STATISTICAL ANALYSIS PLAN

Registry Title:	A Registry for Subjects with Cirrhosis Who Achieve a Sustained Virologic Response Following Treatment with a Sofosbuvir-Based Regimen without Interferon for Chronis Hepatitis C Infection in Gilead-Sponsored Trials
Registry Number:	GS-US-337-1431
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase (SGPT)
APRI	AST to platelet ratio index
AST	aspartate aminotransferase (SGOT)
BMI	body mass index
CLDQ-HCV	chronic liver disease questionnaire - hepatitis C virus
CSR	clinical study report
CTP	Child-Turcotte-Pugh
eCRF	electronic case report form(s)
ELF	enhanced liver fibrosis
EOT	end of treatment
FAS	full analysis set
FIB-4	fibrosis-4 index
GGT	gamma-glutamyl transpeptidase
GSI	Gilead Sciences, Inc.
HbA1C	hemoglobin A1C
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high density lipoprotein
HLGT	high level group term
HLT	high level term
HOMA-IR	homeostatic model assessment - insulin resistance
IFN	interferon
IL28B	IL28B gene
INR	international normalized ratio
IU	international unit
KM	Kaplan-Meier
LDL	low density lipoprotein
LDV	ledipasvir
LLOQ	lower limit of quantification
LLT	lower level term
LOQ	limit of quantitation
LOXL2	lysyl oxidase homolog 2
MedDRA	Medical Dictionary for Regulatory Activities; MedDRA®
MELD	Model for End-Stage Liver Disease
NLP	natural language processing
OAV	oral antiviral
PEG	pegylated interferon

PT	prothrombin time or preferred term
Q1	quartile 1
Q3	quartile 3
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SD	standard deviation
SGPT	serum glutamic pyruvic transaminase (ALT)
SGOT	serum glutamic oxaloacetic transaminase (AST)
SOC	system organ class
SOF	sofosbuvir
SVR	sustained virologic response
TFLs	tables, figures, and listings
ULN	upper limit of the normal range
USA	United States of America
VEL	velpatasvir
VOX	voxilaprevir
WPAI	work productivity and activity impairment questionnaire

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-337-1431. This study presents 5 years of follow-up results for cirrhotic participants with or without decompensated liver disease who have achieved a sustained virologic response (SVR) following treatment with a sofosbuvir (SOF)-based regimen without interferon (IFN) for chronic hepatitis C infection in a Gilead-sponsored HCV study, or an all-oral SOF-based regimen outside a clinical study at sites pre-selected by Gilead (i.e., commercial participants). This SAP is based on study protocol amendment 3 and 3.1 dated 01 June 2017 and 28 September 2017, 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. Registry Objectives

Primary Objectives

The primary objectives of this study are as follows:

- To assess the durability of SVR;
- To assess clinical progression or regression of liver disease, including the incidence of hepatocellular carcinoma (HCC) following SVR.

Secondary Objective

The secondary objective of this study is as follows:

- For participants who received their SOF-based regimen in a Gilead parent protocol, to determine whether subsequent detection of HCV RNA in participants who relapse following SVR represents the re-emergence of pre-existing virus, the development of resistance mutations, or re-infection.

Exploratory Objective

The exploratory objective of this study is as follows:

- CCI [redacted]

1.2. Registry Design

Design Configuration and Participant Population

GS-US-337-1431 is an observational study open to any cirrhotic participant with or without decompensated liver disease who have achieved SVR after receiving a SOF-based regimen

without IFN while participating in a Gilead-sponsored HCV study; or, at a subset of sites preselected by Gilead, who have previously received an all-oral SOF-based regimen outside a clinical study.

For participants enrolling from a Gilead parent protocol, the definitions of cirrhosis and of SVR are defined in the parent Gilead-sponsored treatment protocol. Participants who are enrolled after receiving an all-oral SOF-based regimen outside a clinical study, will have had cirrhosis confirmed prior to initiation of HCV treatment.

Once enrolled in the registry, participants will be followed for up to 5 years. For participants rolling over from a Gilead parent protocol, a Day 1 visit will be scheduled within approximately 60 weeks from a participant's projected SVR 24 visit in the parent protocol, or participants may enroll from the GS-US-248-0122 SVR registry study at any time with Sponsor approval. For participants who are enrolled after receiving an all-oral SOF-based regimen outside a clinical study, a Day 1 visit will be scheduled within approximately 2 years from the participant's SVR 12 date. Clinical visits will then occur every 24 weeks at Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240.

Treatment Groups

This is a long-term observational follow-up registry study. No investigational medicinal product will be administered. The HCV regimen received in the parent studies will be used to assign treatment groups for analysis purposes. All the parent studies included in this registry are listed in Appendix 12.1.

Entry Eligibility Criteria

Participants must meet **all** of the following inclusion criteria to be eligible for participation in this study:

1) Willing and able to provide written informed consent;

2) Have previously participated in a Gilead-sponsored HCV study and received a SOF-containing regimen without IFN; OR

   At pre-selected sites only, have received an all-oral SOF-based regimen outside a clinical study. These participants must have documentation of the regimen, start and end of treatment dates (month and year), and of having achieved SVR12;

3) Have achieved SVR in a Gilead-sponsored study, as defined in the original treatment protocol; OR for participants who enroll after receiving an all-oral SOF-based regimen outside a clinical study, SVR will be defined as HCV RNA < LLOQ approximately 12 weeks following last dose of treatment;

4) Have liver cirrhosis, as defined in the original treatment protocol, and have not had a liver transplant after receiving a SOF-containing regimen; OR

Participants who enroll after receiving an all-oral SOF-based regimen outside a clinical study, will have had cirrhosis as diagnosed prior to initiation of HCV treatment.

Participants who meet **either** of the following exclusion criteria are not to be enrolled in this study:

1) Participant plans to initiate a new course of HCV therapy, including approved products and any investigational agents, during the course of this Registry;

2) History of clinically significant illness or any other major medical disorder that may interfere with participant follow-up, assessments, or compliance with the protocol.

Schedule of Assessments

Consent and demographics will be obtained at the Day 1 visit. The schedule of the full assessments is provided in the protocol and in Appendix 12.2.

Randomization

This is an observational study. Randomization will not be applied.

Registry Duration

Participants included in the study will be followed for up to 240 weeks (approximately 5 years), until early termination or completion of the study.

1.3. Sample Size and Power

No formal power or sample size calculations were applied.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

No formal interim analyses will be conducted.

2.2. Final Analysis

Final analysis will be performed after all participants have completed the registry study or have prematurely discontinued from the registry, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Descriptive statistics will be generated for this registry study. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-participant listings will be presented for all participants in the All Enrolled Analysis Set and sorted by participant ID number, visit date, and time (if applicable). Data collected on log forms, such as adverse events (AEs), will be presented in chronological order within the participant. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes participants who signed the informed consent and enrolled into the study.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all participants who met all inclusion criteria and did not meet any of the exclusion criteria, and with at least one post-enrollment visit measurement available. We have 34 participants in total enrolled but not included in FAS (32 participants recorded with criteria not met in eCRF and 2 more participants who received PEG/INF in the parent study but without exclusion records in eCRF). This is the primary analysis set for endpoint analyses.

3.1.3. Safety Analysis Set

The definition of the safety analysis set will be the same as the definition of the FAS.

3.2. Participant Groups

All analyses will be performed and summarized by treatment groups.

Treatment groups are the treatment regimens that led to SVR during the respective parent studies or the treatment regimens received by commercial participants.

For all analyses, treatment regimens will be classified as SOF+RBV, LDV/SOF±RBV, SOF/velpatasvir (VEL)±RBV, SOF/VEL/voxilaprevir(VOX)±RBV, Other, and Total. Details are shown in Appendix 12.3. Participants completing interferon-based regimens such as those with prior treatment being SOF+PEG+RBV will be excluded from the Full Analysis Set and all analyses.

In addition, analyses of events associated with clinical progression of liver diseases and HCC will be performed and summarized by Child-Turcotte-Pugh (CTP) class calculated upon entry into the registry. CTP score will be classified as A (5-6), B (7-9), or C (10-15) in Table 6-1 and Section 6.1.3.2.3.

3.3. Strata and Covariates

There are no randomization strata or covariates in this observational study.

3.4. Examination of Participant Subsets

No further subset of participants will be examined.

3.5. Multiple Comparisons

No formal statistical hypothesis testing will be conducted. Multiple comparisons are not applicable.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

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

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

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

Age (in years) on the registry start date (i.e., Day 1 Visit of the registry collected from the demographic eCRF) and sex at birth will be used for analyses and presentation in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. For screen failures, the date when the first informed consent was signed will be used for the age derivation.

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

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

When calculating duration of follow-up, time to events such as HCC occurrence and death, partial dates will be imputed as 01 if only day is missing, as 01 January if day and month are missing; and if the imputed death date was before the last available visit date for a participant, the partial death date will be re-imputed as the same of the last available visit date.

For an HCC event that is reported in multiple visits, the earliest diagnosis date is used as the first HCC event occurrence date.

For an endoscopy/liver imaging test conducted on one day but repeatedly reported in multiple visits, it will be assigned to the correct analysis window as in Section 3.8.2. The milder record will be selected for baseline if there are different reported test results (e.g., varices present = "No" will be chosen over varices present = "Yes", varices grade = "Unknown" will be chosen over varices grade = "Small"), and the more severe record will be selected for postbaseline visits.

Data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is one unit less than the lower LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). 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 or <0.1, etc. 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 upper LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.
- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ, respectively).

The Roche Taqman HCV test (lower limit of quantification [LLOQ] = 25 international unit [IU]/mL) was used to measure HCV RNA until 04 JAN 2015 after which the COBAS®AmpliPrep/COBAS® TaqMan® HCV Quantitative Test v2.0 (LLOQ = 15 IU/mL) was used.

For numerical HCV RNA data, values below LLOQ will be set to the LLOQ – 1 IU/mL (i.e., 24 or 14 HCV RNA IU/mL, depending the date of measurement). HCV RNA values reported as "target not detected" will also be set to LLOQ – 1 IU/mL. The original values will be provided in the HCV RNA listings.

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

3.8. Visit Windows

3.8.1. Definition of Visits

Baseline Value will be the first non-missing value taken on or within 30 days of the registry start date (i.e., Day 1 Visit of the registry collected from the demographic eCRF). For questionnaire data, if no data are available within 30 days after the registry start date, the baseline value will be the last non-missing value prior to the registry start date.

Study days are calculated relative to registry start date as follows:

- For measurements that are collected before the registry start date: Visit date – registry start date.
- For measurement or events that are collected on or after the registry start date: Visit date – registry start date +1.

Last Day of the registry is the last recorded non-missing visit or collected data/assessment date in the database. When determining the last day of the registry, partial date will be imputed as 01 if only day is missing and 01 January if day and month are missing.

3.8.2. Analysis Windows

Participant visits might not occur on protocol-specified visit days. Therefore, for the purpose of analysis, observations (corresponding laboratory test or quality of life questionnaires) will be assigned to analysis windows. Windows will be constructed so that the boundaries of windows are the midpoint between consecutive protocol-specified visit days. The analysis windows for liver disease assessment, laboratory data, Model for End-Stage Liver Disease (MELD) score and data from quality of life survey Short Form-36 (SF-36) are defined in Table 3-1. The analysis windows for transient elastography (Fibroscan score) are defined in Table 3-2. Endoscopy will be assigned to either Day 1 or Week 240 with +/- 6 months based on the test performed date as shown in Table 3-3.

Table 3-1. Analysis Windows for Liver Disease Assessment, Laboratory Data, CTP/MELD Score and Quality of Life Surveys

Analysis Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline[a]	1	1	30
Baseline[b]	1	(none)	30
Week 24	168	31	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756
Week 120	840	757	924
Week 144	1008	925	1092
Week 168	1176	1093	1260
Week 192	1344	1261	1428
Week 216	1512	1429	1596
Week 240	1680	1597	>=1680

a Baseline window for laboratory tests, liver disease assessment and CTP/MELD score only.
b Baseline window for Quality of Life Surveys only.

Table 3-2. Analysis Windows for Transient Elastography (Fibroscan Score)

Analysis Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1	-75	168
Week 48	336	169	504
Week 96	672	505	840
Week 144	1008	841	1176
Week 192	1344	1177	1512
Week 240	1680	1513	>=1680

Table 3-3. Analysis Windows for Endoscopy

Analysis Visit ID	Nominal Day	Lower Limit	Upper Limit
Day 1	1	-182 (about -6 months)	182 (about 6 months)
Week 240	1680	1513 (about 6 months prior/Week 216)	>=1680
Others*	-	-	-

* For endoscopy performed to evaluate for varices at time other than the two protocol-defined visits, the test result will be assigned to the closest protocol scheduled liver disease assessment visit.

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

Depending on the statistical analysis method, a single value 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 one value per analysis window.

If multiple valid non-missing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed, unless otherwise specified.

For baseline:

- The record closest to the nominal day for baseline will be selected except for HCV RNA, 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 are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (e.g., normal will be selected over abnormal) for categorical data.

For postbaseline values:

- The record closest to the nominal day for that visit will be selected except for HCV RNA, 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 for continuous data and the worse severity (e.g., abnormal will be selected over normal) will be taken for categorical data, unless otherwise specified.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

A summary of participant enrollment will be provided for each country, each investigator within a country, and overall by baseline Child-Turcotte-Pugh (CTP) class (CTP A, B, C, Unknown and total as defined in Section 6.1.3.2.3) and treatment group. The summary will present the number and percentage of participants in the All Enrolled Analysis Set. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

A summary of participant disposition will be provided by treatment group and baseline CTP class and overall. This summary will present the number of participants enrolled and included in the FAS, the Safety Analysis Set, and the number and percentage of participants who completed the study and who did not complete the study (with summary of reasons for discontinuing registry). The denominator for the percentages of participants in each category will be the number of participants in FAS corresponding to that column. In addition, a flowchart will be provided to depict the overall disposition. A table of participant disposition for premature discontinuation of study by visit and reasons will also be displayed by treatment group and baseline CTP class.

A by-participant disposition listing with reasons for premature discontinuation of study and baseline CTP class will be provided by participant ID number in ascending order to support the above summary tables.

A separate listing of participants who prematurely discontinued registry will also be provided.

4.2. Extent of Exposure

This is a registry study with no active treatment. Extent of exposure to study drug is not applicable.

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but enrolled in the study, will be listed regardless of whether they were exempted by the sponsor or not. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. A by-participant listing of important protocol deviations will be provided.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which had an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment, as described in Appendix 12.3. The summary tables and listing of participants with virtual visits or missing visits due to COVID-19 will be provided. Participants with any protocol deviations due to COVID-19 and registry premature discontinued participants due to COVID-19 will also be listed.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Participant demographics variables (i.e., age, sex, race, ethnicity [Hispanic or non-Hispanic], and region [US or non-US]) will be summarized by treatment group, baseline CTP class (CTP A, B, C, Unknown and total) and overall for safety analysis set. Age will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum). Age categories (< 65 years vs. ≥ 65 years), sex, race, ethnicity, and region will be summarized by the numbers and percentages of participants in each category. Age in years on Day 1 will be used or calculated from the registry start date.

The following items will also be added to the demographic summary table:

- Gap between the end of prior HCV treatment and the start of the registry as categories (<6 months vs. >=6 months) (Registry start date - last day of parent study +1)
- Gap between SVR24 visit in parent study and the start of the registry as categories (<6 months vs. >=6 months) (for non-commercial participants only)
- Duration of follow-up since the start of the most recent treatment in weeks
- Duration of follow-up since end of prior HCV treatment in weeks
- Duration of follow-up since the start of the registry in weeks (Last day of registry – registry start date +1)

A by-participant listing of demographics including the informed consent date, treatment regimen, treatment group, and baseline CTP class will be provided by participant ID number in ascending order.

5.2. Baseline Characteristics

Baseline characteristics include:

- Baseline liver function tests: CTP score/MELD score/AST to Platelet Ratio Index (APRI)/FibroTest score (Fibrosis score)/Elasticity (Fibroscan score)/Enhanced Liver Fibrosis (ELF) score/Fibrosis-4 (FIB-4) index as continuous variables
- Pretreatment HCV genotype and IL28B genotype (CC, CT, TT/missing categories)
- Baseline body mass index (BMI; in kg/m^2) as a continuous variable and as categories (<30 kg/m^2, >=30 kg/m^2)

Baseline values are defined in Section 3.8.1 and 3.8.3. Data for baseline HCV genotype and IL28B (before entry into the parent study) are not collected in the registry study, and data collected at baseline of the parent study will be used for the analysis.

The above baseline characteristics will be summarized by treatment group, baseline CTP class (CTP A, B, C, Unknown and total) and overall for safety analysis set. Continuous variables will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and categorical variables using the numbers and percentages of participants.

A by-participant listing of baseline characteristics including baseline CTP class will be provided by participant ID number in ascending order. Separate baseline characteristics by-participant listings will also be provided for participants who experienced virologic failure and who developed De Novo HCC during the registry study.

5.3. Medical History

Medical history data of clinical liver-associated events will be collected at screening and listed only. Medical history data will not be coded.

6. ENDPOINT ANALYSES

This analysis will be performed after all participants have completed approximately 240 weeks of follow-up or discontinued early from the study.

Primary and secondary endpoints will be summarized on the FAS (Section 3.1.2).

All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

6.1. Primary Endpoints

6.1.1. Definition of the Primary Endpoints

The primary endpoints are:

- The proportion of participants maintaining SVR at Week 240;
- The proportion of participants who develop liver disease progression or regression, as assessed by clinical and laboratory parameters;
- The proportion of participants who develop HCC through Week 240.

6.1.2. Statistical Hypothesis for Primary Endpoints

No formal statistical hypothesis is established for this study.

6.1.3. Primary Analysis of the Primary Endpoints

6.1.3.1. Proportion of Participants Maintaining SVR Through Week 240

Definition of Virologic Failure: Virologic failure is defined as having 2 consecutive blood samples (at least one week apart) with HCV RNA > LLOQ, or last available HCV RNA> LLOQ with no subsequent follow-up values. Date of virologic failure is the date of the first measurement if confirmed by 2 consecutive measurements, or the date of the last available HCV RNA > LLOQ with no subsequent follow-up values.

Participants who early terminated the study by a visit for a reason other than virologic failure are censored for that visit. In addition, participants who completed the study without a virologic failure are censored at the end of study by standard Kaplan-Meier (KM) methods.

Person-time pertaining to KM analysis of time to virologic failure will be calculated as: date of virologic failure (for participants who experienced virologic failure) or last day of registry (for participants who did not experience virologic failure) – registry start date + 1.

SVR end date will be the date to have HCV RNA level that was measurable during the registry study.

The KM estimate of the proportions of participants who maintained SVR, and the cumulative number of participants who experienced virologic failure, were at risk, and had been censored will be summarized by treatment group and by time point (Week 0, 24, 48,…, 216 and 240), where Week 0 to 216 are the exact weeks elapsed since registry start date (i.e. 0, 168, 336, …, and 1512 days), and Week 240 includes 1680 days elapsed since registry start date plus additional 30 days (i.e. 1710 days). The KM plots will also be presented in a figure.

A by-participant, by-visit listing of the actual HCV RNA value and $\log_{10}$ HCV RNA will be provided by participant ID number in ascending order. A separate by-participant, by-visit listing of the actual HCV RNA value and log10 HCV RNA will be provided for participants with virologic failure by participant ID number in ascending order, including time since registry start date to virologic failure, and time since the end of the most recent HCV treatment to virologic failure, parent study ID, most recent HCV treatment, and baseline CTP category.

Participants who experienced virologic failure more than 30 days after 240 weeks elapsed since registry start date (i.e. > 1710 days) will be listed separately.

6.1.3.2. Proportion of Participants Who Develop Liver Disease Progression or Regression

6.1.3.2.1. Liver Disease Assessment Including Hepatocellular Carcinoma

Events related to liver disease progression include:

- Hepatic encephalopathy
- Hepatocellular carcinoma (HCC)
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Hepatic hydrothorax
- Bleeding varices
- Spontaneous bacterial peritonitis
- Liver Transplant
- Ascites
- Liver-related death

Hepatic decompensation events include:

- Hepatorenal syndrome

- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Hepatic hydrothorax
- Hepatic encephalopathy
- Bleeding varices
- Spontaneous bacterial peritonitis
- Ascites
- Liver-related death

Except for ascites (using data collected from liver imaging)/liver transplant/death, other events will be all collected from liver disease assessment page in eCRF. Minimal or trace ascites will not be treated as a liver event. Liver-related death will be identified by Clinical Research based on the immediate cause of death.

Participants with events related to liver disease progression that were identified prior to registry start date will be excluded from the analysis but will be listed.

Participants with De Novo HCC since registry start are defined as participants who were not identified with HCC prior to registry start and only had HCC since registry start.

Summary of participants with liver events will be provided, including the percentage of participants with events among FAS, the percentage of participants for each type of events among all the participants with events, and the percentage of participants with any event prior to registry start among FAS.

Person-time pertaining to KM analysis of time to events in this section will be calculated as: first event date (for participants who experienced events) or last day of registry (for participants who did not experience events) – registry start date + 1.

For time to first liver event since registry start, KM estimate of the proportion of participants with events related to liver disease progression, the cumulative number of participants who experienced events, were at risk, and had been censored will be summarized by treatment group and time point (Week 0, 24, 48,..., 216, and 240), where Week 0 to 216 are the exact weeks elapsed since registry start date (i.e., 0, 168, 336,…, and 1512 days), and Week 240 includes 1680 days elapsed since registry start date plus additional 30 days (i.e. 1710 days). Participants with liver events prior to registry start will be excluded from this analysis.

Same summary table as above will be provided separately for participants with De Novo HCC, with hepatic decompensation events, with liver transplant, and with all-cause death.

Same summary tables will be provided for above endpoints by baseline CTP class (CTP A, B, C, Unknown and total). Time to the first liver event and time to De Novo HCC since registry start will be summarized descriptively (n, mean, SD, median, Q1, Q3, minimum, and maximum) in a table for those participants with events occurring only during the registry study.

The KM plots will also be presented in a figure.

A by-participant, by visit listing of participants who developed above events will be provided by participant ID number in ascending order (events prior to registry start will be flagged). A separate listing will be provided for participants with De Novo HCC since registry start. Participants who experienced an HCC event more than 30 days after 240 weeks elapsed since registry start date (i.e. > 1710 days)/participants with HCC prior to registry start date will be listed separately.

6.1.3.2.2. Laboratory Evaluation of Liver Disease

Laboratory data will be analyzed and summarized by treatment group using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the FAS and will include all available data. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as stated in Section 3.7. Hemolyzed test results will not be included in the analysis, but they will be listed in by-participant laboratory listings.

By-participant, by-visit listings for hematology, coagulation, and serum chemistry laboratory test results will be provided by participant ID number in chronological order. 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.

Hematology: Platelets

Chemistry: Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), albumin, total bilirubin, direct bilirubin, creatinine

Coagulation Test: international normalized ratio (INR), prothrombin time (PT)

A separate by-participant, by-visit listing will be provided for additional laboratory tests including:

- Alpha-fetoprotein (AFP) level
- FibroTest®: alpha-2-macroglobulin, alpha-2-globulin (haptoglobin), apolipoprotein A1, gamma-glutamyl transpeptidase (GGT), and total bilirubin
- Enhanced Liver Fibrosis (ELF) panel: hyaluronic acid, amino-terminal propeptide of type III collagen, and TIMP-1

- Fasting lipid panel: low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, total cholesterol
- Hemoglobin A1C (HbA1c)
- HOMA-IR (Fasting insulin x Fasting glucose / 405)
- LOXL2 levels

A shift table for Fibrotest stage (No or minimal fibrosis/Moderate fibrosis/Severe fibrosis) from baseline to postbaseline visits will be provided by treatment group.

A shift table for ELF class from baseline to postbaseline visits will be provided by treatment group. ELF classes are defined as:

* Class F0-F2: score < 9.8;
* Class F3: score in 9.8 - 11.3;
* Class F4: score > 11.3.

FIB-4 index is calculated by:

FIB-4 Index = round ((age × AST) / (platelet × sqrt (ALT)), 0.01);

Where ALT is in unit of (U/L), platelet is in unit of (x10^3/uL), AST is in unit of (U/L), and age in years.

A shift table for FIB-4 class (defined as subjects with index score of >=25% increase, >=25% reduction at postbaseline from baseline, or the rest as no change from baseline; and baseline classes [<1.3, >=1.3 and <2, >=2 and <=2.67, >2.67]) from baseline to postbaseline visits will be provided by treatment group.

AST to Platelet Ratio Index (APRI) will be calculated as:

APRI = round (AST/AST ULN × 100 / platelet, 0.1);

Where ALT is in unit of (U/L), platelet is in unit of (x10^3/uL), AST ULN is AST upper limit of Normal with unit of (U/L).

For FIB-4 index and APRI calculation, the laboratory parameters need to be measured from the same blood draw. Age (years) should be the actual age at the date when laboratory values are taken.

6.1.3.2.2.1. Quantitative Summaries of Laboratory Results

Descriptive summary statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment group. For each laboratory test as specified in the study protocol, the mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In details, descriptive statistics will be provided for each laboratory test: Baseline values, values at each postbaseline visit, and change from baseline at each postbaseline visit.

Analysis visit windows are as defined in Section 3.8.2. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

6.1.3.2.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Version dated 01 April 2015) will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels and analyses for each direction (i.e., increased, decreased) will be presented separately.

Laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline for any postbaseline value. If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 will be considered a laboratory abnormality.

Laboratory data that are categorical will be summarized using the number and percentage of participants in the registry with the given response at baseline and each scheduled postbaseline visit. All graded laboratory abnormalities/Grade 3 or above abnormalities will be separately summarized (number and percentage of participants) by lab test and overall. Participants will be categorized according to the most severe postbaseline abnormality grade for a given analyte. The denominator for graded laboratory abnormality summaries is the number of participants with non-missing postbaseline values.

By-participant, by-visit listings for laboratory abnormalities will be provided by participant ID number in chronological order with all applicable severity grades displayed, and a separate listing for participants with severe (Grade 3 or Grade 4) laboratory abnormalities.

6.1.3.2.3. Child-Turcotte-Pugh (CTP) Score and MELD Score

Laboratory assessment data will be used to determine the CTP score and MELD score. CTP will be calculated as a summation of all points assigned as shown in Table 6-1.

Table 6-1. Child-Turcotte-Pugh Score Calculations

	Points Assigned		
Parameter	1	2	3
Ascites	Absent	Slight	Moderate

Total Bilirubin	< 2 mg/dL (< 34.2 micromol/liter)	2 - 3 mg/dL (34.2 - 51.3 micromol/liter)	> 3 mg/dL (> 51.3 micromol/liter)
Albumin	> 3.5 g/dL (> 35 g/liter)	2.8 - 3.5 g/dL (28 - 35 g/liter)	< 2.8 g/dL (< 28 g/liter)
Prothrombin Time (Seconds over control, PT) OR International normalized ratio (INR)*	< 4 < 1.7	4 – 6 1.7 – 2.3	> 6 > 2.3
Encephalopathy	None	Grade 1 - 2	Grade 3 - 4

* INR is chosen for this study's CTP calculation per eCRF.

A total CTP score of 5-6 is considered grade A (compensated), 7-9 is grade B (significant functional compromise/decompensated), and 10-15 is grade C (decompensated). A missing CTP score/cirrhosis status not available will be displayed as "Unknown" grade category in summaries. The proportion of participants in each CTP score category (A [5-6], B [7-9] and C [10-15]) will be summarized by visit for each treatment group. A shift table of CTP category by treatment group will be provided as well. By-participant, by-visit listing of CTP score results will be provided by participant ID number in chronological order.

MELD score will be calculated at each visit. Table with descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for MELD score and change from baseline by visit for each treatment group will be provided. A shift table for MELD score category (>= or <15) at each postbaseline visit from baseline will also be provided by treatment group. MELD score results will be listed by participant ID number and visit.

The MELD score will be calculated using the following formula:

$10 \times \{[0.957 \times \text{Ln(Scr)}] + [0.378 \times \text{Ln(Tbil])} + [1.12 \times \text{Ln(INR)}] + 0.643)\}$,

Where Scr = serum creatinine (in mg/dL), Tbil = Total Bilirubin (in mg/dL), INR = international normalized ratio, and Ln = natural log. If any lab value was less than 1.0, then it will be set to 1.0 in the calculation. If the participant received dialysis at least twice in the past week, then Scr will be set to 4.0 mg/dL in the above formula. The result will be rounded to the nearest whole number.

6.2. Secondary Endpoints

The secondary endpoints are:

- The proportion of participants with detectable HCV RNA due to re-emergence of pre-existing virus through Week 240;
- The proportion of participants with detectable HCV resistance mutations through Week 240;

- The proportion of participants with detectable HCV RNA due to re-infection through Week 240.

Virologic relapse is defined as HCV RNA > LLOQ on two samples collected at least one week apart with the same virus present prior to treatment in the parent treatment protocol. Re-infection is defined as HCV RNA > LLOQ on two samples collected at least one week apart with a different virus than that present prior to treatment in the treatment protocol. HCV sequencing will be performed if HCV RNA is sufficient. These results will be listed in CSR by Clinical Virology.

No table will be provided for the secondary endpoints.

6.3. Exploratory Endpoints

6.3.1. Definition of Exploratory Endpoints

CCI [redacted]

6.3.2. Analysis Methods for Exploratory Endpoints

CCI [redacted]

6.3.2.1. Quality of Life Questionnaires SF-36

The Quality of Life Questionnaires SF-36 responses will be listed. The transformed scale scores (0 to 100 scale) and changes from baseline at each scheduled postbaseline visit will be presented

by treatment group for each of the 8 domains of the SF-36 (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), and for the physical component summary and mental component summary. Scoring of the SF-36 scales will be performed as described in Chapter 6 of the SF-36 Health Survey Manual and Interpretation Guide, Version 2 {Ware 2000}.

6.3.2.2. Chronic Liver Disease Questionnaire (CLDQ-HCV)

The Chronic Liver Disease Questionnaire (CLDQ-HCV) responses will be listed. The transformed scale scores (1 to 7 scale) and changes from baseline will be presented by study visit and treatment group for each of the four domains {Younossi 1999}:

- Activity/energy: question items 1, 3, 4, 5, 7, and 18
- Emotional function: question items 6, 8, 9, 11, 16, 23, 24, 27, and 28
- Worry: question items 14, 15, 17, 19, 20, 21, 22, and 29
- Systemic symptoms: question items 2, 10, 12, 13, 25, and 26.

The four domains will be calculated as an average of their non-missing constituent items (each domain score is calculated only if at least half of the corresponding items are not missing; otherwise, the domain score will be set as missing), and the overall CLDQ-HCV score will be the average of four domain scores. When all four domain scores are missing, the overall score will be set as missing as well.

6.3.2.3. Work Productivity and Activity Impairment Questionnaire: Hepatitis C (WPAI: Hepatitis C)

The Work Productivity and Activity Impairment Questionnaire: Hepatitis C (WPAI: Hepatitis C) results will be listed. Questions 5 and 6 will be transformed into a scale score from 0 to 10.

Current employment Yes/No ((item 1 on WPAI: Hepatitis C)) at different scheduled visits will be summarized using frequency and percentage. If the participant had a response of "Yes" to question 1, descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for the percent of work time missed associated with hepatitis C (P1=100×Item2/[Item2+Item4]), percent of impairment while working due to hepatitis C (P2=100×Item5/10), and percent of overall work impairment due to hepatitis C (P3=P1+P2×[1-P1/100]) will be summarized for each scheduled visit. If P1 is not available, P3 will be set as missing as well.

For all participants, percent of daily activity impairment due to hepatitis C (P4=100×Item6/10) will be also calculated.

Change from baseline will be presented for all the percentages above.

6.4. Other Measurements

6.4.1. Limited Physical Exam

The limited physical exam includes height (at Day 1 only) and weight measurements for calculation of BMI. Assessments of ascites and encephalopathy will be conducted at each visit for calculation of CTP score. The results from the limited physical exam will be listed by participant ID and study visit.

6.4.2. Liver Imaging, Biopsy, Endoscopy and Transplant

Imaging of the liver will be performed as part of standard of care (e.g., CT, MRI, or Ultrasound results, if available). Liver biopsy will be performed at any time only if results available from biopsy performed as part of standard of care. An endoscopy will be performed to evaluate for varices at any time or at Day 1 (+/- 6 months) and within 6 months prior to Week 240 visit as in protocol. Liver transplant will be reported during the study.

A shift table of varices grade from endoscopy (no varices/small varices/large varices/unknown) from Day 1 to Week 240 will be provided by treatment group and baseline CTP class (CTP A, B, C, Unknown and total).

The results of all above will be listed by participant ID number and study visit. Results of endoscopy/imaging/biopsy collected at Day 1 visit but with a procedure date before or on the most recent HCV treatment end date will be flagged in the listing.

6.4.3. Transient Elastography

A transient elastography will be performed to assess the liver elasticity at Day 1 (+ 4 weeks) and every 48 weeks (+/- 4 weeks) through Week 240 at sites with a Fibroscan® or comparable equipment. Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by visit and by treatment group as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

Analysis visit windows as defined in Section 3.8.2. Data record with a procedure date prior to the most recent HCV treatment end date will be excluded in the above summary table. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

The results of the transient elastography including the reported interquartile range will be listed by participant ID number and visit. Data record with a procedure date prior to the most recent HCV treatment end date will be flagged.

The shift table for fibroscan category by treatment group will be provided based on following:

- Category F0 to F2: 9.5 kPa or less
- Category F3: 9.6 to 12.5 kPa
- Category F4: greater than 12.5 kPa

6.5. Changes from Protocol-Specified Endpoint Analyses

No change from protocol-specified endpoint analysis is planned.

7. SAFETY ANALYSES

Analysis of safety measures will be descriptive and will include participants in the Safety Analysis Set. All safety data collected on or after the date of enrollment through the remainder of the study will be included.

As there was no intervention in this study, only AEs related to the required procedures by this registry were recorded. Any reference to an AE or serious adverse event (SAE) in this SAP will be referring to AEs and SAEs related to procedures required by this registry. All deaths, regardless of relatedness to study procedures were recorded when available. The immediate cause and date of death were collected when available.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Adverse events 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 provided in the clinical database.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life threatening). The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in the summary presentation.

7.1.3. Serious Adverse Events

Serious adverse events are those identified as serious in the clinical database as defined in the protocol Section 7.2. The clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety Department before data finalization.

7.1.4. Summaries of Adverse Events and Deaths

A brief high-level summary of study procedure related AEs will be provided by treatment group and overall, including the number and percentage of participants who experienced at least 1 AE in the following categories: any AE, any AE of Grade 2 or above, any AE of Grade 3 or above, any SAE, and AE leading to premature discontinuation of study. All deaths (including those that are procedure related and those that are not procedure related) observed during the study will also be summarized and included in this table.

AE summaries will provide the number and percentage of participants for reported AEs by treatment group and by SOC and PT based on the Safety Analysis Set as follows:

- All AEs
- All AEs with Grade 3 or above
- All AEs by grade
- All SAEs
- AEs leading to premature discontinuation of this registry study

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC (and HLT within each SOC if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all AEs, all AEs by grade will be summarized by treatment group and by PT only, in descending order of total frequency.

By-participant listings will be provided by participant ID number in ascending order for the following:

- All AEs
- AEs of Grade 3 or above
- SAEs
- All deaths (with a flag indicating liver-related death identified by Clinical Research)
- All AEs leading to premature discontinuation of this registry study

7.2. Others – Prior and Concomitant Medications

Participants will not receive any antiviral therapy for HCV infection while participating in this Registry. If a participant requires HCV antiviral therapy, they will be discontinued from the Registry. There are no other concomitant medications which would preclude participants from participating in this Registry. The concomitant medication records collected will be listed.

7.3. Changes from Protocol-Specified Safety Analyses

No change from protocol-specified safety analysis is planned.

8. PHARMACOKINETIC ANALYSES

This Registry will not have a pharmacokinetic component.

9. REFERENCES

Ware JE, Kosinski M, Dewey JE. How to Score Version 2 of the SF-36® Health Survey. Chapter 6. Lincoln, RI: Quality Metric Incorporated; 2000:

Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut 1999;45 (2):295-300.

10. SOFTWARE

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

11. SAP REVISION

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

12. APPENDICES

12.1. List of Gilead Parent Studies Included

Study Number
GS-US-334-0109
GS-US-334-0114
GS-US-334-0125
GS-US-334-0153
GS-US-337-0102
GS-US-337-0109
GS-US-337-0115
GS-US-337-0118
GS-US-337-0121
GS-US-337-0122
GS-US-337-0123
GS-US-337-0124
GS-US-337-0133
GS-US-337-1118
GS-US-337-1119
GS-US-337-1468
GS-US-337-1512
GS-US-342-0109
GS-US-342-1137
GS-US-342-1138
GS-US-342-1139
GS-US-342-1140
GS-US-342-1202
GS-US-342-1446
GS-US-342-1553
GS-US-342-2097
GS-US-342-4022
GS-US-367-1168
GS-US-367-1169
GS-US-367-1170
GS-US-367-1171
GS-US-367-1172
GS-US-367-1173
GS-US-367-1871

12.2. Study Procedures Table

Clinical Assessments	Day 1[a]	Study Week 24	48	72	96	120	144	168	192	216	240	ET
Informed Consent[b]	X											
Quality of Life Surveys	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Related to Procedures	X	X	X	X	X	X	X	X	X	X	X	X
Limited Physical Exam[c]	X	X	X	X	X	X	X	X	X	X	X	X
Liver Disease Assessment[d]	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy	X									X		
Transient Elastography[e]	X		X		X		X		X		X	X
Liver Biopsy[f]											X	
Laboratory Assessments												
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X
Viral Sequencing[g]	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[h]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology (Platelets)	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Test (PT/INR)	X	X	X	X	X	X	X	X	X	X	X	X
Additional Tests[i]	X	X	X	X	X	X	X	X	X	X	X	X
HCV RNA Confirmation[j]	X											
CCI [redacted]												

a Day 1 visit to be conducted approximately 48 weeks from the final visit in the treatment protocol
b Informed consent may be obtained prior to Day 1
c Assessment of ascites, encephalopathy, height (at Day 1) and weight; calculated scores include BMI, CTP and MELD
d Liver Disease Assessment: refer to protocol Section 6.3.5
e At sites with a Fibroscan® or comparable equipment
f CCI [redacted].
g Plasma will be collected for possible viral sequencing or other virology studies if indicated.
h Includes ALT/SGPT, AST/SGOT, Albumin, Total bilirubin, Direct Bilirubin, Creatinine
i Includes α-fetoprotein level, FibroTest®, ELF panel, lipid panel, hemoglobin A1C, HOMA-IR and LOXL2
j Only in participants with HCV RNA >LLOQ
k For participants who consent

12.3. Most Recent HCV Treatment Regimen Groups

Most Recent Actual Treatment	Prior HCV Treatment Group	Interferon Contained Treatment
12 Weeks Treatment (SOF + RBV + PEG)	SOF+RBV+PEG	Y
12 Weeks Treatment (SOF + RBV)	SOF+RBV	N
24 Weeks Treatment (SOF + RBV)	SOF+RBV	N
BMS-790052 (DACLATASVIR) [NS5A]+GS-7977 (SOFOSBUVIR) [NUC]	Other	N
BMS-790052 (DACLATASVIR) [NS5A]+GS-7977 (SOFOSBUVIR) [NUC]+RIBAVIRIN (ANY)	Other	N
Cohort 1 Group 3 : Treatment Naive Cirrhotic 3DAA 8 Weeks	SOF/VEL/VOX	N
Cohort 1 Group B : Treatment Naive Cirrhotic 3DAA+RBV 8 Weeks	SOF/VEL/VOX	N
Cohort 2 Group 3 : Treatment Experienced Cirrhotic 3DAA 12 Weeks	SOF/VEL/VOX	N
Cohort 2, Group 1 - LDV/SOF + RBV	LDV/SOF+RBV	N
Cohort 2, Group 2 - LDV/SOF	LDV/SOF	N
Cohort 2, Group 2 - LDV/SOF + GS-9669	Other	N
Cohort 2, Group 6 - LDV/SOF + RBV	LDV/SOF+RBV	N
Cohort 3 : 3DAA 12 Weeks	SOF/VEL/VOX	N
Cohort 3, Group 1 - LDV/SOF	LDV/SOF	N
Cohort 3, Group 2 - LDV/SOF + RBV	LDV/SOF+RBV	N
Cohort 5, Group 1 - LDV/SOF + RBV	LDV/SOF+RBV	N
Cohort 5, Group 2 - VOX + SOF/VEL	SOF/VEL/VOX	N
Cohort 5, Group 3 - VOX + SOF/VEL	SOF/VEL/VOX	N
Cohort 5, Group 4 - VOX + SOF/VEL	SOF/VEL/VOX	N
Cohort 5, Group 5 - VOX + SOF/VEL	SOF/VEL/VOX	N
Cohort 5, Group 6 - VOX + SOF/VEL	SOF/VEL/VOX	N
Cohort 5, Group 7 - VOX + SOF/VEL	SOF/VEL/VOX	N
Cohort 5, Group 8 - VOX + SOF/VEL	SOF/VEL/VOX	N
Cohort A, Group 1 - LDV/SOF+RBV 12 Weeks of Treatment	LDV/SOF+RBV	N
Cohort A, Group 1 - LDV/SOF+RBV 24 Weeks of Treatment	LDV/SOF+RBV	N
Cohort A, Group 2 - LDV/SOF+RBV 12 Weeks of Treatment	LDV/SOF+RBV	N
Cohort A, Group 2 - LDV/SOF+RBV 24 Weeks of Treatment	LDV/SOF+RBV	N
Cohort B, Group 4 - LDV/SOF+RBV 12 Weeks of Treatment	LDV/SOF+RBV	N
Cohort B, Group 4 - LDV/SOF+RBV 24 Weeks of Treatment	LDV/SOF+RBV	N

Most Recent Actual Treatment	Prior HCV Treatment Group	Interferon Contained Treatment
Cohort B, Group 5 - LDV/SOF+RBV 12 Weeks of Treatment	LDV/SOF+RBV	N
Cohort B, Group 5 - LDV/SOF+RBV 24 Weeks of Treatment	LDV/SOF+RBV	N
Cohort B, Group 6 - LDV/SOF+RBV 12 Weeks of Treatment	LDV/SOF+RBV	N
Cohort B, Group 6 - LDV/SOF+RBV 24 Weeks of Treatment	LDV/SOF+RBV	N
FDC tablet (SOF 400 mg/LDV 90 mg) once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks	LDV/SOF+RBV	N
FDC tablet (SOF 400 mg/LDV 90 mg) once daily + RBV (1000 or 1200 mg/day divided BID) for 24 weeks	LDV/SOF+RBV	N
FDC tablet (SOF 400 mg/LDV 90 mg) once daily + RBV (12 weeks)	LDV/SOF+RBV	N
FDC tablet (SOF 400 mg/LDV 90 mg) once daily + RBV (24 weeks)	LDV/SOF+RBV	N
FDC tablet (SOF 400 mg/LDV 90 mg) once daily for 12 weeks	LDV/SOF	N
FDC tablet (SOF 400 mg/LDV 90 mg) once daily for 24 weeks	LDV/SOF	N
GS-5885 (LEDIPASVIR) [NS5A]+GS-7977 (SOFOSBUVIR) [NUC]	LDV/SOF	N
GS-5885 (LEDIPASVIR) [NS5A]+GS-7977 (SOFOSBUVIR) [NUC]+RIBAVIRIN (ANY)	LDV/SOF+RBV	N
GS-7977 (SOFOSBUVIR) [NUC]+PEGINTERFERON ALFA-2A+RIBAVIRIN (ANY)	SOF+RBV+PEG	Y
GS-7977 (SOFOSBUVIR) [NUC]+RIBAVIRIN (ANY)	SOF+RBV	N
GS-7977 (SOFOSBUVIR) [NUC]+RIBAVIRIN (ANY)+TMC-435 (SIMEPREVIR) [NS3]	Other	N
GS-7977 (SOFOSBUVIR) [NUC]+TMC-435 (SIMEPREVIR) [NS3]	Other	N
Group 1 - SOF/GS-5816 FDC once daily for 12 weeks	SOF/VEL	N
Group 1 - SOF/GS-5816 once daily for 12 weeks	SOF/VEL	N
Group 1 - SOF/VEL once daily for 12 weeks	SOF/VEL	N
Group 1 -SOF/GS-5816 for 12 weeks	SOF/VEL	N
Group 1: LDV/SOF + RBV 8 Weeks	LDV/SOF+RBV	N
Group 1: LDV/SOF + VDV 8 weeks	Other	N
Group 1: SOF/VEL/VOX 12 Weeks	SOF/VEL/VOX	N
Group 2 - SOF + RBV for 12 weeks	SOF+RBV	N
Group 2 - SOF + RBV for 24 weeks	SOF+RBV	N
Group 2 -SOF/GS-5816 + RBV for 12 weeks	SOF/VEL+RBV	N
Group 2: LDV/SOF + GS-9669 (250 mg) 8 Weeks	Other	N
Group 2: LDV/SOF + VDV + RBV 8 weeks	Other	N
Group 2: SOF/VEL 12 Weeks	SOF/VEL	N

Most Recent Actual Treatment	Prior HCV Treatment Group	Interferon Contained Treatment
Group 3 -SOF/GS-5816 for 24 weeks	SOF/VEL	N
Group 3: LDV/SOF + GS-9669 (500 mg) 8 Weeks	Other	N
Group 3: SOF/VEL/VOX 12 Weeks	SOF/VEL/VOX	N
HARVONI	LDV/SOF	N
HARVONI+RIBAVIRIN (ANY)	LDV/SOF+RBV	N
LDV/SOF	LDV/SOF	N
LDV/SOF + PLACEBO (RBV) for 24 Weeks	LDV/SOF	N
LDV/SOF + RBV for 12 Weeks	LDV/SOF+RBV	N
LDV/SOF 24 Weeks	LDV/SOF	N
LDV/SOF+RBV 12 Weeks	LDV/SOF+RBV	N
LDV/SOF+RBV 24 Weeks	LDV/SOF+RBV	N
LEDIPASVIR/SOFOSBUVIR [NS5A/NUC]	LDV/SOF	N
LEDIPASVIR/SOFOSBUVIR [NS5A/NUC]+RIBAVIRIN (ANY)	LDV/SOF+RBV	N
OLYSIO+SOVALDI	Other	N
Observation, SOF+RBV	SOF+RBV	N
SOF + RBV + PEG 12 Weeks	SOF+RBV+PEG	Y
SOF + RBV 16 Weeks	SOF+RBV	N
SOF + RBV 24 Weeks	SOF+RBV	N
SOF 400mg + GS-5816 100mg	SOF/VEL	N
SOF 400mg + GS-5816 100mg + RBV	SOF/VEL+RBV	N
SOF 400mg + GS-5816 25mg	SOF/VEL	N
SOF 400mg + GS-5816 25mg + RBV	SOF/VEL+RBV	N
SOF 400mg/VEL 100 mg	SOF/VEL	N
SOF 400mg/VEL 100 mg + RBV 200 mg	SOF/VEL+RBV	N
SOF+RBV	SOF+RBV	N
SOF+RBV 12 WEEKS	SOF+RBV	N
SOF+RBV 24 WEEKS	SOF+RBV	N
SOF/LDV + RBV 12 Weeks (PI Failures)	LDV/SOF+RBV	N
SOF/LDV 12 Weeks (PI Failures)	LDV/SOF	N
SOF/VEL + RBV 12 Weeks	SOF/VEL+RBV	N
SOF/VEL + RBV for 24 Weeks	SOF/VEL+RBV	N
SOF/VEL once daily without regards to food for 12 weeks	SOF/VEL	N

Most Recent Actual Treatment	Prior HCV Treatment Group	Interferon Contained Treatment
SOF/VEL/VOX once daily with food + RBV with food for 12 weeks	SOF/VEL/VOX	N
SOF/VEL/VOX once daily with food for 12 weeks	SOF/VEL/VOX	N
SOF/VEL/VOX once daily with food for 8 weeks	SOF/VEL/VOX	N
TMC-435 (SIMEPREVIR) [NS3]+VELPATASVIR/SOFOSBUVIR [NS5A/NUC]	Other	N
VELPATASVIR/SOFOSBUVIR [NS5A/NUC]	SOF/VEL	N

12.4. Data Collection of COVID-19 Data

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm that will be used to determine which visits are missing and which visits are virtual.

12.4.1. Data Collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by Clinical Data Management to instruct clinical trial sites with data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites were instructed to enter "Visit missed due to COVID-19" and if an in-person visit was conducted virtually, sites were instructed to enter "Virtual visit due to COVID-19".

12.4.2. Determination of Missed and Virtual Visits

Natural Language Processing (NLP) will be used to search the CRF comment fields to identify instances of "COVID-19", "Virtual", or synonyms. The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, "Missed visit" or "Virtual visit will be assigned as follows:

A) If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"

B) If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same participant and the same visit, if one record could be categorized as "Virtual Visit", all records associated with this participant and this visit will be categorized as "Virtual Visit"

C) Otherwise result is missing

Example Search Terms for "COVID-19" and "Virtual" Used to Identify Missed/Virtual Visits are listed below:

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	10-May-2022 15:05:01
PPD	Clinical Research eSigned	10-May-2022 15:56:16