STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naïve and Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection
Name of Test Drug:	Ledipasvir/Sofosbuvir Fixed-Dose Combination
Study Number:	GS-US-337-0131
Protocol Version/Date:	Original: 28 May 2013 Amendment 1.1: 12 December 2013 Amendment 2.0: 01 August 2014 Amendment 3.0: 12 February 2016
Analysis Type	SVR12 and Final Analyses for Subjects from Mainland China and from Overall (China plus Korea plus Taiwan)
Analysis Plan Version:	1.0
Analysis Plan Date:	28 July 2017
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT-TABLES

LIST OF ABBREVIATIONS

β-hCG	β-human chorionic gonadotropin
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BID	twice a day
BLQ	below the lower limit of quantification
BMI	body mass index
BPM	beats per minute
BW	body weight
CI	confidence interval
CL_{cr}	creatinine clearance
CRF	case report form(s)
CRO	Contract (or clinical) research organization
CSR	clinical study report
DAA	Direct acting antiviral
dL	Deciliter
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
eGFR	estimated glomerular filtration rate
E_{max}	maximal effect
EOT	End of Treatment
FDC	fixed-dose combination
FU	follow-up
HCV	hepatitis C virus
HLT	high level term
HLGT	high level group term
HRQoL	Health-Related Quality of Life
H0	null hypothesis
H1	alternative hypothesis
IFN	interferon
INR	International Normalized Ratio of prothrombin time
IVRS	Interactive Voice Response System
LDV	Ledipasvir

LLT	lower level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PG	Pharmacogenomics
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOF	sofosbuvir
SVR	sustained virologic response
SVRx	sustained virologic response x weeks after stopping study drug
TE	treatment-emergent
TFLs	tables, figures, and listings
ULN	upper limit of normal
VF	virologic failure
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in the summary and analysis of data from Study GS-US-337-0131 for Mainland China (hereafter referred to as China), and for the study Overall, i.e., China plus other regions of Korea and Taiwan. This SAP was based on the protocol amendment 3.0 12 February 2016. Related documents are the original study protocol, protocol amendments, and electronic case report form (eCRF). Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR). Analysis of data for subjects enrolled in Korea and Taiwan has previously been conducted in accordance with the SAP dated 22 July 2014 and reported in an interim CSR dated 10 October 2014.

1.1. Study Objectives

1.1.1. Primary Study Objectives

- To determine the antiviral efficacy of treatment with ledipasvir (LDV)/sofosbuvir (SOF) fixed-dose combination (FDC) as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12, defined as HCV RNA < lower limit of quantification [LLOQ] 12 weeks post treatment)

- To evaluate the safety and tolerability of LDV/SOF FDC as assessed by review of the accumulated safety data

1.1.2. Secondary Study Objectives

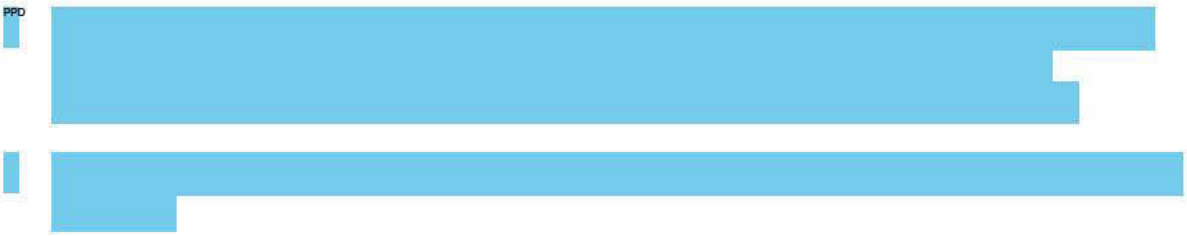
- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)

- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation

- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

1.1.3. Exploratory Study Objectives

PPD



1.2. Study Design

1.2.1. Design Configuration, Subject Population and Treatment Groups

This is an international (China, Korea and Taiwan), multicenter, open-label study in treatment-naïve and treatment experienced adults with chronic genotype 1 HCV infection.

Approximately 180 treatment-naïve and 180 treatment experienced subjects will receive treatment with LDV/SOF 90/400 mg fixed dose combination (FDC) tablet for 12 weeks.

Approximately 200 subjects will be enrolled in China, 80 subjects will be enrolled in Korea, and 80 subjects in Taiwan. Within each country/region approximately 50% (i.e., n~100 or 40) of subjects will be treatment-naïve and 50% will be treatment experienced (i.e., n~100 or 40).

Treatment naïve is defined as having never received treatment for HCV with any interferon (IFN), ribavirin (RBV), or other approved or experimental HCV-specific direct acting antivirals.

Treatment experienced is defined as:

A) IFN intolerant

Note: Subjects intolerant of Peg-IFNα + RBV + HCV protease inhibitor regimens are included in this category.

B) Non-response

C) Relapse/Breakthrough

Note: For treatment experienced subjects, prior exposure to HCV NS3/NS4A protease inhibitors is permitted.

Up to 20% of subjects enrolled in the study may have compensated cirrhosis at Screening.

1.2.2. Study Duration

The total time to complete all study visits is approximately 40 to 42 weeks including:

- 28 to 42 day (4 to 6 weeks) screening period
- 12 week treatment period
- 24 week post-treatment period

1.2.3. Schedule of Assessments

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

1.3. Sample Size and Power

1.3.1. Treatment Naïve Subjects:

A sample size of 100 Chinese subjects in the treatment naïve group will provide at least 90% power to detect a 17% improvement in SVR12 rate from the historical control rate of 57% using 2-sided exact one-sample binomial test at significant level of 0.05. With 100 subjects in China, the two-sided 95% exact confidence interval for the SVR12 rate will extend at most 20% in length.

1.3.2. Treatment Experienced Subjects:

For treatment experienced subjects, a confidence interval approach will be used to justify the sample size given that our goal is to characterize the SVR rate in a population with limited treatment options and not to test a specific hypothesis. With 100 subjects in China, the two-sided 95% exact confidence interval for the SVR12 rate will extend at most 20% in length.

2. TYPE OF PLANNED ANALYSIS

2.1. Posttreatment Week 4 Analysis

A posttreatment Week 4 analysis will be conducted for administrative purposes when all subjects in China have completed the posttreatment Week 4 visit or have prematurely discontinued from the study. All efficacy and safety data through the posttreatment Week 4 visit will be included (SVR12 data 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 or study conduct as a result of this administrative analysis (eg, the analysis would not lead to early termination of the study, and there would be no early stopping, no potential for sample size adjustment, and no changes in the design of the study). This analysis is for evaluation of safety and to facilitate development of the clinical study report.

2.2. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint analysis (for SVR12) will be conducted when all subjects enrolled in China have completed the 12 week post treatment visit or prematurely discontinue from study, and all the safety and efficacy data through the Posttreatment Week 12 visit will be finalized and included in the analysis.

2.3. Final Analysis

The final analysis will be conducted when all subjects enrolled in China have completed the 24 week post treatment 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

3.1. Analysis Sets

Analysis sets define which subjects are included in an analysis. A summary of the number and percentage of subjects in each analysis set will be provided for China and Overall (i.e., China plus Korea plus Taiwan) as part of the subject disposition summary.

3.1.1. Enrolled Analysis Set

The enrolled analysis set includes subjects who were enrolled into the study.

3.1.2. Full Analysis Set

The full analysis set (FAS) includes subjects who were enrolled and received at least 1 dose of study drug, and have chronic genotype 1 HCV infection.

The study drug in this study is LDV/SOF.

3.1.3. Safety Analysis Set

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

3.1.4. Pharmacokinetic Analysis Set

The PK analysis set will include all enrolled subjects who received at least 1 dose of study drug, and for whom at least 1 population PK parameter can be derived for LDV, SOF or its metabolites (as appropriate).

The PK analysis set will be used for the analyses related to the population PK parameters.

3.2. Subject Groups

Subjects will be grouped for analyses according to prior treatment experience (treatment naïve or treatment experienced) for efficacy analysis using the FAS.

3.3. Strata and Covariates

Not Applicable.

3.4. Examination of Subject Subsets

In addition to analyzing by groups according to prior treatment experience, the primary efficacy endpoint, SVR12, will be analyzed for the following subsets:

- age group on date of first dose of study drug (< 65 years, ≥ 65 years)
- sex (male, female)
- baseline BMI (< 25 kg/m^2 , ≥ 25 kg/m^2)
- cirrhosis (cirrhosis, absence of cirrhosis)
- response to prior HCV treatment (nonresponse, relapse/breakthrough, IFN intolerant) for treatment experienced subjects
- IFN eligibility (IFN eligible, IFN ineligible, IFN unwilling) for treatment naive subjects
- baseline HCV RNA (< 800,000 IU/mL, ≥ 800,000 IU/mL) and (< 5 $\log_{10}$ IU/mL, ≥ 5 $\log_{10}$ IU/mL
- baseline ALT (≤ 1.5 × ULN, > 1.5 × ULN)
- IL28B (CC, Non-CC (CT, TT))
- adherence to study drug (<80%, ≥ 80%)

3.5. Data Handling Conventions and Transformations

The COBAS® Taqman® HCV Test v2.0 for use with the High Pure System assay was used to determine HCV RNA results of Korea and Taiwan in this study. The lower limit of quantitation (LLOQ) of the assay is 25 IU/mL. Quantitative HCV RNA data for Korea and Taiwan were reported in the CSR dated 10 October 2014 and the synoptic CSR dated 26 February 2015.

The COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0 is used to determine HCV RNA results of China in this study. The lower limit of quantitation (LLOQ) of the assay is 15 IU/mL.

When the calculated HCV RNA value is within the linear range of the assay, then the result will be reported as the "<< numeric value>> IU/mL". This result will be referred to in this document as the numeric result or as "≥ LLOQ detected" for categorical result.

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

When the HCV RNA IU/mL is detected but less than LLOQ of the assay, the result is reported as "< 15 IU/mL HCV RNA detected" for China subjects and "<25 IU/mL HCV RNA detected" for Korean/Taiwan subjects. These results will be referred to in this document as "< LLOQ detected".

Numerical HCV RNA data with values below LLOQ will be set to the LLOQ minus 1 (ie, 14 IU/mL for China subjects and 24 IU/mL for Korean/Taiwan subjects). HCV RNA values returned as "target not detected" will also be set to 14 IU/mL or 24 IU/mL for China and Korean/Taiwan subjects, respectively.

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

HCV RNA data for China will be summarized. No analysis of quantitative HCV RNA data for Overall (China plus Korea plus Taiwan) will be conducted.

Categorical data (HCV RNA < LLOQ or ≥ LLOQ for China and for Korea and Taiwan) will be summarized for China and Overall (China plus Korea plus Taiwan) regardless of the LLOQs.

Total bilirubin values entered as < 0.2 mg/dL will be analyzed as 0.1 mg/dL; direct bilirubin values entered as < 0.1 mg/dL will be analyzed as 0.05 mg/dL {Nehls 1973}. In general, other than the above 2 exceptions, laboratory 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 to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

Exposure parameters that are selected for statistical analysis will be natural log-transformed.

Concentration values that are BLQ will be excluded for any ratio or natural log-transformed statistical analysis.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

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

For analyses of categorical HCV RNA data, if a data point is missing and is preceded and followed in time by values that are "< LLOQ TND", then the missing data point will be set to "< LLOQ TND". If a data point is missing and preceded and followed by values that are "< LLOQ detected", or preceded by "< LLOQ detected" and followed by "< LLOQ TND", or

preceded by "< LLOQ TND" and followed by "< LLOQ detected", then the missing value will be set to "< LLOQ detected"; otherwise the data point will be termed a failure (ie, ≥ LLOQ detected).

Subjects with missing data due to premature discontinuation of the study will have missing data imputed up to the time of their last dose (for on-treatment displays). If study days 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, then the value will be imputed. If the study days 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 no HCV RNA values are obtained after the last dose of any study drug, the subject will be considered a treatment failure for SVR endpoints. However, 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 {Chen 2013}.

For the analyses of continuous HCV RNA efficacy data for China, any subject with a missing value in a visit window that is bracketed by prior and subsequent values of "< LLOQ TND" will be set to "< LLOQ TND" (ie, 14 IU/mL). Subjects with a missing data point preceded and followed by values that are "< LLOQ detected", preceded by "< LLOQ detected" and followed by "< LLOQ TND", or preceded by "< LLOQ TND" and followed by "< LLOQ detected" will be set to "< LLOQ detected" (ie, 14 IU/mL). No other imputation will be performed for continuous data. No Overall analysis of continuous HCV RNA data will be conducted.

For health-related quality of life data (ie, SF-36), missing data will not be imputed.

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

3.6.2. Outliers

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

3.7. Visit Windows

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

Study Day 1 is defined as the **first dose date of study drug (ie, LDV/SOF)**.

The ***date of last dose of study drug*** will be the end date on study drug administration CRF for the record where the "subject permanently discontinued" flag is 'Yes'.

Study Day 1 of ***post-treatment follow-up*** will be ***last dose date of study drug*** + 1.

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, the date of last dose will be estimated using the maximum of nonmissing study drug start or stop dates and on-treatment visit dates and laboratory collection dates (post-treatment visits and unscheduled visits are not included).

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

3.7.2. Analysis Windows

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

Visit windows are defined for HCV RNA, vital signs and safety laboratory data. No analysis windows will be defined for health related quality of life data and pregnancy data.

All available HCV RNA data will be included in efficacy analysis, unless a subject starts alternative HCV medication. HCV RNA data collected after starting alternative HCV medication will be excluded. Imputation for missing HCV RNA values are described in Section 3.6. For safety data, subjects who are permanently discontinued from study drug will be included in safety analyses to last dosing date of any study drug + 30 days unless otherwise specified.

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

Visit windows will be calculated from **Study Day 1** (ie, Study Day = collection date minus date **Study Day 1**; +1 if result is ≥ 0) for HCV RNA, vital signs and other safety laboratory data as shown in Table 3-1.

Table 3-1. On-Treatment Visit Windows for Selected Tests

Visit ID	On-Treatment Visit Windows for HCV RNA, Vital Signs and Safety Laboratory Data
Baseline	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11
Week 2	12 ≤ Study Day ≤ 21
Week 4	22 ≤ Study Day ≤ 35
Week 6	36 ≤ Study Day ≤ 49
Week 8	50 ≤ Study Day ≤ 63
Week 10	64 ≤ Study Day ≤ 77
Week 12	78 ≤ Study Day ≤ 98

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

Table 3-2. Post-treatment Visit Windows for Selected Tests

Off-Treatment FU Visit ID	Post-treatment Visit Windows for HCV RNA [a] (Days from Last Dose Date)	Vital Signs and Safety Laboratory Data [b] (Days from Last Dose Date)
FU-4	21 ≤ FU Day ≤ 69	3 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	N/A
FU-24	147 ≤ FU Day ≤ 190	N/A

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

Qualitative assessments of whether the ECG is normal or abnormal will be assessed based on the following visit windows shown in Table 3-3:

Table 3-3. On-Treatment Visit Windows for ECGs

Visit ID	On-Treatment Visit Windows for ECG Data
Baseline	Study Day ≤ 1
Week 1	2 < Study Day ≤ 18
End of Treatment	18 < Study Day ≤ Study Day of Last dose date +2

Note: ECGs are to be collected at screening, baseline, Week 1, Week 12 and End of Treatment. For purposes of analysis, Baseline will be the last available value prior to first dose and End of treatment is last available ECG on/prior to last dose date of study drug +2 day.

3.7.3. Selection of Data in the Event of Multiple Records in a Window

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

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

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

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment

The number and percentage of subjects enrolled and treated by each investigator will be summarized by prior treatment experience (treatment naive and treatment experienced subjects) for China and Overall. The denominator for this calculation will be the number of subjects in the safety analysis set for that column.

4.2. Disposition of Subjects

A summary of subject disposition will be provided for China and Overall. This summary will present the number of subjects screened, rescreened, subjects not enrolled (with reasons), enrolled, enrolled and treated (ie, Safety Analysis Set), FAS, PK Analysis Set, and the number and percentage of subjects meeting the following criteria:

- Completed study treatment
- Discontinued study treatment (with summary of reasons for not completing the study treatment period)
- On study treatment (if applicable)
- Completed the study
- Did not complete the study (with summary of reasons for not completing the study)
- On study (ongoing; if applicable)

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

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

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

No inferential statistics will be generated.

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

4.3. Extent of Exposure

4.3.1. Duration of Exposure to Study Drug

Duration of exposure to study treatment will be defined as (Last Dose Date of Study Drug – First dose Date of Study Drug + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks (recorded to 1 decimal place, eg, 12.1 weeks).

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

Summaries will be provided by prior treatment experience for China and Overall for the safety analysis set.

4.3.2. Adherence to Study Drug

Adherence will be calculated for LDV/SOF (tablets) as:

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

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

4.3.2.1. Calculation of Number of Tablets Prescribed for Study Drug

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

- Prescribed LDV/SOF (90 mg/400 mg) would require 84 tablets (ie, 1 tablet/day x 84 days) for the 12-week treatment period.

Subjects who prematurely discontinue study drug for lack of efficacy (ie, virologic failure) will have prescribed medications calculated for the number of study days at the first date when virologic stopping criteria were met (ie, substitute number of days to virologic failure [date of first of 2 consecutive measurements or a last available value meeting criteria] for 84 days).

4.3.2.2. Calculation of Number of Tablets Taken

The number of tablets taken for LDV/SOF during the treatment period will be calculated as the sum of (number of tablets dispensed – number of tablets returned) at each distinct dispensing period across all bottles/blister packs dispensed. For subjects who discontinue for virologic failure, bottles dispensed after the subject first met virologic failure criteria will not be included in calculations. If a bottle is dispensed, and the bottle is returned empty, then the number of tablets returned will be entered as zero. If a bottle is dispensed but not returned (missing), the number of tablets taken from that bottle will be counted as zero.

Descriptive statistics for adherence to LDV/SOF (sample size, mean, SD, median, Q1, Q3, minimum and maximum) along with the number and percentage of subjects belonging to adherence categories (e.g., $< 80\%$, ≥ 80 to $< 90\%$, $\geq 90\%$) will be provided by prior treatment experience for China and Overall for the safety analysis set.

No inferential statistics will be provided.

4.4. Protocol Deviations

In Section 3.1.4, PK analysis set definition is slightly different from protocol amendment 3 Section 8.2.1.3 Pharmacokinetics: The PK analysis set will include all subjects who are enrolled and have received at least one dose of study drug, and for whom concentration data of analytes [SOF, LDV, and metabolite(s), as appropriate] are available. The rationale for this change in PK analysis set definition in SAP from protocol is because if there is concentration record for a subject but is not usable for POP PK modeling, this concentration record is considered no value for PK interpretation.

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

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

The following subject demographic and baseline characteristics will be summarized by prior treatment experience (treatment naive and treatment experienced subjects) for China and Overall (i.e., China plus Korea plus Taiwan) using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percent of subjects for categorical data. Variables to be summarized include the following:

- age (on date of first dose of study drug) as a continuous variable and for categories (< 65 years, ≥ 65 years)
- sex (male, female)
- race and race subcategory (Chinese, Korean, Taiwanese and Other)
- ethnicity (Hispanic or Latino, non-Hispanic or Latino)
- body mass index as a continuous variable and for categories (< 25 kg/m^2 and ≥ 25 kg/m^2)
- HCV genotype subtype
- cirrhosis (cirrhosis, absence of cirrhosis)
- IL28B (CC, Non-CC (CT, TT))
- baseline HCV RNA as a continuous variable and for categories (<800,000 IU/mL, ≥ 800,000 IU/mL) and (< 5 $\log_{10}$ IU/mL, ≥ 5 $\log_{10}$ IU/mL)
- baseline ALT as a continuous variable and for categories (≤1.5 x ULN, > 1.5 x ULN)
- response to prior HCV treatment (nonresponse, relapse/breakthrough, IFN intolerant) for treatment experienced subjects
- interferon eligibility (IFN eligible, IFN ineligible, IFN unwilling) for treatment naive subjects
- estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation

Age is calculated as the integer of age in years at first dose of study drug. 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.

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

5.2. Medical History

General medical history (ie, conditions not specific to the disease being studied) data will be listed only. General medical history data will not be coded.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is SVR 12 (HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs) in the FAS population. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0 will be used to determine HCV RNA results of China in this study. The LLOQ of the assay is 15 IU/mL.

The COBAS® Taqman® HCV Test v2.0 for use with the High Pure System was used to measure HCV RNA of Korea and Taiwan. The LLOQ of the assay was 25 IU/mL.

6.1.2. Primary Analysis of the Primary Efficacy Endpoint

The primary efficacy analysis described below will compare the observed SVR12 rate for the investigational regimen (i.e., LDV/SOF FDC for 12 weeks) versus the adjusted historical SVR null rate in treatment–naïve, Chinese subjects only.

In addition, a point estimate with a two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method{Clopper 1934}) will be constructed for the SVR12 rate by prior treatment experience for China and Overall (i.e., Korea , Taiwan and China).

Treatment Naïve Subjects

In the primary efficacy analysis the SVR12 rate from China will be compared to the adjusted historical SVR null rate of 57% (as calculated in Appendix 3) using a two-sided exact one-sample binomial test.

The hypothesis for superiority in China is:

H0: SVR12 rate = 57%,

H1: SVR12 rate ≠ 57%.

Treatment Experienced Subjects:

There is no treatment option available in China, Korea or Taiwan for treatment experienced patients with GT-1 infection. In the absence of effective antiviral therapy, spontaneous clearance of the HCV is rare. Consequently a nominal SVR rate of 5% is assumed for treatment-experienced subjects.

No statistical hypothesis testing will be performed in treatment experienced subjects. For China and Overall (i.e., China plus Korea plus Taiwan), a point-estimate with two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate.

6.1.3. Subgroup Analysis of the Primary Efficacy Endpoint

Point estimates and 95% exact confidence intervals of the SVR12 rates by prior treatment experience for China and Overall (i.e., China plus Korea plus Taiwan) will be displayed for each subgroup outlined in Section 3.4. The 2-sided 95% exact confidence intervals will be based on Clopper-Pearson method {Clopper 1934}.

A Forest plot will graphically present estimates and 95% confidence intervals of SVR12 rates for each of the subgroups.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- The proportion of subjects who attain SVR at 4 and 24 weeks after stopping therapy, defined as HCV RNA < LLOQ 4 and 24 weeks after stopping treatment (SVR 4 and SVR 24)
- The proportion of subjects with HCV RNA below LLOQ by study visit
- HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through Week 12 for China only
- The proportion of subjects with virologic failure as the following:
  - On-treatment virologic failure
    1) 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)
    2) > 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)
    3) HCV RNA persistently ≥ LLOQ through 8 weeks of treatment (ie. nonresponse)
  - Relapse
    1) 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
- Characterization of HCV drug resistance substitutions at baseline, during, and after therapy with LDV/SOF

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

For analyses of HCV RNA < LLOQ by visit while on treatment and during the post-treatment (SVR) follow-up period, subjects will be assigned a value at each visit based on the categorical imputation rules described in Section 3.5. The 2-sided 95% exact confidence interval based on Clopper-Pearson exact method will be provided for the proportion by prior treatment experience for China and Overall {Clopper 1934}. The "HCV RNA < LLOQ" category will be split into the following 2 subcategories: "< LLOQ TND" for subjects with target not detected and "< LLOQ detected" for subjects with < LLOQ in tabular displays.

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

Summary statistics will be presented for absolute values and change from baseline in HCV RNA (log_{10} IU/mL) by visit and by prior treatment experience through Week 12 in China. Since LLOQ is 15 IU/mL of COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0 used to determine HCV RNA results of China, while LLOQ is 25 IU/mL of the COBAS® Taqman® HCV Test v2.0 for use with the High Pure System used in Korea and Taiwan, summary statistics for absolute values and change from baseline in HCV RNA for Overall (ie, China, Korea, plus Taiwan) will not be provided. Results for Korea and for Taiwan using the LLOQ of 25 IU/mL have been reported separately in the GS-US-337-0131 interim CSR dated 10 October 2014. Imputation rules described in Section 3.5 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 Week 12 for subjects in China 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 by prior treatment experience. 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 summarized 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.

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

PPD

6.3.2. Analysis Methods for Exploratory Efficacy Endpoints

PPD

PPD

6.4. Changes From Protocol-Specified Efficacy Analyses

There are no changes from protocol-specified efficacy analyses.

7. SAFETY ANALYSES

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

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

7.1. Adverse Events

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator according to the Gilead Sciences, Inc. (Gilead) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities as specified in the clinical study protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

The relationship of AE to study drug will be assessed by investigators as "Yes" or "No". Events for which the investigator did not record the relationship to study drug will be considered to be related to study drug for summary purposes. However, data listings will present the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events 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 AEs are

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

7.1.5.2. Incomplete Dates

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

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

7.1.6. Summaries of Adverse Events and Deaths

A brief summary of AEs will show, for China and Overall (i.e., China plus Korea plus Taiwan), the number and percentage of subjects who (1) had any TE AE, (2) had any Grade 3 and 4 TE AE, (3) had any Grade 2, 3 and 4 TE AE, (4) had any TE treatment-related AE, (5) had any Grade 3 and 4 TE treatment-related AE, (6) had any Grade 2, 3 and 4 TE treatment-related AE, (7) had any TE SAE, (8) had any TE treatment-related SAE, (9) AEs leading to permanent discontinuation from LDV/SOF (10) had any AE leading to interruption of LDV/SOF and (11) TE death during the study.

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

- All TE AEs
- Combined Grade 3 or 4 TE AEs
- Combined Grade 2, 3 or 4 TE AEs
- TE treatment-related AEs
- Combined Grade 3 or 4 TE treatment-related AEs
- Combined Grade 2, 3 or 4 TE treatment-related AEs

- TE SAEs
- TE treatment-related SAEs
- Adverse Events Leading to permanent discontinuation from LDV/SOF
- All deaths

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

In addition to the presentation by SOC and PT, summaries will also be presented by PT only, ordered by decreasing total frequency for: (1) TE treatment-related AEs; (2) TE AEs that occurred in more than 5% of subjects within any region; (3) AEs leading to permanent discontinuation of LDV/SOF; (4) TE SAEs; and (5) TE grade 3 or 4 AEs.

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

- All AEs
- SAEs
- Deaths
- AEs leading to permanent discontinuation from LDV/SOF
- Grade 3 and 4 AEs

7.2. Laboratory Evaluations

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

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum and maximum) will be provided for China and Overall for ALT, AST, total bilirubin, alkaline phosphatase , hemoglobin, reticulocytes, white blood cell (WBC) counts, neutrophils, lymphocytes, platelets, and INR as follows:

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

The mean, median, Q1, Q3, minimum and maximum will be displayed to reported number of digits, standard deviation to reported number of digits +1 for visits up to Week 12 (end of treatment). The Week 4 safety follow-up visit will be presented as an additional separate visit.

Median (Q1, Q3) of the absolute values for these laboratory parameters will be plotted for China and Overall by visit. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

The number of subjects with hemoglobin < 10 g/dL or < 8.5 g/dL at any postbaseline visit (up to 30 days after the last dose of any study drug) will be summarized for China and Overall.

7.2.2. Graded Laboratory Values

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

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

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

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

7.2.2.2. Summaries of Laboratory Abnormalities

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

- TE graded laboratory abnormalities
- TE Grade 3 and 4 laboratory abnormalities

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

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

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

7.3. Body Weight, Height, BMI and Vital Signs

Absolute value and change from baseline in vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP] and pulse) at each visit will be summarized for the safety analysis set using descriptive statistics for China and Overall for each post baseline analysis window. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3. No inferential statistics will be generated.

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

7.4. Concomitant Medications

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

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

missing) that is prior to the study drug start date will be excluded from the summary. If a partial start date is entered, then the month and year (if day is missing) or year (if day and month are missing) that is after the study drug stop date will be excluded from the summary.

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

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

7.5. Electrocardiogram Results

A shift table of the investigator's assessment of ECG results at baseline (normal, abnormal but not clinically significant, abnormal and clinically significant, or missing) versus the investigator's assessment at each on-treatment visit (normal, abnormal but not clinically significant, abnormal and clinically significant, or missing) will be presented for China and Overall. The number and percent of subjects in each cross-classification group will be presented (subjects with a missing value at baseline or on-treatment visit will not be included in the denominator for percent calculation).

A listing of ECG results including comments regarding clinically significant abnormalities will be provided.

7.6. Other Safety Measures

A data listing for cirrhosis determination will be provided for all subjects at screening.

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

8. PHARMACOKINETIC ANALYSES

Single PK samples are collected at weeks 1, 2, 4, 6, 8, 10, and 12 (sparse PK sampling). Concentration of LDV and SOF (and its metabolites) in plasma will be determined using validated bioanalytical assays.

Population PK models for LDV, SOF, and GS-331007, previously developed for the phase 2/3 LDV/SOF US NDA population analyses, will be applied to the data from all PK samples (intensive and sparse) collected in this study. PK parameters (AUC_{tau}, C_{max} and C_{tau} of LDV; AUC_{tau} and C_{max} of SOF and GS-331007) will be estimated from the simulated LDV, SOF, and GS-331007 concentration data using the population PK model. The population PK model-derived PK parameters will be listed and summarized.

The population PK parameters of LDV, SOF and GS-331007 will be summarized by China and overall.

The population PK parameters of LDV, SOF, and GS-331007 in this study will also be compared to the population PK parameters of LDV, SOF, and GS-331007 in the phase 2/3 LDV/SOF US NDA population to assess the difference in PK exposure between subjects from China and Overall in GS-US-337-0131 versus the phase 2/3 LDV/SOF US NDA population. The geometric mean ratios and corresponding 90% confidence interval will be provided.

9. REFERENCES

Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier Sustained Virologic Response End Points for Regulatory Approval and Dose Selection of Hepatitis C Therapies. Gastroenterology 2013;144 (7):1450-5.

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.

Heo N-Y, Lim Y-S, Lee HC, Lee YS, Kim KM, Byum KS, et al. High effectiveness of peginterferon alfa-2a plus ribavirin therapy in Korean patients with chronic hepatitis C in clinical practice. Clin Mol Hepatol 2013;19 (1):60-9.

Nehls G, Akland G. Procedures for Handling Aerometric Data. Journal of the Air Pollution Control Association 1973;23 (3):180-4.

Park SY, Rim MY, Yo IK, Ha MS, Kim JS, Lee JW, et al. [Efficacy of peginterferon and ribavirin combination therapy of chronic hepatitis C: a pooled analysis]. The Korean journal of gastroenterology = Taehan Sohwagi Hakhoe chi 2012;60 (5):306-14.

10. SOFTWARE

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

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

11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings
Appendix 2. Schedule of Assessments
Appendix 3. Calculation of Historical Control SVR12 for Treatment naïve Chinese Subjects with Chronic GT-1 HCV Infection

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

Table Number	Title	Analysis Set
1	Subjects Enrolled and Treated by Investigator	Safety Analysis Set
2	Subject Disposition	Screened Subjects
3	Reasons for Screen Failure	Screened Subjects
4	Demographics and Baseline Characteristics	Safety Analysis Set
4.1	Summary of Categories for Interferon Eligibility and Reasons for Interferon Ineligible	Safety Analysis Set
4.2	Summary of Categories for Response to Prior HCV Treatment and Reasons for Interferon Intolerance	Safety Analysis Set
5	Duration of Exposure to Study Drug	Safety Analysis Set
6	Concomitant Medications	Safety Analysis Set
7	Adherence to Study Drug	Safety Analysis Set
8.1	SVR12	Full Analysis Set
8.2	SVR12 by Subgroup	Full Analysis Set
9	Concordance between SVR12 and SVR24	Full Analysis Set
10	Virologic Outcome	Full Analysis Set
11	Proportion of Subjects with HCV RNA Less than LLOQ While on Treatment by Visit	Full Analysis Set
12	SVR by Visit During Posttreatment Follow-Up	Full Analysis Set
13	HCV RNA ($\log_{10}$ IU/mL) and Change from Baseline by Visit Through Week 12	Subjects in China in Full Analysis Set
14	Proportion of Subjects with ALT Normalization by Visit	Full Analysis Set with ALT>ULN at Baseline
15	Adverse Events: Brief Summary	Safety Analysis Set
16	All Treatment-Emergent Adverse Events	Safety Analysis Set
17	Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set
17.1	Treatment-Emergent Treatment-Related Adverse Events by Preferred Term	Safety Analysis Set
18	Grade 3 or 4 Treatment-Emergent Adverse Events	Safety Analysis Set
19	Grade 3 or 4 Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set
20	Grade 2, 3, or 4 Treatment-Emergent Adverse Events	Safety Analysis Set
21	Grade 2, 3, or 4 Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set

Table Number	Title	Analysis Set
22	Adverse Events Leading to Permanent Discontinuation from LDV/SOF	Safety Analysis Set
23	Treatment-Emergent Serious Adverse Events	Safety Analysis Set
24	Treatment-Emergent Treatment-Related Serious Adverse Events	Safety Analysis Set
25	All Deaths	Safety Analysis Set
27	Treatment-Emergent Adverse Events Occurring in At Least 5% of Subjects by Preferred Term	Safety Analysis Set
28	Adverse Events Leading to Permanent Discontinuation of LDV/SOF by Preferred Term	Safety Analysis Set
29	Treatment-Emergent Serious Adverse Events by Preferred Term	Safety Analysis Set
30	Treatment-Emergent Grade 3 or 4 Adverse Events by Preferred Term	Safety Analysis Set
31.1	ALT (U/L) and Change from Baseline by Visit	Safety Analysis Set
31.2	AST (U/L) and Change from Baseline by Visit	Safety Analysis Set
31.3	Total Bilirubin (mg/dL) and Change from Baseline by Visit	Safety Analysis Set
31.4	Alkaline Phosphatase (U/L) and Change from Baseline by Visit	Safety Analysis Set
31.5	Hemoglobin (g/dL) and Change from Baseline by Visit	Safety Analysis Set
31.6	Subjects with Postbaseline Hemoglobin < 10 g/dL or < 8.5 g/dL	Safety Analysis Set
31.7	Reticulocytes (x 10^3 /μL) and Change from Baseline by Visit	Safety Analysis Set
31.8	WBC (x 10^3 /μL) and Change from Baseline by Visit	Safety Analysis Set
31.9	Neutrophils (x10^3 /μL) and Change from Baseline by Visit	Safety Analysis Set
31.10	Lymphocytes (x10^3 /μL) and Change from Baseline by Visit	Safety Analysis Set
31.11	Platelets (x 10^3 /μL) and Change from Baseline by Visit	Safety Analysis Set
31.12	INR and Change from Baseline by Visit	Safety Analysis Set
32	Treatment-Emergent Graded Laboratory Abnormalities	Safety Analysis Set
33	Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set
34	Shift Table of Baseline versus On-Treatment 12-lead ECG Assessment by Visit	Safety Analysis Set
35.1	Systolic Blood Pressure (mmHg) and Change from Baseline by Visit	Safety Analysis Set
35.2	Diastolic Blood Pressure (mmHg) and Change from Baseline by Visit	Safety Analysis Set

Table Number	Title	Analysis Set
35.3	Pulse (bpm) and Change from Baseline by Visit	Safety Analysis Set
36	Summary of SF-36 Quality of Life Questionnaire	Full Analysis Set
38	Individual and Summary of Population PK Model-derived PK Parameters Overall and by Region	PK Analysis Set
40.1	Summary of Population PK Parameters in Study GS-US-337-0131 (Overall and by Region) Compared to the LDV/SOF US NDA Population Following Administration of LDV/SOF	PK Analysis Set

Figure Number	Title	Analysis Set
1	Subject Disposition	Safety Analysis Set
2	Forest Plot of SVR12 by Subgroup	Full Analysis Set
3	Proportion of Subjects with HCV RNA < LLOQ While on Treatment by Visit	Full Analysis Set
4.1	Mean ± SD Change from Baseline in HCV RNA (log_{10} IU/mL) by Visit Through Week 12	Subjects in China in Full Analysis Set
4.2	Median (Q1, Q3) Change from Baseline in HCV RNA (log_{10} IU/mL) by Visit Through Week 12	Subjects in China in Full Analysis Set
4.3	Mean ± SD in HCV RNA (log_{10} IU/mL) by Visit Through Week 12	Subjects in China in Full Analysis Set
4.4	Median (Q1, Q3) in HCV RNA (log_{10} IU/mL) by Visit Through Week 12	Subjects in China in Full Analysis Set
5.1	Median (Q1, Q3) ALT (U/L) by Visit	Safety Analysis Set
5.2	Median (Q1, Q3) AST (U/L) by Visit	Safety Analysis Set
5.3	Median (Q1, Q3) Total Bilirubin (mg/dL) by Visit	Safety Analysis Set
5.4	Median (Q1, Q3) Alkaline Phosphatase (U/L) by Visit	Safety Analysis Set
5.5	Median (Q1, Q3) Hemoglobin (g/dL) by Visit	Safety Analysis Set
5.6	Median (Q1, Q3) Reticulocytes (x 10^3 /μL) by Visit	Safety Analysis Set
5.7	Median (Q1, Q3) WBC (x 10^3 /μL) by Visit	Safety Analysis Set
5.8	Median (Q1, Q3) Neutrophils (x 10^3 /μL) by Visit	Safety Analysis Set
5.9	Median (Q1, Q3) Lymphocytes (x 10^3 /μL) by Visit	Safety Analysis Set
5.10	Median (Q1, Q3) Platelets (x 10^3 /μL) by Visit	Safety Analysis Set
6	Mean ± SD Change from Baseline in SF-36 Quality of Life Questionnaire by visit	Full Analysis Set

Listing Number	Title	Analysis Set
1	Inclusion and Exclusion Criteria	Subjects Not Treated
2.1	Subjects Who were Excluded from Safety and Full Analysis Sets	All Enrolled Subjects
2.2	Subjects Enrolled and Treated Who Did Not Meet Eligibility Criteria	Safety Analysis Set
3	Subject Disposition	Safety Analysis Set
4.1	Subject Demographics and Baseline Characteristics	Safety Analysis Set
4.2	Cirrhosis Determination	Safety Analysis Set
4.3	Interferon Ineligible Reasons	Safety Analysis Set
4.4	Interferon Intolerant Reasons	Safety Analysis Set
4.5	Response to Prior HCV Treatment	Safety Analysis Set
5	Medical History	Safety Analysis Set
6.1	Study Drug Administration	Safety Analysis Set
6.2	Study Drug Accountability and Adherence	Safety Analysis Set
7	Prior and Concomitant Medications	Safety Analysis Set
8.1	HCV RNA (log10 IU/mL) and Change from Baseline	Safety Analysis Set
8.2	Subjects with Virologic Failure	Safety Analysis Set
8.3	Subjects with Postbaseline Hemoglobin < 10 g/dL or < 8.5 g/dL	Safety Analysis Set
9	SF-36 Quality of Life Questionnaire	Safety Analysis Set
10	All Adverse Events	Safety Analysis Set
11	Grade 3 or 4 Adverse Events	Safety Analysis Set
12	Adverse Events Leading to Permanent Discontinuation from LDV/SOF	Safety Analysis Set
13	Serious Adverse Events	Safety Analysis Set
14	Pregnancy	Safety Analysis Set
15	Deaths	Safety Analysis Set
16	Central Laboratory (Covance) Reference Ranges	Safety Analysis Set
17	Subjects with Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set
18	Screen Labs: HBsAg, Anti-HIV Ab, Anti-HCV Ab, HbA1c, and Serum Beta hCG	Safety Analysis Set
19.1	Hematology: Hematocrit, Hemoglobin, Reticulocyte Count, MCV, RBC, WBC, and Platelets	Safety Analysis Set
19.2	Hematology: WBC, Neutrophils, and Lymphocytes	Safety Analysis Set
19.3	Hematology: Eosinophils, Basophils, and Monocytes	Safety Analysis Set

Listing Number	Title	Analysis Set
20.1	Chemistry: Sodium, Potassium, Serum Creatinine, Estimated GFR (Cockcroft-Gault), and Glucose	Safety Analysis Set
20.2	Chemistry: AST, ALT, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, GGT, Albumin, and Lipase	Safety Analysis Set
20.3	Coagulation and Other Laboratory Tests: INR, APTT, and TSH	Safety Analysis Set
21.1	Urinalysis: Urine Blood, Glucose, pH, Protein, Urobilinogen, and Leukocyte Esterase	Safety Analysis Set
21.2	Microscopic Urinalysis for Subjects with Abnormal Leukocyte Esterase	Safety Analysis Set
22	12-Lead Electrocardiogram Results	Safety Analysis Set
23.1	Vital Signs	Safety Analysis Set
23.2	Height, Weight, and BMI	Safety Analysis Set

Appendix 2. Schedule of Assessments

Appendix Table 1. Screening and On-Treatment Study Visits

	Screening[a]	On Treatment Period								
Clinical Assessments	**Day -28 to Day -1**	**Baseline/ Day 1[b]**	**Week 1 (±3 days)**	**Week 2 (±3 days)**	**Week 4 (±3 days)**	**Week 6 (±3 days)**	**Week 8 (±3 days)**	**Week 10 (±3 days)**	**Week 12 (±3 days)**	**ET**
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X							X	X
Liver Imaging (Cirrhotics Only)	X									
Height	X									
Weight	X	X							X	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X
12-lead ECG[d]	X	X	X						X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X	X
Health Related Quality of Life		X		X	X		X		X	X
Hematology & Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X							X	X
Serum HCV RNA	X	X	X	X	X	X	X	X	X	X
Single PK Sample			X	X	X	X	X	X	X	X

Clinical Assessments	Screening[a]	On Treatment Period								
	Day -28 to Day -1	Baseline/ Day 1[b]	Week 1 (±3 days)	Week 2 (±3 days)	Week 4 (±3 days)	Week 6 (±3 days)	Week 8 (±3 days)	Week 10 (±3 days)	Week 12 (±3 days)	ET
Viral RNA Sequencing /Phenotyping Sample (Plasma)[e]		X	X	X	X	X	X	X	X	X
Archive Sample[j]		X							X	X
Serum or Urine Pregnancy Test[k]	X	X			X		X		X	X
Urinalysis	X									
IL28B Genotype, HCV Genotype	X									
HCV Ab, HIV Ab and HBsAg	X									
Hemoglobin A1c, TSH	X									
PK Substudy Collection[f]				X	X					
Single Pharmacogenomic Sample[g]		X								
Review of Study Drug Adherence and Drug Accountability[h]			X	X	X	X	X	X	X	X
Study Drug Dispensing[i]		X			X		X			

a The screening window can be extended to 42 days for subjects requiring liver biopsy or additional HCV genotype testing.

b Baseline/Day 1 assessments must be performed prior to dosing.

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 gross abnormalities.

e Serum samples will be collected and stored for potential HCV sequencing and other virology studies.

f The optional PK substudy is conducted in Taiwan and Korea only. Subjects that consent to the optional PK substudy will have serial PK samples drawn at Week 2 or Week 4 visit.

g Only for subjects who have provided consent for this sample and testing (Taiwan and Korea only). This sample can be obtained at a subsequent visit if not obtained at Day 1.

h Study medication and dosing diary, will be reconciled at every post-baseline visit by the investigator or designee in order to monitor the subject's adherence with the medication regimen.

i Study Drug will be dispensed per IWRS directions. Subjects must be instructed to bring back all bottles of study medication(s) in the original container at every post baseline study visits through the end of treatment.

j Archive plasma samples will be collected at the Baseline/Day 1 visit and at the end of treatment for subjects who have not opted out of sample collection

k For female subjects of childbearing potential. In the event of a positive urine test, a serum pregnancy test will be done.

Appendix Table 2. Post Treatment Study Visits

Clinical Assessments	Post Treatment Period[a]		
	Post Treatment Week 4 (±5 days)	**Post Treatment Week 12 (±5 days)**	**Post Treatment Week 24 (±5 days)**
Weight		X	X
Vital Signs[b]	X	X	X
Adverse Events	X		
Concomitant Medications	X		
Pregnancy Prevention Counseling	X		
Health Related Quality of Life	X	X	
Hematology & Chemistry	X		
Serum HCV RNA	X	X	X
Viral Sequencing Sample (Plasma)[c]	X	X	X
Serum or Urine Pregnancy Test[d]	X		

a All subjects will complete both 4-week and 12-week Post-Treatment visits regardless of the treatment duration. Subjects with HCV RNA < LLOQ at their 12-week Post-Treatment visit will complete a 24-week Post-Treatment visit, unless viral relapse is determined. The end of study will occur at the 24-week Post-Treatment visit.

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

c Plasma samples will be collected and stored for potential HCV sequencing and other virology studies.

d For female subjects of childbearing potential. In the event of a positive urine test, a serum pregnancy test will be done.

Appendix 3. Calculation of Historical Control SVR12 for Treatment naïve Chinese Subjects with Chronic GT-1 HCV Infection

This section details the calculation for the historical control SVR12 rate for Treatment naïve Chinese subjects with chronic GT-1 HCV infection.

For China, the historical control rate has been calculated according to the reference studies in Appendix Table 3. SVR rates are not reported separately for elderly patients or those with cirrhosis in these references. Consequently, the calculated historical SVR rate of 57% has not been adjusted by different population.

Appendix Table 3. Literature References for Historical Control Rate Calculations in China

SVR Rates in China			
Population	**SVR%**	**SVR n/N**	**Reference**
GT-1 Treatment Naïve (Peg-IFN/RBV 48 Weeks)	70.3	102/145	{Heo 2013}
	43.9	18/41	{Heo 2013}
	46.0	58/126	{Park 2012}
Overall SVR Rate	**(102+18+58)/(145+41+126)=57%**		