



## STATISTICAL ANALYSIS PLAN

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**Study Title:** A Phase 3b, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 2 Hepatitis C Virus (HCV) Infection

**Name of Test Drug:** Ledipasvir/Sofosbuvir (HARVONI<sup>®</sup>, LDV/SOF) Fixed-Dose Combination (FDC)

**Study Number:** GS-US-337-1903

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**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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## LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BLQ	below the limit of quantitation
BMI	body mass index
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
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FAS	full analysis set
FDC	fixed dose combination
FU	follow-up
HCV	hepatitis C virus
HLGT	high level group term
HLT	high level term
ID	Identification
INR	international normalized ratio
IWRS	Interactive Web Response System
LDV	Ledipasvir
LLT	lower level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
Peg-IFN	pegylated interferon
PT	preferred term
Q1	first quartile
Q3	third quartile
RBV	ribavirin
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
ULN	upper limit of the normal range
WBC	white blood cell
WHO	World Health Organization

## 1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-337-1903. This SAP is based on the study protocol amendment 2 dated 23 February 2016 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

### 1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the antiviral efficacy of therapy with ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) as measured by sustained virologic response (SVR) 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of each regimen 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 cessation of treatment (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 each treatment regimen
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after cessation of treatment

The exploratory objectives of this study are as follows:



### 1.2. Study Design

This is a multicenter, randomized, open-label Phase 3 study to evaluate the safety, tolerability and antiviral efficacy of LDV/SOF for 12 weeks compared with SOF + Ribavirin (RBV) for 12 weeks in subjects with treatment-naïve and treatment-experienced adults with chronic genotype 2 HCV infection.

Cohort 1: approximately 200 subjects will be randomized in a 1:1 ratio to one of the following two treatment groups:

- 1) LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks
- 2) SOF tablet (400 mg) once daily and RBV (600-1000 mg daily as a divided dose) for 12 weeks

At least 20 subjects will have Child-Pugh-A compensated cirrhosis. Approximately 50% of subjects will be treatment-naïve and 50% will be treatment-experienced.

Randomization will be stratified by cirrhosis status (presence/absence) and prior treatment experience (treatment-naïve/treatment-experienced).

Cohort 2: up to 25 subjects who are ineligible or intolerant for RBV therapy will receive LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks. Approximately 2 subjects will have Child-Pugh-A compensated cirrhosis.

The total time to complete all study visits is up to approximately 42 weeks, including the following periods:

- 42-day (6-week) screening period
- 12-week treatment period
- Up to 24-week posttreatment period

### 1.3. Sample Size and Power

For Cohort 1, a sample size of 100 per treatment group will provide over 90% power to establish non-inferiority in the SVR12 rates between the two groups. It is based on the assumptions that the clinically meaningful non-inferiority margin is 10%, both groups have a SVR12 rate of 96%, and the significance level is 0.025 one-sided.

Sample size for Cohort 2 is based on practical considerations. With a sample size of 25 subjects in Cohort 2, the 2-sided 95% exact confidence intervals (CIs) for different observed HCV SVR12 rates are presented in the table below:

Cohort	Observed HCV SVR12 rate	2-sided 95% exact CI
Cohort 2	80% (20 out of 25)	[59.3%, 93.2%]
	92% (23 out of 25)	[74.0%, 99.0%]

## **2. TYPE OF PLANNED ANALYSIS**

### **2.1. Data Monitoring Committee**

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

### **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 (SVR12 will not be evaluated at this time). 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 endpoint SVR12 will occur after all subjects complete the posttreatment Week 12 visit or prematurely discontinue from study. All safety and efficacy data through the posttreatment Week 12 visit will be cleaned, finalized and included for the analysis.

### **2.3. Final Analysis**

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

### **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.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

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

#### **3.1. Analysis Sets**

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

##### **3.1.1. All Enrolled/Randomized Analysis Set**

All Enrolled/Randomized Analysis Set includes all subjects enrolled (Cohort 2) or randomized (Cohort 1) in the study after screening. All analyses based on the All Enrolled/Randomized Analysis Set will be performed according to the treatment subjects enrolled/randomized within each cohort.

##### **3.1.2. Full Analysis Set**

The Full Analysis Set (FAS) includes all subjects who were either randomized or enrolled into the study, and received at least 1 dose of study drug. The study drugs in this study are LDV/SOF and SOF+RBV for Cohort 1 and LDV/SOF for Cohort 2. For Cohort 1, subjects are grouped within the FAS by the treatment group to which they were randomized.

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 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 Enrolled/Randomized Analysis Set or FAS, subjects in Cohort 1 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, subjects will be grouped according to the actual treatment received. The actual treatment received for Cohort 1 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.

### **3.3. Strata and Covariates**

For Cohort 1, subjects will be randomly assigned to treatment groups via the interactive web response system (IWRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- Cirrhosis status (presence versus absence)
- Prior treatment experience (treatment-naive versus treatment-experienced)

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.

Subjects with missing cirrhosis status in the clinical database will be analyzed as cirrhosis absence in the Cochran-Mantel-Haenszel (CMH) test or stratum-adjusted Mantel-Haenszel (MH) proportions.

For Cohort 2, this study does not use a stratified randomization schedule for enrolling subjects.

### **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.

Other subject subsets will also be explored for the primary efficacy endpoint (SVR12), including the following:

- age (< 65 years,  $\geq$  65 years)
- sex (male, female)
- baseline BMI ( $< 25 \text{ kg/m}^2$ ,  $\geq 25 \text{ kg/m}^2$ )
- HCV genotype subtype (if applicable)
- cirrhosis (cirrhosis, absence of cirrhosis, missing)

- IL28B (CC, non-CC; with non-CC further broken down to CT, TT)
- Baseline HCV RNA (< 800,000 IU/mL,  $\geq$  800,000 IU/mL, and  $< 5 \log_{10}$  IU/mL,  $\geq 5 \log_{10}$  IU/mL)
- baseline alanine aminotransferase (ALT) ( $\leq 1.5 \times$  upper limit of normal [ULN],  $> 1.5 \times$  ULN)
- prior HCV treatment experience (treatment naive, treatment-experienced)
- most recent prior HCV treatment response (non-responder, relapse/breakthrough, early treatment discontinuation, met a virologic stopping rule, not otherwise listed, unknown) for treatment-experienced subjects
- completed study treatment, discontinued study treatment
- adherence to study regimen (<80%,  $\geq$  80%)

The primary efficacy endpoint for Cohort 2 will be examined using the applicable subsets above.

### **3.5. Multiple Comparisons**

No multiplicity adjustment will be made for testing.

### **3.6. Missing Data and Outliers**

#### **3.6.1. Missing Data**

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

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

If an HCV RNA data point is missing and is preceded and followed in time by values that are “< lower limit of quantitation (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,  $\geq$  LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (ie,  $\geq$  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 (HRQoL) data including 36-Item Short Form Health Survey (SF-36), Chronic Liver Disease Questionnaire (CLDQ-HCV), Fatigue Index (FACIT-F), and Work Productivity and Activity Impairment Questionnaire: Hepatitis C, v2.0 (WPAI: Hepatitis C), missing data at on-treatment visits and posttreatment follow-up Week 4 (FU-4) visit, and posttreatment follow-up Week 12 (FU-12) visit will not be imputed. Last observation carried forward will be used for imputation of missing data at posttreatment follow-up Week 24 (FU-24) visit.

### **3.6.2. Outliers**

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

### **3.7. Data Handling Conventions and Transformations**

By-subject listings will be presented for all subjects in the Safety Analysis Set 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 for each 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 first dose date of study drug. For some countries, only birth year is collected on the case report form (CRF). 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.

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 “ $\leq x$ ” or “ $\geq x$ ” (where  $x$  is considered the limit of quantitation).

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

When the calculated 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 “ $\geq$  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 14 IU/mL.

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

### **3.8. Visit Windows**

#### **3.8.1. Definition of Study Day**

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

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

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

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

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

#### **3.8.2. Analysis Windows**

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

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

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

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

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	7	2	11
Week 2	14	12	18
Week 3	21	19	25
Week 4	28	26	32
Week 5	35	33	39
Week 6	42	40	49
Week 8	56	50	63
Week 10	70	64	77
Week 12	84	78	≥ 85

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

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

Nominal FU <sup>a</sup> Visit	HCV RNA			Vital Signs and Safety Laboratory Data <sup>b</sup>		
	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).

ECG data collected up to the last dose date + 3 days are considered to be on-treatment data. Qualitative assessments of whether the ECG is normal or abnormal will be assessed for on-treatment data based on the visit windows as shown in Table 3-3.

**Table 3-3. Analysis Windows for On-treatment ECG Data**

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	7	2	45
Week 12	84	46	(none)

Note: ECGs are to be collected at screening, baseline, Week 1, and Week 12 or End of Treatment. For purposes of analysis, baseline value will be the last available value prior to the first dose of study drug and end of treatment value will be the last available value on or prior to the last dose date + 3 days.

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

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

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

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

For Cohort 1, a similar enrollment table will be provided by randomization stratum for each treatment group and overall. The denominator for the percentage of subjects in the stratum will be the total number of subjects in the Safety Analysis Set in Cohort 1 within that stratum for each treatment group and overall. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database including CRF and laboratory data, the value collected in the clinical database will be used for the summary. A listing of subjects with the IWRS randomization strata that differ from stratification factor data entered in the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group and overall for each cohort. This summary will present the number of subjects screened, the number of subjects randomized/enrolled, the number of subjects randomized/enrolled but never treated, and the number and percentage of subjects in each of the categories listed below. For the “Treated” category, the denominator for the percentage calculation will be the total number of subjects enrolled for each column. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column.

- Treated (Safety Analysis Set)
- In FAS
- 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 and thereafter)
- Who had HCV posttreatment Week 4 assessment but no HCV posttreatment Week 12 assessment and thereafter (With HCV FU-4 but No FU-12 and thereafter)

If a subject did not have any HCV RNA assessment  $\geq$  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  $\geq$  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 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 (ie, cumulative counts) and percentage of subjects exposed through the following time periods: baseline (Day 1), Week1 (Day 7), Week 2 (Day 14), Week 3 (Day 21), Week 4 (Day 28), Week 5 (Day 35), Week 6 (Day 42), Week 8 (Day 56), Week 10 (Day 70), and Week 12 (Day 84). A 3-day window will be applied to the last planned on-treatment visit to match with the protocol-

specified visit window (ie, the 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). Summaries will be provided by treatment group within each cohort for the Safety Analysis Set.

#### **4.2.2. Adherence to Study Drug**

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

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

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

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 Cohort 1, for Group 1, the total amount of LDV/SOF (90 mg/400 mg) prescribed for 12 weeks would require 84 tablets; for Group 2, the total amount of SOF (400 mg) prescribed for 12 weeks would require 84 tablets and weight-based RBV (200 mg) prescribed for 12 weeks would require 252 (3 tablets/day for baseline weight  $\leq$  60 kg) or 336 (4 tablets/day for baseline weight  $>$  60 kg to  $\leq$  80 kg) tablets or 420 (5 tablets/day for baseline weight  $>$  80 kg) tablets.

In Cohort 2, the total amount of LDV/SOF (90 mg/400 mg) prescribed for 12 weeks would require 84 tablets.

Subjects who prematurely discontinue study drug for lack of efficacy (ie, virologic failure) will have the total amount of study drug prescribed calculated up to the first date when virologic failure criteria were met. 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%,  $\geq$  80 to  $<$  90%,  $\geq$  90%) will be provided by treatment group for the Safety Analysis

Set for both cohorts. Categorical displays will be provided for the number of subjects who are at least 80% adherent to their drug regimen for both cohorts and all drugs (ie, adherence is  $\geq 80\%$  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 randomized treatment assignment will be listed with the start and stop dates that they received incorrect study drug.

## 5. BASELINE CHARACTERISTICS

### 5.1. Demographics

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

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

### 5.2. Other Baseline Characteristics

Other baseline characteristics include:

- body mass index (BMI; in  $\text{kg}/\text{m}^2$ ) as a continuous variable and as categories ( $< 25 \text{ kg}/\text{m}^2$ ,  $\geq 25 \text{ kg}/\text{m}^2$ )
- HCV genotype subtype (if applicable)
- cirrhosis (cirrhosis, absence of cirrhosis, missing)
- IL28B (CC, non-CC; with non-CC further broken down to CT, TT)
- baseline HCV RNA ( $\log_{10}$  IU/mL) as a continuous variable and as categories ( $< 800,000 \text{ IU/mL}$ ,  $\geq 800,000 \text{ IU/mL}$ , and  $< 5 \log_{10} \text{ IU/mL}$ ,  $\geq 5 \log_{10} \text{ IU/mL}$ )
- baseline ALT (U/L) as a continuous variable and as categories ( $\leq 1.5 \times \text{ULN}$ ,  $> 1.5 \times \text{ULN}$ )
- prior HCV treatment experience (treatment-naive, treatment-experienced)
- most recent prior HCV treatment response (non-responder, relapse/breakthrough, early treatment discontinuation, met a virologic stopping rule, not otherwise listed, unknown) for treatment-experienced subjects
- estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation

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

These baseline characteristics will be summarized for both cohorts by treatment group and total 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 and prior HCV treatment and response will be provided for all subjects at screening.

### **5.3.            Medical History**

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

A by-subject listing of disease-specific medical history will be provided by subject ID number in ascending order.

## 6. EFFICACY ANALYSES

### 6.1. Primary Efficacy Endpoint

#### 6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with SVR12, defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after cessation of treatment. The primary analysis will be performed after all randomized/enrolled subjects have been followed through 12 weeks posttreatment or discontinued from study. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 will be used to measure HCV RNA.

#### 6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

In Cohort 1, the primary analyses will consist of a non-inferiority (NI) test of treatment LDV/SOF FDC for 12 weeks versus SOF+RBV for 12 weeks at the 0.05 significance level (two-sided). A clinically meaningful non-inferiority margin of 10% will be applied.

If we denote SVR12 rate for treatment group 1 (LDV/SOF for 12 weeks) as  $P_1$ , and SVR12 rate for treatment group 2 (SOF+RBV for 12 weeks) as  $P_2$ , the null and alternative hypotheses for non-inferiority for Cohort 1 are as follows:

$$H_0: P_1 - P_2 \leq -10\%$$

$$H_1: P_1 - P_2 > -10\%$$

In the primary efficacy analysis of Cohort 2, no statistical hypothesis testing will be performed.

#### 6.1.3. Primary Analysis of the Primary Efficacy Endpoint

In Cohort 1, the primary analyses will consist of a non-inferiority (delta=10%) of LDV/SOF for 12 weeks to SOF+RBV for 12 weeks at the 0.05 significance level (two-sided). Non-inferiority will be demonstrated (ie, non-inferiority null hypothesis will be rejected) if the lower bound of the two-sided 95% CI for the difference ( $P_1 - P_2$ ) in SVR12 is greater than -10%.

The two-sided 95% CI on the difference in SVR12 rates between the 2 treatment groups will be constructed based on stratum-adjusted MH proportions for the assessment of non-inferiority as follows {Koch 1989}:

$$P_1 - P_2 \pm Z_{(1-\alpha/2)} * SE(P_1 - P_2),$$

where

- $(P_1 - P_2) = \frac{\sum w_h d_h}{\sum w_h}$ , is the stratum-adjusted MH proportion difference, where  $d_h = p_{1h} - p_{2h}$  is the difference in the proportion of SVR12 of Treatment Groups 1 and Treatment Group 2 in stratum h (h=1 and 2).
- $w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$ , is the weight based on the harmonic mean of sample size per treatment group for each stratum where  $n_{1h}$  and  $n_{2h}$  are the sample sizes of Treatment Groups 1 and 2 in stratum h.
- $SE(P_1 - P_2) = \sqrt{\frac{\sum w_h^2 \left[ \frac{p_{1h}^*(1-p_{1h}^*)}{n_{1h}-1} + \frac{p_{2h}^*(1-p_{2h}^*)}{n_{2h}-1} \right]}{(\sum w_h)^2}}$ , where  $p_{1h}^* = \frac{m_{1h} + 0.5}{n_{1h} + 1}$  and  $p_{2h}^* = \frac{m_{2h} + 0.5}{n_{2h} + 1}$  and  $m_{1h}$  and  $m_{2h}$  are the number of SVR12 in Treatment Groups 1 and 2 in stratum h.
- $\alpha = 0.05$  for this study
- $Z_{(1-\alpha/2)} = Z_{0.975} = 1.96$  is the 97.5th percentile of the normal distribution

If the computed lower confidence bound is less than -1, the lower bound is defined as -1. If the computed upper confidence bound is greater than 1, then the upper bound is defined as 1.

The two-sided 95% exact CI based on binomial distribution (Clopper-Pearson method) will be provided for the SVR12 rate for each treatment group in Cohort 1 {Clopper 1934}.

In the primary efficacy analysis of Cohort 2, the SVR12 rate will be calculated along with two-sided 95% exact CI using Clopper-Pearson method.

#### 6.1.4. Subgroup Analysis of the Primary Efficacy Endpoint

Point estimates and 95% exact CIs of the SVR12 rates for each treatment group in each cohort, and of the difference (Group 1 – Group 2) in SVR12 rates will be displayed for each subgroup outlined in Section 3.4 for cohort 1.

The two-sided 95% exact CI based on Clopper-Pearson method will be provided for the SVR12 rate within each treatment group and subgroup. CIs on the difference of SVR12 rates within each subgroup will be constructed based on the standardized statistic and inverting two 1-sided tests {Chan 1999}.

A Forest Plot will graphically present point estimates and the two-sided 95% exact CIs on the treatment differences (Group 1 – Group 2) in SVR12 rates for each of the subgroups for Cohort 1.

## **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 4 and 24 weeks after discontinuation of treatment (SVR 4 and SVR 24)
- 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  $\geq$  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  $\geq$  LLOQ through 8 weeks of treatment (ie, nonresponse)

#### **Relapse**

- HCV RNA  $\geq$  LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available posttreatment measurement
- Characterization of HCV drug resistance substitutions at baseline, during, and after therapy with LDV/SOF and SOF+RBV

## 6.2.2. Analysis Methods for Secondary Efficacy Endpoints

For analyses of HCV RNA < LLOQ by visit while on treatment and during the posttreatment (SVR) follow-up period, subjects will be assigned a value at each visit based on the analysis visit windows specified in Section 3.8.2. Missing values will be imputed based on the categorical imputation rules described in Section 3.6.1. The two-sided 95% exact confidence interval based on Clopper-Pearson method will be provided for the percentage of subjects with HCV RNA < LLOQ at each visit in each treatment group. The overall category for “HCV RNA < LLOQ” will be split into the following 2 subcategories: “< LLOQ TND” for subjects with target not detected and “< LLOQ detected” for subjects with < LLOQ detected in tabular displays.

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

Summary statistics will be presented for absolute values and change from baseline in HCV RNA ( $\log_{10}$  IU/mL) by visit through EOT. Imputation rules described in Section 3.6.1 will be used to assign HCV RNA values for missing values at a visit that are bracketed by “< LLOQ TND” and/or “< LLOQ detected”. Otherwise, a missing = excluded analysis will be performed. Plots of the mean  $\pm$  SD and median (Q1, Q3) of absolute values and changes from baseline in HCV RNA through EOT will be presented.

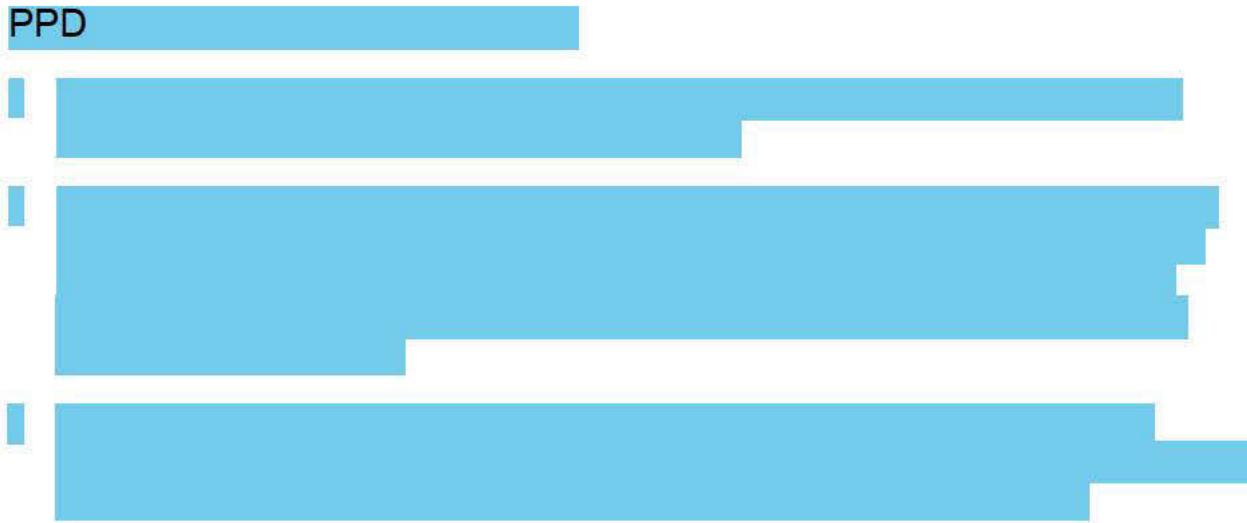
For the SVR12 endpoint analysis, a summary table of the number and percentage of subjects with SVR12, virologic failure (VF), and Other will be created. All subjects who achieve SVR12 will be categorized as SVR12. Virologic failure will be descriptively summarized as “on-treatment virologic failure”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

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

Drug resistant substitutions will be analyzed as part of the Virology Study Report.

### 6.3. Exploratory Efficacy Endpoints

#### 6.3.1. Definition of Exploratory Efficacy Endpoints



#### 6.3.2. Analysis Methods for Exploratory Efficacy Endpoints



## PPD

### 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

#### 7.1.1. Adverse Event Dictionary

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

#### 7.1.2. Adverse Event Severity

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

#### 7.1.3. Relationship of Adverse Events to Study Drug

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

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

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

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

#### 7.1.6. Summaries of Adverse Events and Deaths

A brief high-level summary of TEAEs will be provided in each cohort by treatment group and by the number and percentage of subjects who had the following: any AE; any AE of Grade 3 or above; any AE of Grade 2 or above; any treatment-related AE; any treatment-related AE of Grade 3 or above; any treatment-related AE of Grade 2 or above; any SAE; any treatment-related SAE; any AE that led to premature discontinuation of any study drug, any AE that led to premature discontinuation of LDV/SOF, any AE that led to premature discontinuation of 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 interruption of SOF, and 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.

A brief summary of AEs by age group (ie, <65 years, ≥65 years) and by cirrhotic status will also be explored.

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT, by age group, treatment group and overall based on the Safety Analysis Set for both cohorts 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 any study drug
- AEs leading to premature discontinuation of LDV/SOF
- AEs leading to modification or interruption of any study drug
- AEs leading to interruption of LDV/SOF

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

For each cohort, in addition to the above summary tables, TEAEs will be summarized by PT only, in order of descending incidence within the treatment group (Cohort 2) or pooled (Cohort 1) treatment groups 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 modification or interruption of any study drug
- AEs leading to interruption of LDV/SOF

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
- AE with changes other than resolution dates between the SVR12 and SVR24 analyses
- (provided only at the final analysis)

## **7.2.            Laboratory Evaluations**

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug or all available data at the time of the database snapshot for subjects those who were ongoing at the time of an interim analysis. The analysis will be based on values reported in conventional units. When values are below the limit of quantitation, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics. For example, if “< 0.2” was recorded, a value of 0.1 will be used for the purpose of calculating summary statistics; if “< 0.1” was recorded, a value of 0.09 will be used for the purpose of calculating summary statistics. Hemolyzed test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

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, aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, hemoglobin, reticulocytes, red blood cell (RBC), white blood cell (WBC), neutrophils, lymphocytes, platelets, Albumin, and 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 the reported number of digits; SD to the reported number of digits plus 1.

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

For hemoglobin, the descriptive statistics and Median (Q1, Q3) plot will also be provided by age group within each cohort and treatment.

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 and age group for each cohort.

## **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 the 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 will be 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 for each cohort. 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. 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 [ $^{\circ}\text{C}$ ]) 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 and stopped prior to or on the date of first study drug administration
- 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)

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

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

#### **7.5.           Electrocardiogram Results**

A shift table of the investigators' assessment of ECG results at each visit compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No inferential statistics will be provided.

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. REFERENCES

Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics* 1999;55 (4):1202-9.

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

## **9. SOFTWARE**

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

nQuery Advisor(R) Version 7.0. Statistical Solutions, Cork, Ireland.

## 10. APPENDICES

- Appendix 1. Study Procedures Table
- Appendix 2. QOL Score Calculation Algorithm

**Appendix 1. Study Procedures Table**

	Screening	Day1 <sup>a</sup>	Treatment Week (±3 days)									ET <sup>b</sup>	Posttreatment Week (±5 days)		
			1	2	3	4	5	6	8	10	12/EOT		4	12	24
<b>Clinical Assessments</b>															
Informed Consent		X													
Determine Eligibility	X	X													
Medical History	X														
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG <sup>d</sup>	X	X									X	X			
Adverse Events and Concomitant Medications <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling			X								X	X	X	X	
Health Related Quality of Life <sup>f</sup>			X			X			X		X	X	X	X	
Imaging for HCC <sup>g</sup>	X														
Review of Study Drug Adherence and Drug Accountability <sup>h</sup>			X	X	X	X	X	X	X	X	X	X			
Study Drug Dispensing <sup>i</sup>		X			X			X							

	Screening	Day 1 <sup>a</sup>	Treatment Week (±3 days)									ET <sup>b</sup>	Posttreatment Week (±5 days)		
			1	2	3	4	5	6	8	10	12/EOT		4	12	24
<b>Laboratory Assessments</b>															
Hematology & Chemistry		X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation (PT, aPTT and INR)		X	X	X	X	X	X	X	X	X	X	X			
HCV RNA (Plasma)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral RNA Sequencing /Phenotyping Sample (Plasma) <sup>b</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test <sup>j</sup>		X	X			X			X		X	X	X	X	X
Urinalysis		X	X			X			X		X	X			
HCV Genotype, IL28B Genotype		X													
HCV Ab, HIV Ab and HBsAg		X													
HbA1c		X													
Fibrotest® with APRI		X													
Archive plasma sample			X	X	X	X	X	X	X	X	X	X	X	X	X
Single Genomic Sample <sup>k</sup>			X												

a Day 1 assessments must be performed prior to dosing.

b ET = Early Termination; at all unscheduled visits initiated for the purpose of confirmatory testing, a viral sequence analysis plasma sample must be obtained.

c Vital signs include resting blood pressure, pulse, respiratory rate and temperature.

d Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording. The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities. On treatment ECGs should be compared to the subject's Day 1 as part of routine safety monitoring.

e Adverse events and Concomitant Medications will be collected up to 30 days after the last dose of all study drug.

f 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.

g Liver imaging (e.g., ultrasound or CT scan, at the discretion of the investigator) should be performed to exclude the presence of hepatocellular carcinoma (HCC) in all subjects. For subjects without cirrhosis, imaging must have been performed within 6 months prior to Day 1. For subjects with cirrhosis, imaging must have been performed within 4 months of Day 1.

h Study medication will be reconciled at every post- Day 1 visit by the investigator in order to monitor the subject's adherence with the medication regimen. Subjects must be instructed to bring back all bottles of study medication(s) in the original container at every post- Day 1 visit through the end of treatment.

i Dispense study drugs as directed by the IWRs

- j All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period. Females of childbearing potential in treatment groups without RBV will have a urine pregnancy test at the posttreatment Week 4 visit only. Females of childbearing potential in the treatment group containing RBV 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 in the treatment group containing RBV after the posttreatment Week 4 visit. 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.
- k Only for subjects who have provided separate consent for this sample and testing. This sample can be obtained at a subsequent visit if not obtained at Day 1

## **Appendix 2. QOL Score Calculation Algorithm**

### **CLDQ – HCV**

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

- Activity/Energy (AE) = Mean of  $\{R_1, R_3, R_4, R_5, R_7, R_{18}\}$
- Emotion (EM) = Mean of  $\{R_6, R_8, R_9, R_{11}, R_{16}, R_{23}, R_{24}, R_{27}, R_{28}\}$
- Worry (WO) = Mean of  $\{R_{14}, R_{15}, R_{17}, R_{19}, R_{20}, R_{21}, R_{22}, R_{29}\}$
- Systemic (SY) = Mean of  $\{R_2, R_{10}, R_{12}, R_{13}, R_{25}, R_{26}\}$

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 Well-Being (PWB) =  $7 \times$  Mean of {of GP1-GP7}
- Social/Family Well-Being (SWB) =  $7 \times$  Mean of {GS1-GS7}
- Emotional Well-Being (EWB) =  $6 \times$  Mean of {GE1-GE6}
- Functional Well-Being (FWB) =  $7 \times$  Mean of {GF1-GF7}
- Fatigue Subscale (FS) =  $13 \times$  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 items included 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 =  $100 \times Q2 / (Q2 + Q4)$
- Percent impairment while working due to hepatitis C =  $100 \times Q5 / 10$
- 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 =  $100 \times Q6 / 10$ .