:

Subject PPD
Issue: Subject was cirrhotic and wrongly randomized to Cohort 1 Group 1 (LDV/SOF 12 weeks);
Decision: LDV/SOF was extended to 24 weeks
Actual treatment group: Cohort 2 Group 4 (LDV/SOF 24 weeks)

Subject PPD

Issue: Subject was non-cirrhotic and randomized to Cohort 1 Group 2 (LDV/SOF +RBV 12 weeks) but no RBV was provided;
Decision: Subject was kept to take LDV/SOF without RBV for 12 weeks
Actual treatment group: Cohort 1 Group 1 (LDV/SOF 12 weeks)

Subject PPD

Issue: Subject was non-cirrhotic and wrongly randomized to Cohort 2 Group 3 (LDV/SOF+RBV 12 weeks)
Decision: Subject was kept to take LDV/SOF+RBV for 12 weeks
Actual treatment group: Cohort 1 Group 2 (LDV/SOF+RBV 12 weeks)

Subject PPD

Issue: Subject was non-cirrhotic and wrongly randomized to Cohort 2 Group 4 (LDV/SOF 24 weeks);
Decision: Subject need to take LDV/SOF for only 12 weeks
Actual treatment group: Cohort 1 Group 1 (LDV/SOF 12 weeks)

6.4.2. Change on Sample Size

The initial sample size planned was 430, with 90 each in groups 1 and 2, and 125 each in group 3 and 4 to obtain a 10% non-inferiority margin at 1-sided 0.025 level and 90% power, for the comparisons between group 1 and 2, and between group 3 and 4.

Due to lack of feasibility of enrolling subjects, the study was early terminated after 87 subjects enrolled, with 17, 17, 26, 27 randomized in groups 1-4 respectively. Five subjects randomized were never dosed so final analyses set has only 82 subjects (15, 17, 26, 24 for randomization groups 1-4 respectively, while 16, 17, 25, 24 for actual treatment groups 1-4 respectively). Details for subjects with different treatment groups in the two FAS populations are specified in Section 6.4.1.

6.4.3. Non-inferiority Comparisons

Although the non-inferiority comparisons of SVR12 in the non-cirrhotic cohort (group 1 vs. 2) and in the compensated cirrhotic cohort (group 3 vs. 4) were performed, the results are for exploratory purpose only and the interpretation needs to be cautious since the actual sample size does not have enough power for the test.

7. SAFETY ANALYSES

All the safety analyses are conducted on Safety Analysis Set, unless specified otherwise.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the most recent available MedDRA code. 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 (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Treatment-emergent adverse events (TEAEs) are defined as 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 treatment group for each cohort and overall and by the number and percentage of subjects who had the following: any AE, any AE of Grade 3 or above, any treatment-related AE, any treatment-related AE of Grade 3 or above, any SAE, any treatment-related SAE, any AE that led to premature discontinuation of any study drug, any AE that led to premature discontinuation of LDV/SOF, any AE that led to premature discontinuation of RBV, any AE that led to modification or interruption of any study drug, any AE that led to interruption of LDV/SOF, any AE that led to modification or interruption of RBV. 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, by treatment group in each cohort on the Safety Analysis Set as follows:

- All AEs
- AEs of Grade 3 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- All SAEs
- All treatment-related SAEs
- AEs leading to premature discontinuation of any study drug
- Adverse Events Leading to Modification or Interruption of Any Study Drug

Multiple events will be counted once only per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in order of descending incidence of the overall treatment group 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 within the overall treatment group for:

- AEs that occurred in at least 5% of subjects within any treatment group
- AEs of Grade 3 or above
- All treatment-related AEs
- All SAEs
- AEs leading to premature discontinuation of any study drug
- AEs leading to premature discontinuation of LDV/SOF
- AEs leading to premature discontinuation of RBV (groups 2 and 3 only)
- AEs leading to premature discontinuation of all study drugs
- AEs leading to modification or interruption of any study drug
- AEs leading to modification or interruption of RBV (groups 2 and 3 only)

In addition to the by-treatment 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 any study drug
- Adverse Events Leading to Modification or Interruption of Any Study Drug

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to 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, 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 by treatment group for ALT, AST, total bilirubin, alkaline phosphatase, white blood cell (WBC) counts, neutrophils, lymphocytes, hemoglobin, platelets, reticulocytes, and international normalized ratio (INR) as follows:

- Baseline values
- Values at each postbaseline visit for hemoglobin and platelets, and at EOT and FU4 for other analytes specified above
- Change from baseline at each postbaseline visit for hemoglobin and platelets, and at EOT and FU4 for other analytes specified above

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 hemoglobin and platelets will be plotted using a line plot by treatment group and visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3 (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 by treatment group.

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.

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 and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for a given analyte:

- Graded laboratory abnormalities
- Grade 3 or above laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after 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) by treatment group. The baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

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

A by-subject listing of vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min], respiration [breaths/min], and body temperature [°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. Prior and Concomitant Medications

Medications collected at Screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary. The medications will be categorized as prior, concomitant, or both using the following definitions:

- Prior medications: any medications taken 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 Anatomical Therapeutic Chemical (ATC) drug class Level 2, and preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary of concomitant medications will be ordered by descending active treatment group frequency of ATC drug classes and then preferred names within an ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

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

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

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

7.5. Electrocardiogram Results

ECG examination is only conducted at baseline visit, a summary of the investigators' assessment of ECG results at baseline will be presented by treatment group for each cohort using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects will be presented.

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

7.6. Other Safety Measures

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

7.7. Changes From Protocol-Specified Safety Analyses

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

8. REFERENCES

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.

9. SOFTWARE

SAS® Software Version 9.2 or higher. SAS Institute Inc., Cary, NC, USA.

10. SAP REVISION

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

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Appendix 2. Schedule of Assessments

			On-Treatment Study Week (±3 Days)									Posttreatment Study Week (±5 Days)		
	Screen	**Baseline/ Day 1[a]**	**1**	**2**	**4**	**8**	**12**	**16[b]**	**20[b]**	**24[b]**	**ET**	**4[c]**	**12[c]**	**24**
Clinical Assessments														
Informed Consent	X													
Determine Eligibility	X	X												
Medical History	X													
Historical Resistance Test Data[d]	X													
Physical Examination	X	X					X[e]			X[e]	X			
Height	X													
Weight	X	X												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X													
Imaging for HCC[f]	X													
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X
Health Related Quality of Life Surveys		X			X		X			X	X	X	X	
Study Drug Dispensing		X[g]			X	X	X[h]	X[h]	X[h]					
Review of Study Medication Adherence (Pill Count)			X	X	X	X	X	X	X	X	X			

			On-Treatment Study Week (±3 Days)									Posttreatment Study Week (±5 Days)		
	Screen	**Baseline/ Day 1[a]**	**1**	**2**	**4**	**8**	**12**	**16[b]**	**20[b]**	**24[b]**	**ET**	**4[c]**	**12[c]**	**24**
Laboratory Assessments														
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation Tests	X	X					X			X	X			
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral Sequencing/phenotyping[i]		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing[j]	X	X			X	X	X	X	X	X	X	X[k]	X[k]	X[k]
Urinalysis & Urine Drug Screen	X													
HCV Genotyping, IL28B	X													
HCV, HIV, HBV Serology	X													
TSH, HbA1c, Fibrotest®/APRI	X													
Future Research Blood Sample[l]		X					X			X	X			

a Baseline/Day 1 assessments must be performed prior to dosing
b On-Treatment Visits at Weeks 16, 20 and 24 are only applicable to subjects in study group 4
c All subjects will complete the posttreatment Week 4 and Week 12 visits ; subjects with HCV RNA < LLOQ at the posttreatment (PT) Week 12 visit will complete the PT Week 24 visit
d Collect and record information regarding historical resistance test data if available
e A physical exam will be performed at the end of treatment visit (Week 12 for study groups 1,2,3; and Week 24 for study group 4)
f Liver imaging within 6 months prior to Baseline/Day 1 is required in subjects with cirrhosis to exclude HCC
g The IWRS will provide randomization to study Group
h Study drug dispensing at Week 12, 16 and 20 is only applicable to study group 4
i Plasma samples will be collected and stored for potential HCV sequencing/phenotyping and other virology studies.
j For females of childbearing potential only: serum β-hCG at Screening, urine test thereafter. If urine is positive, confirm immediately with serum β-hCG

k Females of childbearing potential in study Groups 2 & 3 will have additional urine pregnancy testing every 4 weeks for a minimum of 6 months following last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. In the event of a positive urine pregnancy result, subjects will be instructed to return to the clinic as soon as possible for a serum pregnancy test. Pregnancy test kits will be dispensed to female subjects of childbearing potential at the 4 and 12 Week posttreatment visits to self-monitor for pregnancy. The subject will be contacted by telephone monthly to confirm that urine pregnancy testing has been performed posttreatment and to record the outcome. Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine pregnancy tests.

l Sample for optional future research will be collected at the Baseline/Day 1 visit and at the end of treatment (Week 12 for study groups 1,2,3; and Week 24 for study group 4) for subjects who have not opted out

Appendix 3. QOL Score Calculation Algorithms

CLDQ – HCV

CLDQ-HCV scores are calculated using subject responses to 29 questions in the questionnaire. If Ri is the score for the patient's response to the item i, for i=1, 2, …., 29 then the 4 domain scores are calculated as follows:

- Activity/Energy (AE) = Mean of {R1, R3, R4, R5, R7, R18}
- Emotion (EM) = Mean of {R6, R8, R9, R11, R16, R23, R24, R27, R28}
- Worry (WO) = Mean of {R14, R15, R17, R19, R20, R21, R22, R29}
- Systemic (SY) = Mean of {R2, R10, R12, R13, R25, R26}

Here "Mean" is the average of nonmissing items (SAS mean function). Each score is calculated only if at least half of corresponding items are not missing. Otherwise, the score will be missing.

Over all CLDQ-HCV score is calculated by taking the mean of 4 domain scores {AE, EM, WO, SY}.

FACIT-F

Patient responses to 40 questions in FACIT-F questionnaire are rated in 0-4 score.

If less than 50% of responses in the corresponding domain are missing, the subscales for five domains are calculated as follows:

- Physical WEL
- l-Being (PWB) = 7 × Mean of {GP1-GP7}
- Social/Family Well-Being (SWB) = 7 × Mean of {GS1-GS7}
- Emotional Well-Being (EWB) = 6 × Mean of {GE1-GE6}
- Functional Well-Being (FWB) = 7 × Mean of {GF1-GF7}
- Fatigue Subscale (FS) = 13 × Mean of {HI7, HI12, An1-An5, An7, An8 An12, An14-An16}

  and

- FACIT-F Trial Outcome Index (TOI) = PWB+FWB+FS

If less than 20% of all 40 questions are not missing,

- TACIT-F Total Score = PWB+SWB+EWB+FWB+FS

WAPI: Hepatitis C

The response to Question 1 of this questionnaire provides the binary endpoint whether or not the subject had been in a paid employment during the week prior to assessment.

If the subject had been in a paid employment (Response to Q1 is "Yes") at the visit when questionnaire was given, then following three scores are derived:

- Percent work time missed due to hepatitis C = 100 × Q2 / (Q2 + Q4)
- Percent impairment while working due to hepatitis C = 100 × Q5 / 10
- Percent overall work impairment due to hepatitis C =

$$100 \times \left[\frac{Q2}{(Q2+Q4)} + \left(1 - \frac{Q2}{Q2+Q4)} \right) \times \frac{Q5}{10} \right]$$

Question 6 is applicable to all subjects:

- Percent activity impairment due to hepatitis C = 100 × Q6 / 10.
-