STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Pharmacokinetics, Safety and Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed Dose Combination in Adolescents and Children with Chronic HCV Infection
Name of Test Drug:	Sofosbuvir/Velpatasvir/Voxilaprevir Fixed Dose Combination
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CSR	clinical study report
CTX	C-type collagen sequence
DAA	direct-acting antiviral
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FAS	Full Analysis Set
FDC	Fixed Dose Combination
FU	follow-up
Gilead	Gilead Sciences, Inc.
Hb	hemoglobin
HCV	hepatitis C virus
HLT	high level term
HLGT	high level group term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification
LLT	lower level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PedsQL™	Pediatric Quality of Life Inventory™
PK	pharmacokinetics
PT	preferred term
P1NP	Procollagen type 1 N-terminal propeptide
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid

SAE	serious adverse event
SAP	statistical analysis plan
SI (units)	International system of units
SOC	system organ class
SOF	sofosbuvir
SVR	sustained virologic response
SVRx	sustained virologic response x weeks after stopping study drug
TEAE	treatment-emergent adverse events
TFLs	tables, figures, and listings
TND	target not detected
ULN	upper limit of normal
VEL	velpatasvir
VF	virologic failure
VOX	voxilaprevir
WBC	white blood cell
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

AUC	area under the plasma/serum concentration versus time curve
AUC_{tau}	area under the plasma/serum concentration versus time curve over the dosing interval
C_{max}	maximum observed plasma/serum concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for Study GS-US-367-1175. This SAP is based on study Protocol Amendment 1 dated 27 March 2019 and electronic case report form (eCRF). Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the steady-state pharmacokinetics (PK) and confirm age-appropriate dose of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection
- To evaluate the antiviral efficacy of SOF/VEL/VOX FDC treatment in pediatric subjects with chronic HCV infection, as assessed by the proportion of pediatric subjects with sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12)
- To evaluate the antiviral efficacy SOF/VEL/VOX FDC treatment in pediatric subjects with chronic HCV infection, as assessed by the proportion of pediatric subjects with SVR 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of pediatric subjects with virologic failure, including on-treatment virologic failure and relapse
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF, VEL, and VOX during treatment and after cessation of treatment
- To evaluate the effect of SOF/VEL/VOX FDC on growth and development of pediatric subjects during and after treatment
- To evaluate acceptability, including palatability, and swallowability of formulations (as applicable) used in the study
- To assess the effect of treatment with SOF/VEL/VOX FDC on quality of life as measured by PedsQL™ Pediatric Quality of Life survey including neuropsychiatric assessments

[redacted]

1.2. Study Design

This is an open-label, multi-cohort study evaluating the PK, safety, and antiviral activity of SOF/VEL/VOX FDC in pediatric subjects with chronic HCV infection.

Overall, the study will enroll both direct-acting antiviral (DAA)-naïve and DAA-experienced pediatric subjects with chronic HCV infection of any HCV genotype. Three sequential age-based cohorts will be enrolled:

- Cohort 1: at least 20 subjects 12 to < 18 years old
- Cohort 2: at least 20 subjects 6 to < 12 years old
- Cohort 3: at least 20 subjects 3 to < 6 years old

Eligible DAA-naive subjects without cirrhosis will receive treatment for 8 weeks. Eligible DAA-naive subjects with cirrhosis and DAA-experienced subjects with or without cirrhosis will receive treatment for 12 weeks.

The total time to complete all study visits is up to approximately 36 weeks for subjects treated with 8 weeks of therapy and 40 weeks for subjects treated for 12 weeks of therapy including the following periods:

- 28-day (4-week) screening period
- 8 or 12-week treatment period
- 24-week posttreatment period

The schedules of assessments for the study are provided as appendices to the SAP (see Study Procedures Table, Appendix 1).

1.3. Sample Size and Power

Assuming similar variability for SOF, GS-331007, VEL, or VOX AUC_{tau} in the pediatric population compared to adults, a sample size of 20 pediatric subjects per cohort will provide at least 80% power to target a 90% confidence interval of the geometric mean ratio (GMR) within the bounds of 50% to 200% when comparing with the adult population.

2. TYPE OF PLANNED ANALYSIS

2.1. DMC Analyses

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will recommend to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

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

2.2. Final Analysis

The European Medicines Agency (EMA) granted Gilead a waiver to study SOF/VEL/VOX in children under 12 years of age. As a result, after all adolescent subjects (12 to < 18 years of age) have completed through the post-treatment week 24 visit or have prematurely discontinued from the study, outstanding data queries have been resolved, and the database has been cleaned and finalized, the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

3.1. Analysis Sets

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

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all adolescent subjects enrolled in the study after screening.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes HCV infected adolescent subjects who were enrolled into the study and received at least one dose of study drug. The study drug in this study is SOF/VEL/VOX FDC.

This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all adolescent subjects who took at least 1 dose of study drug (ie, SOF/VEL/VOX FDC).

This is the primary analysis set for safety analyses.

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Population PK Analysis Set

The Population PK Analysis Set includes all enrolled adolescent subjects who received at least one dose of study drug and for whom at least one non-missing PK concentration data value is available from all types of PK sampling. This is the primary analysis set for the Population PK modeling and PK exposure analyses.

The PK Analysis Set is equivalent to the Population PK Analysis Set.

3.2. Subject Grouping

For analyses based on the All Enrolled Analysis Set or FAS, subjects will be grouped according to the treatment to which they were enrolled. For analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received is defined as the enrolled treatment except for subjects who received treatment that differs from the enrolled treatment for the entire treatment duration. In this case, the actual treatment received is defined as the treatment received for the entire treatment duration. Given the fact that only DAA-naïve subjects without cirrhosis have been enrolled in this study, there will be only one treatment group (ie, SOF/VEL/VOX FDC 8 weeks).

The efficacy analyses will be performed on the FAS, and for selected efficacy analyses, by HCV genotype (1 [further broken down to 1a and 1b], 2, 3, 4, 5, 6, or other, as appropriate, and total). The safety analysis will be performed on the Safety Analysis Set.

For other selected analyses, for example, the summary of responses to the acceptability and palatability questionnaire, the analysis of tanner pubertal stage assessment data, please refer to the relevant sections for the detailed description of subject grouping.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule for enrolling subjects. No covariates will be included in efficacy and safety analyses.

3.4. Examination of Subject Subsets

The efficacy endpoint SVR12 will be analyzed for the following subsets:

- sex (male, female)
- race (black, non-black)
- ethnicity (Hispanic or Latino, non-Hispanic or Latino)
- baseline weight (≤ median, > median)
- IL28B (CC, non-CC [further broken down to CT, TT])

- baseline HCV RNA (< 800,000 IU/mL, ≥ 800,000 IU/mL)
- baseline alanine aminotransferase (ALT) (≤1.5 × ULN, > 1.5 × ULN)
- prior HCV treatment experience (treatment naive, treatment experienced - DAA-naïve, DAA experienced)
- number of prior HCV treatments
- most recent response to prior DAA-naïve and DAA HCV treatment (non-response, relapse/breakthrough) for treatment experienced subjects
- study treatment status (completed study treatment, discontinued study treatment)
- adherence to study drug (< 80%, ≥ 80%)

3.5. Missing Data and Outliers

3.5.1. Missing Data

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

For missing last dosing date of study drug, imputation rules are described in Section 3.7.1. The handling of missing or incomplete dates for adverse event (AE) onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.8.

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

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

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

In the analysis of the PedsQL™ Pediatric Quality of Life Inventory V4.0 Short Form (SF15) questionnaire, missing data at on-treatment visits and posttreatment follow-up Week 12 (FU-12) visit will not be imputed. Last posttreatment observation carried forward will be used for imputation of missing data at posttreatment follow-up Week 24 visit.

3.5.2. 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..

3.6. Data Handling Conventions and Transformations

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

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

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

Non-PK data that are continuous in nature but are less than the LLOQ or above the upper LOQ will be imputed as follows:

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

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

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

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

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

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

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

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

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

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (eg, $\log_{10}$ scale) or nonparametric analysis methods may be used, as appropriate.

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

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

3.7. Visit Windows

3.7.1. Definition of Study Day

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

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

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

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

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

3.7.2. Analysis Windows

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

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

HCV RNA, vital signs, and safety laboratory data collected up to the last dose date + 3 days are considered to be on-treatment data and HCV RNA, vital signs and safety laboratory data collected after the last dose date + 3 days are considered posttreatment data. Given the fact that only DAA-naïve subjects without cirrhosis have been enrolled in this study, the analysis windows for on-treatment HCV RNA, vital signs and safety laboratory data are provided in Table 3-1.

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

Nominal Visit	SOF/VEL/VOX 8 Weeks		
	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	7	2	11
Week 2	14	12	21
Week 4	28	22	42
Week 8	56	43	≥ 57

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

Table 3-2. Analysis Windows for Posttreatment HCV RNA, Body Weight, Height, Vital Sign and Safety Laboratory Data

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

a FU x visit posttreatment Week x follow up visit.
b Vital signs (blood pressure, pulse, respiratory rate, and temperature) and safety labs will only be summarized for the FU 4 visit (up to 30 days after last dose).

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

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

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

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, average (arithmetic mean) will be used for the baseline value.

- For postbaseline visits:

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

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

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

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

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided for each country, investigator within a country, and overall. The summary will present the number and percentage of subjects in the Safety Analysis Set. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A summary of subject disposition will be provided. This summary will present the number of subjects screened, enrolled, enrolled but never treated, and the number and percentage of subjects in each of the categories listed below. For the "Treated" category, the denominator for the percentage calculation will be the total number of subjects enrolled. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set.

- Treated (Safety Analysis Set)
- In FAS
- In Intensive PK Analysis Set
- In Population PK Analysis Set
- Completed study treatment
- Did not complete study treatment with reasons for premature discontinuation of study treatment
- Completed the study
- Did not complete the study with reason for premature discontinuation of study

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

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

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

HCV RNA assessment ≥ 70 days after the last dose of any study drug (ie, lower bound of FU-12 visit for HCV RNA data), the subject is categorized as having "With HCV FU-4 but No FU-12 and thereafter".

In addition, the total number of subjects who were enrolled, and the number of subjects in each of the disposition categories listed above will be displayed in a flowchart.

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

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

4.2. Extent of Exposure

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

4.2.1. Durations of Exposure to Study Regimen

Total duration of exposure to study drug will be defined as last dose date minus first dose date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

The total durations of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: Baseline (Day 1), Week 1 (Day 7), Week 4 (Day 28), and Week 8 (Day 56) given the fact that only DAA-naïve subjects without cirrhosis have been enrolled in this study. A 3-day window is applied to the last planned on-treatment visit to match with the protocol-specified visit window. Summaries will be provided for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

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

The adherence will be calculated based on the amount of SOF/VEL/VOX (mg) by the following formula:

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

Where the presumed total amount of study drug (mg) administered to a subject will be determined by the data collected on the drug accountability eCRF using the following formula:

$$\text{Total Amount of Study Drug (mg) Administered} = \left(\sum \text{Total Amount of Study Drug (mg) Dispensed}\right) - \left(\sum \text{Total Amount of Study Drug (mg) Returned}\right)$$

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

For adolescent subjects aged 12 to < 18 years receiving the SOF/VEL/VOX 400/100/100 mg once daily, the total amount of drug prescribed for 8 weeks would require 33,600 mg (ie, 400+100+100 mg/day, 56 days).

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

Descriptive statistics for the level of adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) with the number and percentage of subjects belonging to adherence categories (e.g. < 80%, ≥ 80 to < 90%, ≥ 90%) will be provided for the Safety Analysis Set. No inferential statistics will be provided for duration of exposure and adherence to study drug.

A separate by-subject listing of study drug administration and drug accountability will be provided by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

A summary of important protocol deviations will be provided by the Clinical Operations group for subjects in the Safety Analysis Set.

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

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by HCV genotype (1 [further broken down to 1a and 1b], 2, 3, 4, 5, 6, or other, as appropriate, and total) using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for age, and using the numbers and percentages of subjects for sex, race, and ethnicity. Age is calculated in years at the date of initial study drug administration. If a subject did not receive study drug after enrollment, the subject's age will be calculated from the date that the subject signed the informed consent form. The summary of demographic data will be provided for the Safety Analysis Set.

A by-subject demographic listing will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- weight in kg
- height in cm
- body mass index (BMI; in kg/m^2)
- HCV genotype (1 [further broken down to 1a and 1b], 2, 3, 4, 5, 6, or other, as appropriate, and as determined by sequencing if available)
- cirrhosis (presence, absence, not determined)
- primary assessment method used to make the cirrhosis determination (liver biopsy, transient elastography, Fibrotest and APRI, APRI, Fibrotest, liver imaging, other)
- transient elastography in kPa
- Fibrotest as a continuous and as categorical variable
- APRI
- FIB-4 ($ie, \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count (10\^3/uL)} \times \sqrt{\text{ALT (U/L)}}}$)
- IL28B (CC, CT, TT)
- baseline HCV RNA (IU/mL) (< 800,000 IU/mL, ≥ 800,000 IU/mL)

- baseline HCV RNA (log_{10} IU/mL) as a continuous variable and as categories (< 6 log_{10} IU/mL, ≥ 6 log_{10} IU/mL)
- baseline ALT (U/L) as a continuous variable and as categories (≤1.5 × ULN, > 1.5 × ULN)
- estimated glomerular filtration rate (eGFR) using Schwartz Formula (mL/min/1.73m^2)
- prior treatment experience (treatment naïve, treatment experienced[DAA-naïve, DAA-experienced])
- number of prior HCV treatments
- most recent response to prior HCV treatment (non-response, relapse/breakthrough) for treatment experienced subjects
- mode of HCV Infection
- bone age in years
- Tanner Stage

Estimated glomerular filtration rate will be calculated using Schwartz Formula (mL/min/1.73m^2)
k × L/Scr [(k is a proportionality constant, for adolescent females ≥ 12 years old is 0.55; for adolescent males ≥ 12 years old is 0.70); L is height in centimeters (cm); and Scr is serum creatinine (mg/dL)]

These baseline characteristics will be summarized by HCV genotype (1 [further broken down to 1a and 1b], 2, 3, 4, 5, 6, or other, as appropriate, and as determined by sequencing, and total) using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using the numbers and percentages of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set.

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

5.3. Swallowability Assessment for SOF/VEL/VOX FDC Placebo Tablets

For subjects in the 12 to <18 years of age group, swallowability of SOF/VEL/VOX FDC placebo tablets will be summarized using the numbers and percentages of subjects in each swallowability category (ie, Able to Swallow, Unable to Swallow).

A by-subject listing of Swallowability of SOF/VEL/VOX FDC placebo tablets will be provided by subject ID number in ascending order.

5.4. Acceptability and Palatability of SOF/VEL/VOX FDC

A questionnaire will be administered to subjects to assess acceptability and palatability of the formulation they received on Day 1, End of Treatment and Early Termination (as applicable). If the subject is unable to complete the questionnaires, the parent/legal guardian will assist to complete the questionnaire on their behalf. The subject's parent/legal guardian will also complete a questionnaire on End of Treatment or Early Termination (as applicable) for their assessment of acceptability of the formulation the subject received.

Acceptability and palatability will be assessed by character response to questions about how the study drug tasted, how easy it was to swallow the study drug, and also at the end of treatment about how it was to take the study drug and, for those who received that tablet formulation, how they felt about the number of tablets they had to swallow in the following categories, as applicable:

- Did Not Taste the Study Drug (for question regarding study drug taste only)
- Very Bad/Hard
- Bad/Hard
- Maybe Bad/Hard or Maybe Good/Easy
- Good/Easy
- Very Good/Easy

Responses to the acceptability and palatability questionnaire by subjects and their parent/legal guardian at Day 1, End of Treatment and Early Termination (as applicable) will be respectively summarized using the numbers and percentages of subjects in the corresponding categories, as applicable, for each question.

A by-subject listing of acceptability and palatability of SOF/VEL/VOX FDC will be provided by subject ID number in ascending order.

5.5. Medical History

General medical history (ie, conditions not specific to the disease being studied) data will be collected at screening and listed only. General medical history data will not be coded. A by-subject listing of disease-specific medical history will be provided by subject ID number (in ascending order) and medical history of abnormalities (in chronological order).

6. EFFICACY ANALYSES

6.1. Key Efficacy Endpoint

6.1.1. Definition of the Key Efficacy Endpoint

The key efficacy endpoint is SVR12 defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after discontinuation of the study drug in the FAS. The COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 for use with the High Pure System will be used to measure HCV RNA.

6.1.2. Analysis Methods for the Key Efficacy Endpoint

No inferential statistics will be provided for efficacy endpoints. No statistical comparison will be conducted.

The point estimates of SVR12 rate and 2-sided 95% exact CI based on Clopper-Pearson method {Clopper 1934} will be provided by HCV genotype (1 [further broken down to 1a and 1b], 2, 3, 4, 5, 6, or other, as appropriate, and total).

6.1.3. Subgroup Analysis of the Key Efficacy Endpoint

The point estimates of SVR12 rate and 2-sided 95% exact CIs based on Clopper-Pearson method {Clopper 1934} will be provided within each subgroup specified in Section 3.4

A Forest plot will graphically present estimates and 95% confidence intervals of SVR12 rates within each subgroup.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

- The percentage of subjects who attain SVR at 4 and 24 weeks after stopping therapy, defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 4 and 24 weeks after stopping treatment (SVR 4 and SVR 24)
- The percentage 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 end of treatment (EOT)

- The percentage of subjects with virologic failure as the following:

  On-treatment virologic failure

  HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ, while on treatment, confirmed with 2 consecutive values (note, second confirmation value can be posttreatment), or last available on-treatment measurement with no subsequent follow-up values (ie, breakthrough)

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

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

  Relapse

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

- The proportion of subjects with ALT normalization (defined as ALT > ULN at baseline and ALT ≤ ULN at each visit), presented by study visit

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

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

For analyses of HCV RNA < LLOQ by visit while on treatment and during the posttreatment (SVR) follow-up period, subjects will be assigned a value at each visit based on the analysis visit windows specified in Section 3.7.2. Missing values will be imputed based on the categorical imputation rules described in Section 3.5.1. The 2-sided 95% exact confidence interval based on Clopper-Pearson method will be provided for the percentage of subjects with HCV RNA < LLOQ at each visit. The overall category for "HCV RNA < LLOQ" will be split into the following 2 subcategories: "< LLOQ TND" for subjects with target not detected and "< LLOQ detected" for subjects with < LLOQ detected in tabular displays.

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

Summary statistics will be presented for absolute values and change from baseline in HCV RNA ($\log_{10}$ IU/mL) by visit through EOT. Imputation rules described in Section 3.5.1 will be used to assign HCV RNA values for missing values at a visit that are bracketed by "< LLOQ TND" and/or "< LLOQ detected". Otherwise, a missing excluded analysis will be performed. Plots of the mean ± SD and median (Q1, Q3) of absolute values and changes from baseline in HCV RNA through EOT will be presented.

For the SVR12 endpoint analysis, a summary table of the number and percentage of subjects with SVR12, virologic failure (VF), and Other will be created by HCV genotype (1 [further broken down to 1a and 1b], 2, 3, 4, 5, 6, or other, as appropriate, and total). All subjects who achieve SVR12 will be categorized as SVR12. Virologic failure will be descriptively summarized as "on-treatment virologic failure" and relapse (which will be broken down by study drug completed yes/no). Subjects who do not achieve SVR12 and do not meet criteria for VF will be categorized as Other. The denominator for relapse will be the number of subjects who had HCV RNA < LLOQ on their last observed on-treatment HCV RNA measurement; otherwise, the denominator will be the number of subjects in the FAS.

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

In addition, a summary table of the number and percentage of subjects with HCV RNA < LLOQ and ≥ LLOQ at the posttreatment follow-up visit (observed and imputed, with reasons for imputed) will be provided for each posttreatment follow-up visit. 95% Clopper-Pearson exact CIs will be presented for the overall proportion of subjects with HCV RNA < LLOQ.

Tables for ALT normalization by visit will use similar methodology to the analyses of HCV RNA < LLOQ, but will use a missing excluded analysis. Only those subjects with ALT greater than the ULN range at baseline (defined as the last ALT value collected prior to first dose of study drug) will be included in the analysis of ALT normalization.

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

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

6.4. Changes From Protocol-Specified Efficacy Analyses

There are no changes from protocol-specified efficacy analyses.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using 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 AE dataset.

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment Emergent

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

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

7.1.5.2. Incomplete Dates

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

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

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

7.1.6. Summaries of Adverse Events and Deaths

A brief high-level summary of TEAEs will be provided by presenting the number and percentage of subjects who had the following: any AE; any AE of Grade 3 or above; any AE of Grade 2 or above; any treatment-related AE; any treatment-related AE of Grade 3 or above; any treatment-related AE of Grade 2 or above; any SAE; any treatment-related SAE; any AE that led to premature discontinuation of SOF/VEL/VOX; any AE that led to interruption of SOF/VEL/VOX. All deaths (including those that are treatment emergent and those that are not treatment emergent) observed during the study will also be summarized and included in this table.

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT, based on the Safety Analysis Set as follows:

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- All treatment-related SAEs

- AEs leading to premature discontinuation of SOF/VEL/VOX
- AEs leading to interruption of SOF/VEL/VOX

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in order of descending incidence overall within each SOC. In summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, TEAEs will be summarized by PT only, in order of descending incidence for:

- AEs that occurred in at least 5% of subjects within this age group
- AEs of Grade 3 or above
- All treatment-related AEs
- All SAEs
- AEs leading to premature discontinuation of SOF/VEL/VOX
- AEs leading to interruption of SOF/VEL/VOX

In addition to the summaries described above, data listings will be provided for the following:

- All AEs (with a variable indicating whether the event is treatment emergent)
- AEs of Grade 3 or above
- SAEs
- Deaths
- AEs leading to premature discontinuation of SOF/VEL/VOX
- AEs leading to interruption of SOF/VEL/VOX

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug. The analysis will be based on values reported in conventional units. When values are below the limit of quantitation, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics. For example, if "< 0.2" was recorded, a value of 0.1 will be used for the purpose of calculating summary statistics; if "< 0.1" was recorded, a value of 0.09 will be used for the purpose of calculating summary statistics.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided for ALT, aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, hemoglobin, reticulocytes, white blood cell (WBC), neutrophils, lymphocytes, platelets, and international normalized ratio (INR) as follows:

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

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

Median (Q1, Q3) of the observed values for these laboratory parameters will be plotted using a line plot by visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3 (Selection of Data in the Event of Multiple Records in a Window).

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

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning toxicity grades to laboratory results for analysis as Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4. 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; analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

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

7.2.2.2. Summaries of Laboratory Abnormalities

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

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

- Graded laboratory abnormalities
- Grade 3 or above laboratory abnormalities

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

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

For subjects with at least one event of treatment-emergent Grade 3 or above laboratory abnormality of creatine kinase (CK) or lipase, a listing of AEs will be provided.

7.2.2.3. On-Treatment Liver-Related Laboratory Events

The following liver-related laboratory events will be summarized using data from all the on-treatment postbaseline visits (up to 3 days after the last dose of any study drug):

- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- ALT > 5 × ULN
- Total bilirubin > 2 × ULN

For the composite criterion of AST or ALT and total bilirubin, AST or ALT and total bilirubin must meet the specified cut-offs at a given postbaseline time point; subjects will be counted once when the criterion is met. The denominator will be the number of subjects in the Safety Analysis

Set with at least 1 postbaseline value of AST or ALT and total bilirubin at the same time point. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values when the criterion is met. The denominator will be the number of subjects in the Safety Analysis Set with at least 1 nonmissing postbaseline value for the test. A listing will be provided including ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, HCV RNA (log_{10}) and yes/no flag for subjects meeting at least 1 of the 3 criteria. All the available data for the subjects will be listed.

7.3. Vital Signs

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

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3 (Selection of Data in the Event of Multiple Records in a Window). No inferential statistics will be generated.

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

7.4. Body Weight, Height and BMI

An age- and sex-specific percentile will be derived for each weight, height and BMI measurement according to the downloadable SAS program available on the Centers for Disease Control (CDC) website using the year 2000 growth charts. Methods and SAS program published on the following CDC website will be applied to calculate the percentile {Centers for Disease Control and Prevention (CDC) 2016a, Centers for Disease Control and Prevention (CDC) 2016b}.

Body weight, height, BMI and percentiles for body weight, height, BMI at each visit, and change from baseline at each visit will be summarized for the Safety Analysis Set using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum).

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3 (Selection of Data in the Event of Multiple Records in a Window). No inferential statistics will be generated.

A by-subject listing of body weight, weight percentile, height, height percentile, BMI and BMI percentile will be provided by subject ID number and visit in chronological order.

7.5. Mid-Parental Height Assessment

The calculation of mid-parental height has been a standard procedure for assessing individual child's future adult height since it was first described by Tanner {Tanner 1970}. Mid-parental height will be calculated as the average of father's and mother's height. For boys, the sex-adjusted mid-parental height will be calculated by adding 2.5 inch or 6.5 cm from the mean of the parents' heights. For girls, will be calculated by subtracting 2.5 inch or 6.5 cm from the mean of the parents' heights. If any one of parents' heights is missing, the calculation will be excluded.

A by-subject listing of parents' heights and derived mid-parental height will be provided by subject ID number in ascending order.

7.6. Bone Age Assessment

Radiographic bone age assessment is performed on Day 1 and End of Treatment.

Radiographic bone age at baseline visit, End of Treatment and change from baseline visit will be summarized for the Safety Analysis Set using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum).

Fasting blood samples for bone age biomarkers CTX (C-type collagen sequence) and Procollagen type 1 N-terminal propeptide (P1NP), will be collected at Day 1, Early Termination (if applicable) and posttreatment Week 24.

Each of bone age biomarkers (CTX and P1NP) at baseline visit, Early Termination (if applicable), FU-24 visit and change from baseline visit will be summarized respectively for the Safety Analysis Set using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum).

A by-subject listing of radiographic bone age assessment and bone age biomarkers will be provided by subject ID number in ascending order and visit in chronological order.

7.7. Tanner Pubertal Stage Assessment

The Tanner stages will be used to evaluate the onset and progression of pubertal changes. Females will be rated for pubic hair growth and breast development, and males will be rated for pubic hair growth and genitalia development. If the subject is at a Tanner 5 at Day 1, no further Tanner Pubertal Stage Assessments are to be completed. The Tanner stages (Pubic Hair and Breasts for female; Pubic Hair and Genitalia for male) at EOT, FU-12 and FU-24 visit will be summarized by baseline Tanner stages using frequency count and percentage by sex.

Tanner stage results at baseline and during the study will be listed.

7.8. Prior and Concomitant Medications

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

- Prior medications: any medications taken and stopped prior to or on the date of first study drug administration

- Concomitant medications: any medications taken after the date of first study drug administration and up to the last dosing date of study drug

Concomitant medications will be summarized by preferred name using the number and percentage of subjects for the Safety Analysis Set. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary of concomitant medications will be ordered by preferred term in descending frequency. For drugs with the same frequency, sorting will be done alphabetically.

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

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

A summary of prior medications will not be provided.

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

7.9. Neuropsychiatric assessments as measured by PedsQL™ Pediatric Quality of Life survey

The Pediatric Quality of Life (PedsQL™ SF 15) Questionnaires will be completed by all subjects and their parent/legal guardian up to 24-Week Posttreatment visits. The transformed scale scores (0 to 100 scale) at baseline, EOT, or at Early Termination, if applicable, 12-Week Post-Treatment, and 24-Week Post-Treatment visits and change from baseline, change from EOT to posttreatment will be presented for each of the 4 domains of the SF-15 (physical functioning, emotional functioning, social functioning, and school functioning), the psychosocial health summary (emotional, social, and school functioning domains), and the Total Score. Scoring of

the SF15 scales will be performed as described in Scaling and Scoring of the Pediatric Quality of Life Inventory™ (PedsQLTM) by James W. Varni. A Wilcoxon signed rank test will be used to explore changes in status from baseline to EOT, or at Early Termination, if applicable, and from EOT to each of the posttreatment time points. Results (p values) will be presented but should be interpreted with caution as multiple endpoints are being tested, and the study has not been powered to test these endpoints. Plot of the mean ± SD of change from baseline in SF15 summary scores will be presented.

7.10. Other Safety Measures

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

7.11. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

8.1. Population PK Analysis

Population PK modeling will be applied on CCI [redacted] sparse PK samples to characterize the PK of SOF, GS-331007, VEL and VOX using mixed-effect modeling techniques. SOF, GS-331007, VEL and VOX exposures (AUC_{tau}, C_{max}, and C_{tau}, if applicable) in pediatric subjects will be summarized using descriptive statistics (n, arithmetic mean, geometric mean and its 95% confidence interval, coefficient of variation [%CV], SD, median, Q1, Q3, minimum, and maximum), and will be compared with SOF/VEL/VOX adult populations. The primary PK endpoint of this analysis will be evaluated by carrying out an analysis of variance (ANOVA) for log-transformed SOF, GS-331007, VEL and VOX AUC_{tau}. The secondary PK endpoints of this analysis will be the C_{max} and C_{tau} (if applicable), of SOF, GS-331007, VEL and VOX. The 90% confidence intervals will be constructed for the ratio of geometric means of each PK parameter. Population PK Analysis will be performed in ad hoc fashion upon estimated PK parameters using the population PK model are available.

9. REFERENCES

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10. SOFTWARE

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

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Study Procedures Table

Appendix Table 1. Screening and On-Treatment Study Visits

	Screening	Day 1[a]	On-Treatment Study Week (±3 Days)					Early Termination[a]
			Week 1	Week 2[t,v]	Week 4 [s]	Week 8[b]	End of Treatment[c]	
Clinical Assessments								
Informed Consent/Assent	X							
Determine Eligibility	X	X						
Medical History	X							
Parental Height, if known		X						
Complete Physical Examination	X	X					X	X
Symptom Directed Physical Examination			X	X	X	X		
Tanner Pubertal Stage Assessment		X					X	X
Vital Signs[d]	X	X	X	X	X	X	X	X
Body Weight and Height	X	X	X	X	X	X	X	X
Radiographic Bone Age Assessment		X					X	X
AEs and Concomitant Medications	X[e]	X	X	X	X	X	X	X
FibroScan® (if available)	X[f]	X[f]						
Pregnancy Prevention Counseling[g]		X			X	X	X	X
SOF/VEL/VOX Swallowability Assessment	X[h]	X[h]						
SOF/VEL/VOX Acceptability Questionnaire[i]		X					X	X
Quality of Life Survey[j]		X					X	X
Review of Study Medication Compliance				X[k]	X	X	X	X
Study Drug Dispensing		X			X	X		
Return of Study Drug Bottles					X	X	X	X
Review Dosing Diary				X[k]	X[k]			

	Screening	Day 1[a]	On-Treatment Study Week (±3 Days)					Early Termination[a]
			Week 1	Week 2[t,v]	Week 4 [s]	Week 8[b]	End of Treatment[c]	
Laboratory Assessments								
Hematology, Chemistry	X	X	X	X	X	X	X	X
Coagulation	X	X					X	X
HCV RNA	X	X	X	X	X	X	X	X
HBV DNA[l]		X	X	X	X	X	X	X
Viral Sequencing[m]		X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing[n]	X	X		X[o]	X	X	X	X
Single sparse PK sample collected at anytime			X			X	X	X
Two sparse PK Samples collected pre dose and between 15 minutes and up to 4 hours postdose				X[p]	X[p]			
CCI								
Pharmacogenomics Sample[r]		X	X	X	X	X	X	X
Urinalysis	X	X		X[k]	X[k]			
Urine Drug Screen	X							
IL28B Genotyping	X[f]	X[f]						
Bone Age Biomarkers		X						X[w]
HCV Genotyping	X							
HIV testing, HAV Antibody, HCV Antibody, HBsAg, HBsAb, HBcAb	X							
HbA1c, Fibrotest®, APRI	X							
TSH	X						X	X
Alpha 1 anti trypsin	X							

	Screening	Day 1[a]	On-Treatment Study Week (±3 Days)					Early Termination[a]
			Week 1	Week 2[t,v]	Week 4 [s]	Week 8[b]	End of Treatment[c]	
Approximate amount of blood drawn (mL) Cohort 1	22.1	12.3	9.3	11.3 (no IPK) 23.3 (if IPK)[s]	11.3	9.3	13.2	16.8
Approximate amount of blood drawn (mL) Cohort 2	22.1[u]	12.3	9.3	18[t]	11.3	9.3	13.2	16.8
Approximate amount of blood drawn (mL) Cohort 3	22.1[u]	12.3	8.3	8[v]	9.3	8.3	12.2	12.2

a Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to Day 1 and Early Termination (if applicable) to ensure an approximate 8 hour fast prior to the blood sample collection the next morning.
b The Week 8 Visit will only be completed for subject DAA naïve with cirrhosis or DAA experienced with or without cirrhosis, who are on 12 weeks of treatment.
c For subjects that are DAA naive without cirrhosis, who are on 8 weeks of treatment, the End of Treatment visit will occur at Week 8.
For subjects that are DAA naive with cirrhosis or DAA experienced with or without cirrhosis, who are on 12 weeks of treatment, the End of Treatment Visit will occur at Week 12.
d Vital signs include blood pressure, pulse, respiratory rate, and temperature.
e From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol mandated procedures.
f FibroScan® and IL28B genotyping may be performed at Day 1 if not completed at Screening.
g Including partner pregnancy prevention for male participants (all subjects ≥ 12 years old and subjects < 12 years old at the discretion of the Investigator based on subject's pubertal status).
h Swallowability may occur at Day 1 if not completed during Screening.
i A questionnaire will be administered to subjects to assess acceptability, including palatability, on Day 1, EOT (Week 8 or Week 12), or Early Termination (as applicable). If the subject is unable to complete the questionnaires, the parent/legal guardian will assist to complete the questionnaire. The subjects' parent/legal guardian will also complete a questionnaire on EOT (Week 8 or Week 12) or Early Termination (as applicable).
j Quality of life survey will be completed by all subjects and their parent/legal guardian. Subject and parent/legal guardian is to review questionnaire and write/mark answers directly onto the questionnaire.
[redacted] CCI [redacted]
l HBV DNA testing for subjects HBcAb positive at Screening.
m Plasma samples will be collected and stored for potential HCV sequencing and other virology studies. CCI [redacted]
n All females of childbearing potential will have a serum pregnancy test at Screening. In addition, all females of childbearing potential will perform a urine pregnancy test at Day 1 and every 4 weeks during the dosing period and for a minimum of 30 days following the last dose of SOF/VEL/VOX FDC.
[redacted]

p Two sparse PK samples collected pre dose and between 15 minutes and 4 hours postdose CCI

r Only for subjects that have provided consent, an appropriate blood sample for PG analysis will be collected at Day 1. If the sample was not collected Day 1 visit, the sample may be drawn at subsequent visits CCI

u In cohort 2 and cohort 3, for subject weighing ≤ 25 kg, the screening visit will be performed in two different days. Samples for chemistry, hematology, coagulation, TSH, HIV/HAV/HCV testing will be performed on one day (12 ml of blood will be collected) and all other samples including for HCV RNA, HCV genotype and IL28B will be collected on a different day within the screening window (10.1 ml of blood will be collected). If the subject's weight is > 25 kg, the screening visit blood draw can be completed in one day.

w In cohort 3 , Bone age biomarkers (CTX and P1NP) samples will not be collected at the Early Termination visit

Appendix Table 2. Posttreatment Visits

	Posttreatment Study Week (±5 Days)		
	4 Weeks Posttreatment	**12 Weeks Posttreatment**	**24 Weeks Posttreatment[a]**
Clinical Assessments			
Symptom directed Physical Exam	X	X	X
Tanner Pubertal Stage assessment		X	X
Vital Signs	X	X	X
Body weight and Height	X	X	X
AEs	X	X[b]	X[b]
Concomitant Medications	X		
Pregnancy Prevention Counseling[c]	X		
Quality of Life Survey		X	X
Laboratory Assessments			
Hematology, Chemistry	X		
HCV RNA	X	X	X
HBV DNA[d]	X	X	X
Viral Sequencing[e]	X	X	X
Pharmacogenomics Sample[f]	X	X	X
Urine Pregnancy Test	X		
Bone Age Biomarkers			X
Approximate amount of blood drawn (mL) All Cohorts	7.3	5	8.6

a Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to posttreatment Week 24 to ensure an approximate 8 hour fast prior to the blood sample collection the next morning.
b Only SAEs will be captured at posttreatment Week 12 and 24
c Including partner pregnancy prevention for male participants (all subjects ≥ 12 years old and subjects < 12 years old at the discretion of the Investigator based on subject's pubertal status)
d HBV DNA testing for subjects HBcAb positive at Screening
e Plasma samples will be collected and stored for potential HCV sequencing and other virology studies
f Only for subjects that have provided consent, an appropriate blood sample for PG analysis will be collected at Day 1. If the sample was not collected Day 1 visit, the sample may be drawn at subsequent visits [redacted]

Appendix 2. Tanner Stages*

1. Pubic hair (male and female)	
Tanner I	no pubic hair at all (prepubertal Dominic state)
Tanner II	small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females)
Tanner III	hair becomes more coarse and curly, and begins to extend laterally
Tanner IV	adult-like hair quality, extending across pubis but sparing medial thighs
Tanner V	hair extends to medial surface of the thighs
2. Genitals (male) (One standard deviation around mean age)	
Tanner I	Testes, scrotum, and penis about same size and proportion as in early childhood
Tanner II	Enlargement of scrotum and testes; skin of scrotum reddens and changes in texture; little or no enlargement of penis (10.5-12.5)
Tanner III	Enlargement of penis, first mainly in length; further growth of testes and scrotum (11.5-14)
Tanner IV	Increased size of penis with growth in breadth and development of glans; further enlargement of testes and scrotum and increased darkening of scrotal skin (13.5-15)
Tanner V	Genitalia adult in size and shape
3. Breasts (female)	
Tanner I	no glandular tissue: areola follows the skin contours of the chest
Tanner II	breast bud forms, with small area of surrounding glandular tissue; areola begins to widen
Tanner III	breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast
Tanner IV	increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast
Tanner V	breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla.

* Chart referenced from Marshall WA, Tanner JM, variations in the pattern of pubertal changes in boys and girls {Marshall 1969, Marshall 1970}

Appendix 3. PedsQL™ Score Calculation Algorithms

The **Parent Report for Toddlers** (ages 2-4) and **the Child & Parent Reports** for **Young Children** (ages 5-7), **Children** (ages 8-12) and **Teens** (ages 13-18) of the **PedsQL™** 4.0 SF15 Generic Core Scales are composed of 15 items comprising 4 dimensions.

DESCRIPTION OF THE SF15 QUESTIONNAIRE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	5	1-5	1-5	Higher scores indicate better HRQOL
Emotional Functioning	4	1-4	1-4	
Social Functioning	3	1-3	1-3	
School Functioning	3	1-3	1-3	

SCORING OF DIMENSIONS:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always) 3-point scales: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Young Child self-report
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. **Step 2: Calculate Scores** Score by Dimensions: • If more than 50% of the items in the scale are missing, the scale scores should not be computed, • Mean score = Sum of the items over the number of items answered. Psychosocial Health Summary Score = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. Physical Health Summary Score = Physical Functioning Scale Score **Total Score**: Sum of all the items over the number of items answered on all the Scales.
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	16-Apr-2020 21:27:04
PPD	Clinical Research eSigned	16-Apr-2020 22:39:23