STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination ± Ribavirin in Adolescents and Children with Chronic HCV-Infection
Name of Test Drug:	Ledipasvir/Sofosbuvir Fixed Dose Combination
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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
eCRF	electronic case report form
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	Full Analysis Set
FDC	Fixed Dose Combination
Gilead	Gilead Sciences, Inc.
GT	genotype
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)
LDV	Ledipasvir
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
Q1	first quartile
Q3	third quartile
RBV	ribavirin
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
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma/serum concentration versus time curve of the drug
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
CL	systemic clearance of the drug after intravenous administration
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
C_{max}	maximum observed plasma/serum concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
E_{max}	maximum (pharmacodynamic) effect
$t_{½}$	estimate of the terminal elimination half-life of the drug in serum/plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{max}	time (observed time point) of C_{max}

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-337-1116. This SAP is based on the study Protocol Amendment 6 dated 08 June 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. Study Objectives

The primary objectives of this study are as follows:

- The primary objective of the pharmacokinetics (PK) Lead-in Phase of this study is to evaluate the steady state PK and confirm the dose of Ledipasvir/Sofosbuvir Fixed Dose Combination (LDV/SOF FDC) in hepatitis C virus (HCV)-infected pediatric subjects.
- The primary objective of the Treatment Phase of this study is to evaluate the safety and tolerability of LDV/SOF FDC ± ribavirin (RBV) for 12 or 24 weeks in HCV-infected pediatric subjects.

The secondary objectives of this study are as follows:

- The secondary objective of the PK Lead-in Phase of this study is to evaluate the safety and tolerability of 10 days of dosing of LDV/SOF FDC in HCV-infected pediatric subjects.
- The secondary objectives of the Treatment Phase of this study are:
  - To determine the antiviral efficacy of 12 or 24 weeks of LDV/SOF FDC ± RBV treatment in chronic HCV-infected subjects (including the impact of HCV genotype, IL28B genotype, and prior treatment experience), as assessed by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)
  - To determine the antiviral efficacy of 12 or 24 weeks of LDV/SOF FDC ± RBV treatment in chronic HCV-infected subjects, as assessed by the proportion of subjects with sustained viral response 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)
  - To evaluate the kinetics of circulating HCV RNA during treatment and after completion of treatment
  - To evaluate the emergence of viral resistance to LDV and SOF during treatment and after completion of treatment
  - To evaluate the acceptability assessed by swallowability of tablets and palatability of granules
  - To evaluate the effect of growth and development on pediatric subjects during and after treatment

The exploratory objective of this study is as follows:

- PPD

1.2. Study Design

This is an open-label, multi-cohort, two-part study evaluating the PK, safety, and efficacy of LDV/SOF FDC ± RBV in chronic HCV-infected pediatric subjects.

The study will enroll both treatment-naive and treatment–experienced pediatric subjects with up to 40 subjects allowed to be treatment experienced. Approximately 220 total subjects will be enrolled as follows:

- Approximately 100 adolescents aged 12 to < 18 years
- Approximately 120 children aged 3 to < 12 years

Subjects of 3 age groups will be enrolled in a sequential fashion: 12 to <18 years old, followed by 6 to <12 years old, and 3 to <6 years old.

Eligible subjects will receive the following treatment regimens based on HCV genotype, prior treatment experience, cirrhosis status and country of enrollment:

Table 1-1. Subject Enrollment by HCV Genotype, Country, and Treatment Duration

<table>
<tr><th></th><th colspan="2">GT1, GT4, GT5, & GT6</th><th>GT1</th><th>GT4, GT5, & GT6</th><th>GT3</th></tr>
<tr><th></th><th>Cirrhotic or Non-cirrhotic Subjects (TN)</th><th>Non - cirrhotic Subjects (TE)</th><th>Cirrhotic Subjects (TE)</th><th>Cirrhotic Subjects (TE)</th><th>Non-cirrhotic or Cirrhotic Subjects (TE)</th></tr>
<tr><td>United States, Australia, New Zealand</td><td rowspan="2">12 Weeks of treatment with LDV/SOF FDC</td><td rowspan="2">12 Weeks of treatment with LDV/SOF FDC</td><td rowspan="2">24 Weeks of treatment with LDV/SOF FDC</td><td>12 Weeks of treatment with LDV/SOF FDC</td><td>N/A</td></tr>
<tr><td>United Kingdom</td><td>24 Weeks of treatment with LDV/SOF FDC</td><td>24 Weeks of treatment with LDV/SOF FDC + RBV</td></tr>
</table>

TN = Treatment Naïve, TE = Treatment Experienced, N/A = Not Applicable

Therefore, subjects actually enrolled are grouped into the treatment groups according to their age groups, HCV genotype, prior treatment experience, cirrhosis status, and treatment duration, as specified in Section 3.2.

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

1.2.1. PK Lead-in Phase

The PK Lead-in Phase will evaluate and/or confirm the age appropriate LDV/SOF FDC dose by analyzing PK, safety, and antiviral activity of LDV/SOF FDC through 10 days of dosing.

At least 10 treatment-naïve subjects without history of cirrhosis will be sequentially enrolled into each of the following 3 cohorts:

- Cohort 1: 12 to < 18 years old, weighing ≥ 45kg
- Cohort 2: 6 to < 12 years old, weighing ≥ 17kg and < 45kg
- Cohort 3: 3 to < 6 years old
  - At least 4 subjects weighing ≥ 17 kg
  - At least 4 subjects weighing < 17 kg

Intensive PK and safety results through Day 10 of each Cohort will be reviewed to confirm the appropriateness of the LDV/SOF FDC dose for that age group as well as to determine the age-appropriate dose to be evaluated in the PK Lead-in Phase of the next age Cohort.

Subjects enrolled in the PK Lead-in Phase will immediately enroll in the Treatment Phase as they complete Day 10 of PK Lead-in. They will continue dosing with LDV/SOF FDC with no interruption of study drug administration until the appropriateness of the dose is confirmed by PK and safety data from the PK Lead-in Phase.

Cohort 1 subjects received LDV/SOF FDC (90 mg/ 400 mg adult tablet or 4 × 22.5 mg/100 mg tablets if determined necessary based on LDV/SOF FDC swallowability assessment) for 10 days with intensive PK conducted on Day 10.

Cohort 2 subjects received LDV/SOF FDC 45 mg/ 200 mg (2 × 22.5 mg/ 100 mg tablets) for 10 days with intensive PK conducted on Day 10.

Cohort 3 subjects weighing ≥17 kg received LDV/SOF FDC 45 mg/ 200 mg (4 × 11.25 mg/ 50 mg packets containing granules) for 10 days with intensive PK conducted on Day 10.
Cohort 3 subjects weighing <17 kg received LDV/SOF FDC 33.75 mg/ 150 mg (3 × 11.25 mg/ 50 mg packets containing granules) for 10 days with intensive PK conducted on Day 10.

1.2.2. Treatment Phase

Additional HCV-infected children will be enrolled into the Treatment Phase upon confirmation of the appropriateness of the dose from the PK Lead-in Phase. The Treatment Phase will be initiated sequentially by age group as defined in Cohorts 1, 2, and 3 of the PK Lead-in Phase.

Subjects who participated in the PK Lead-in Phase will immediately roll over into the Treatment Phase with no interruption of study drug administration until the appropriateness of the dose has been confirmed by PK and safety results from the PK Lead-in Phase. The first visit in the Treatment Phase for these subjects will be the Week 2 visit.

After dose confirmation in the PK Lead-in Phase of each age group, the identical dose was used in subjects of the corresponding age group enrolled in the Treatment Phase.

1.2.3. Study Duration

The total time to complete all study visits is up to approximately 40 weeks for subjects treated with 12 weeks of therapy and 52 weeks for subjects treated for 24 weeks of therapy including the following periods:

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

1.3. Sample Size and Power

With approximately 100 subjects enrolled into the 12 to <18 years of age group, a two-sided 95.0% confidence interval of the SVR12 rate will extend at most 5.9% in both directions from the observed SVR12 rate, assuming the expected SVR12 rate is 90%.

With approximately 120 subjects enrolled into the 3 to < 12 years of age group, a two-sided 95.0% confidence interval of the SVR12 rate will extend at most 5.4% in both directions from the observed SVR12 rate, assuming the expected SVR12 rate is 90%.

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 safety data and provide recommendation to Gilead about whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

Specific activities of the DMC will be defined by a mutually agreed charter, which will define DMC membership, conduct and meeting schedule.

2.2. Final Analysis

After all subjects 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 subjects enrolled in the study after screening. All analyses based on the All Enrolled Analysis Set will be performed according to the treatment group to which subjects were enrolled.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes HCV infected subjects who were enrolled into the study and received at least one dose of study drug. The study drugs in this study include LDV/SOF FDC and RBV. Subjects are grouped within the FAS by the treatment group to which they were enrolled.

This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug (ie, LDV/SOF FDC ± RBV). Subjects will be grouped according to the treatment they actually received.

This is the primary analysis set for safety analyses.

3.1.4. Pharmacokinetic Analysis Set

PK Lead-in Phase Intensive PK Analysis Set

The PK Lead-in Phase Intensive PK Analysis Set includes all PK Lead-in Phase 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 the PK Lead-in Phase intensive sampling. This is the primary analysis set for PK Lead-in Phase intensive PK analysis.

Population PK Analysis Set

The Population PK Analysis Set includes all enrolled 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 the 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.

Generally, subjects are analyzed, except for the safety analysis, by treatment groups based on age group, HCV genotype, prior treatment experience, cirrhosis status, and treatment duration:

Table 3-1. Non-safety Treatment Groups*

12 to < 18 Years Old		3 to < 12 Years Old			
LDV/SOF (90/400 mg) 12 Weeks		LDV/SOF (45/200 mg or 33.75/150 mg) 12 Weeks		LDV/SOF (45/200 mg) 24 Weeks	LDV/SOF+RBV (45/200 mg) 24 Weeks
GT1 TN w/ or w/o cirrhosis (N =)	GT1 TE without cirrhosis (N =)	GT1, GT4 TN w/ or w/o cirrhosis (N =)	GT1 TE without cirrhosis (N =)	GT1 TE with cirrhosis (N =)	GT3 TE w/ or w/o cirrhosis (N =)
6 to < 12 Years Old				3 to < 6 Years Old	
LDV/SOF (45/200 mg) 12 Weeks		LDV/SOF (45/200 mg) 24 Weeks	LDV/SOF+RBV (45/200 mg) 24Weeks	LDV/SOF (45/200 mg or 33.75/150 mg) 12 Weeks	
GT1, GT4 TN w/ or w/o cirrhosis (N =)	GT1 TE without cirrhosis (N =)	GT1 TE with cirrhosis (N =)	GT3 TE w/ or w/o cirrhosis (N =)	GT1, GT4 TN w/ or w/o cirrhosis (N =)	

GT = genotype, TN = Treatment Naïve, TE = Treatment Experienced, w/ = with, w/o = without
*Treatment Groups reflect the subjects actually enrolled.

For the safety analysis, subjects will be analyzed by the following groups based on age group, treatment regimen and duration:

Table 3-2. Safety Treatment Groups

12 to < 18 Years Old	3 to < 12 Years Old		
LDV/SOF (90/400 mg) 12 Weeks (N =)	LDV/SOF (45/200 mg or 33.75/150 mg) 12 Weeks (N =)	LDV/SOF (45/200 mg) 24 Weeks (N =)	LDV/SOF+RBV (45/200 mg) 24 Weeks (N =)
6 to < 12 Years Old			3 to < 6 Years Old
LDV/SOF (45/200 mg) 12 Weeks (N =)	LDV/SOF (45/200 mg) 24 Weeks (N =)	LDV/SOF+RBV (45/200 mg) 24 Weeks (N =)	LDV/SOF (45/200 mg or 33.75/150 mg) 12 Weeks (N =)

Subjects in the 3 to < 6 years of age group will have additional selected efficacy and safety analyses performed according to baseline weight in the following subgroups:

Table 3-3. Subgroups for Selected Analyses in 3 to < 6 years of Age

3 to < 6 Years Old	
< 17 kg LDV/SOF (33.75/150 mg) 12 Weeks (N =)	≥ 17 kg LDV/SOF (45/200 mg) 12 Weeks (N =)

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 ALT (≤1.5 × ULN, > 1.5 × ULN)
- Interferon (IFN) eligibility (IFN-eligible, IFN-ineligible)
- most recent response to prior HCV treatment (non-response, relapse/breakthrough, IFN-intolerant) for treatment experienced subjects
- study treatment status (completed study treatment, discontinued study treatment)
- adherence to study regimen (< 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 "< 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. For some countries, only birth year is collected on the eCRF. In those cases, "01 January" will be used for the unknown birth day and month for the purpose of age calculation, unless age is captured on the eCRF.

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

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

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

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

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

When the calculated HCV RNA 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 for determination of summary and order statistics and will be excluded in any calculation of geometric means or ratios.

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

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

3.7.2. 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 + 2 days are considered to be on-treatment data and HCV RNA, vital signs and safety laboratory data collected after the last dose date + 2 days are considered posttreatment data. The analysis windows for on-treatment HCV RNA, vital signs and safety laboratory data are provided in Table 3-4.

Table 3-4. Analysis Windows for On-treatment HCV RNA, Vital Signs and Safety Laboratory Data

	LDV/SOF FDC 12 Weeks			LDV/SOF FDC ± RBV 24 Weeks		
Nominal Visit	Nominal Day	Lower Limit	Upper Limit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1	1	(none)	1
Week 1	7	2	11	7	2	11
Week 2	14	12	21	14	12	21
Week 4	28	22	42	28	22	42
Week 8	56	43	70	56	43	70
Week 12	84	71	≥ 85	84	71	98
Week 16	NA			112	99	126
Week 20				140	127	154
Week 24				168	155	≥ 169

Subjects who participated in the PK Lead-in Phase will immediately roll over into the Treatment Phase with no interruption of study drug administration until the appropriateness of the dose is confirmed by PK and safety data from the PK-Lead-in Phase. These subjects will start at the Week 2 visit of the Treatment Phase. Week 1 records for these subjects will be chosen from Day 10 in the PK Lead-in Phase.

HCV RNA, vital sign, and safety laboratory data collected after the last dose date + 2 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 3-5.

Table 3-5. 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	3	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 by treatment group 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 by treatment group. This summary will present the number of subjects screened, the number of subjects enrolled, the number of subjects enrolled but never treated, and the number and percentage of subjects in each of the categories listed below. For the "Treated" category, the denominator for the percentage calculation will be the total number of subjects enrolled for each column. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column.

- Treated (Safety Analysis Set)
- In FAS
- In 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 study treatment and who discontinued study treatment, the number and percentage of subjects will be summarized for:

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

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

In addition, the total number of subjects who were 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 regimen and individual study drug will be examined by assessing the total durations of study regimen and individual study drug exposure and the level of adherence to any study drug and individual study drug specified in the protocol.

4.2.1. Durations of Exposure to Study Regimen and Individual Study Drug

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

The total durations of exposure to study regimen and individual 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 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56), and Week 12 (Day 84) for all subjects and additionally Week 16 (Day 112), Week 20 (Day 140), and Week 24 (Day 168) for subjects receiving 24 weeks of treatment. 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 by treatment group for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

The level of adherence to individual study drug will be assessed separately based on the total amount of individual study drug administered relative to the total amount of individual study drug prescribed. In this study, LDV/SOF FDC 90/400 mg tablets, LDV/SOF FDC 22.5/100 mg tablets, and LDV/SOF 11.25/50 mg packets containing granules have been used. For RBV, both REBETOL capsules and REBETOL RBV oral solution could be used. Each capsule contains 200 mg RBV and the oral solution contains 40 mg RBV per mL.

Given the fact that multiple formulations of the study drug have been used in this study, the adherence will be calculated based on the amount of LDV/SOF FDC (mg) or RBV (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%.

The total amount of prescribed LDV/SOF FDC (mg) for 12 weeks and 24 weeks are as follows:

Age Group and Body Weight	LDV/SOF Daily Dose	Total Amount of LDV/SOF Prescribed for 12 Weeks	Total Amount of LDV/SOF Prescribed for 24 Weeks
12 to <18 years any weight	490 mg/day	41160 mg	N/A*
6 to <12 years any weight	245 mg/day	20580 mg	41160 mg
3 to <6 years weighing ≥17 kg	245 mg/day	20580 mg	N/A*
3 to < 6 years weighing <17 kg	183.75 mg/day	15435 mg	N/A*

*Note: No subject 12 to <18 or 3 to <6 years old was assigned to 24 weeks of treatment.

For subjects infected with HCV GT3, RBV was prescribed by weight at baseline. The total amount of RBV (mg) prescribed for 24 weeks is as follows:

Body Weight kg (lbs.)	RBV Daily Dose	RBV Number of Capsules	Total Amount of RBV Prescribed for 24 Weeks
<47 (<103)	15 mg/kg/day	Use Oral Solution. Divided dose in the morning and evening.	2,520 mg/kg
47-49 (103-108)	600 mg/day	1 × 200-mg capsules A.M. 2 × 200-mg capsules P.M.	504 capsules (100800 mg)
50-65 (110 – 143)	800 mg/day	2 × 200-mg capsules A.M. 2 × 200-mg capsules P.M.	672 capsules (134400 mg)
66-80 (145 – 176)	1000 mg/day	2 × 200-mg capsules A.M. 3 × 200-mg capsules P.M.	840 capsules (168000 mg)
81-105 (178-231)	1200 mg/day	3 × 200-mg capsules A.M. 3 × 200-mg capsules P.M.	1,008 capsules (201600 mg)
>105 (>231)	1400 mg/day	3 × 200-mg capsules A.M. 4 × 200-mg capsules P.M.	1,176 capsules (235200 mg)

Note: Subjects with a body weight greater than or equal to 47 kg may utilize the RBV oral solution if necessary.

Weight reported as a decimal number was rounded to the whole number to determine the prescribed RBV dosage. For example, a subject weighing 49.5 kg fell into the 50-65 kg category and received 800 mg/day.

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 $< 90\%$, $\geq 90\%$) will be provided by treatment group for the Safety Analysis Set. No inferential statistics will be provided for duration of exposure and adherence to study drug. Categorical displays will be provided for the number of subjects who are at least 80% adherent to individual study drug and study regimen (ie, adherence is $\geq 80\%$ for each of the study drugs). No inferential statistics will be provided.

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 treatment group and total in each age group 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.

In addition, for subjects 3 to < 6 years of age, demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group as defined in Table 3-3 and total.

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 (genotype 1 [further broken down to 1a, 1b, and other], genotype 3, genotype 4, and other as applicable)
- cirrhosis (presence, absence, unknown)
- IL28B (CC, CT, TT)
- baseline HCV RNA (log_{10} IU/mL) as a continuous variable and as categories (< 800,000 IU/mL, ≥ 800,000 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)
- IFN eligibility (IFN-eligible, IFN-ineligible)

- most recent response to prior HCV treatment (non-response, relapse/breakthrough, IFN-intolerant) for treatment experienced subjects
- mode of HCV Infection
- bone age in years
- Tanner Stage

Estimated Glomerular Filtration Rate (GFR) 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, and for children 3- <12 years old is 0.55); L is height in centimeters (cm); and Scr is serum creatinine (mg/dL)]

These baseline characteristics will be summarized by treatment group and total in each age group 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.

In addition, for subjects 3 to < 6 years of age, baseline characteristics will be summarized by treatment group as defined in Table 3-3 and total.

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

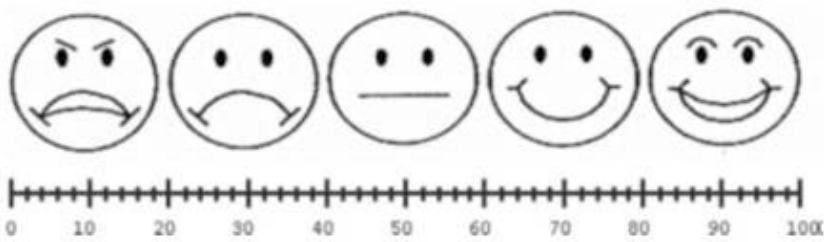
5.3. Swallowability Assessment for LDV/SOF Placebo Tablets

For subjects in the 12 to <18 and 6 to <12 age groups, swallowability of LDV/SOF 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 LDV/SOF FDC tablets will be provided by subject ID number in ascending order.

5.4. Palatability of LDV/SOF Oral Granules

For subjects in any age group, dosed with granules, palatability will be assessed by numeric response marked on line between numbers 0-100 (higher scores indicate better taste).



Palatability of LDV/SOF oral granules will be summarized using the numbers and percentages of subjects by age group in the following palatability categories:

- Did Not Taste the Study Drug
- Tasted the Study Drug:
  - Taste score > 60 to 100
  - Taste score 40 to 60
  - Taste score 0 to < 40

A by-subject listing of Palatability of LDV/SOF oral granules 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 all study drugs 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 will be provided for the SVR12 rate by treatment group and total in each age group {Clopper 1934}.

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 will be provided for each treatment group within each subgroup specified in Section 3.4 {Clopper 1934}.

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

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- 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 LDV/SOF

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

For analyses of HCV RNA < LLOQ by visit while on treatment and during the 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 in each treatment group. The overall category for "HCV RNA < LLOQ" will be split into the following 2 subcategories: "< LLOQ TND" for subjects with target not detected and "< LLOQ detected" for subjects with < LLOQ detected in tabular displays.

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

Summary statistics will be presented for absolute values and change from baseline in HCV RNA ($\log_{10}$ IU/mL) by visit through EOT. Imputation rules described in Section 3.5.1 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. 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. Additional summary table will be provided by treatment group defined in Table 3-3 for 3 to < 6 years of age subjects.

A concordance table between SVR12 and SVR24 will be provided by treatment group and total in each age group. 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.

6.3. Exploratory Efficacy Endpoints

PPD

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 treatment group and by the number and percentage of subjects who had the following: any AE; any AE of Grade 3 or above; any AE of Grade 2 or above; any treatment-related AE; any treatment-related AE of Grade 3 or above; any treatment-related AE of Grade 2 or above; any SAE; any treatment-related SAE; any AE that led to premature discontinuation of any study drug; any AE that led to premature discontinuation of all study drugs; any AE that led to premature discontinuation of LDV/SOF FDC; any AE that led to premature discontinuation of RBV; any AE that led to modification or interruption of any study drug; any AE that led to interruption of LDV/SOF FDC; any AE that led to modification or interruption of RBV. All deaths (including those that are treatment emergent and those that are not treatment emergent) observed during the study will also be summarized and included in this table. Additionally, for subjects 3 to < 6 years of age, a brief high-level summary of TEAEs will be provided by treatment group defined Table 3-3.

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT, by treatment group 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 any study drug
- AEs leading to premature discontinuation of all study drugs
- AEs leading to premature discontinuation of LDV/SOF FDC
- AEs leading to premature discontinuation of RBV
- AEs leading to modification or interruption of any study drug
- AEs leading to interruption of LDV/SOF FDC
- AEs leading to modification or interruption of RBV

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 of the pooled treatment groups within each SOC. In summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

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

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

In addition to the by-treatment 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 any study drug
- AEs leading to modification or interruption of any study drug

7.2. Laboratory Evaluations

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

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

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment group for ALT, AST, total bilirubin, alkaline phosphatase, hemoglobin, reticulocytes, white blood cell (WBC), neutrophils, lymphocytes, platelets, and 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 treatment group and visit.

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

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, or all available data in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

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

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

- Graded laboratory abnormalities
- Grade 3 or above laboratory abnormalities

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

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

7.2.2.3. 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 2 days after the last dose of any study drug):

- Aspartate aminotransferase (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) by treatment group. The baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3 (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) by treatment group.

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 was calculated as the average of father's and mother's height. For boys, calculate the sex-adjusted mid-parental height by adding 2.5 inch or 6.5 cm from the mean of the parents' heights. For girls, subtract 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

A single X-ray of the left wrist, hand, and fingers will be performed at Day 1 Visit and post-treatment Week 24. Local radiologist will determine the bone age from x-ray.

Bone age at baseline visit, FU-24 visit 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) by treatment group.

A by-subject listing of bone age 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 overall and by sex within each treatment group.

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 each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary of concomitant medications will be ordered by 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. Other Safety Measures

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

7.10. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

8.1. PK Analysis in the PK Lead-in Phase (Intensive PK Analysis)

Intensive PK Analysis will be performed using the PK Lead-in Phase Intensive PK Analysis Set. Concentrations of SOF, GS-331007 and LDV from subjects in the PK lead-in Phase over sampling time will be listed and 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) by nominal time and cohort. For Cohorts 1 and 2, plasma samples will be collected for PK analyses following dosing of study drugs on Day 10 at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 5, 8, and 12 hours postdose. For Cohort 3, plasma samples for PK analyses will be collected at the following time points: 0 (predose), 0.5, 2, 4, 8, and 12 hours postdose. PK parameters from subjects in the PK lead-in Phase will be summarized (e.g; AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, $T_{1/2}$, volume of distribution and clearance, as appropriate) by cohort.

To confirm the appropriateness of LDV/SOF FDC dose for each age group, PK parameters for SOF, GS-331007 and LDV will be compared between each age group from this study and the LDV/SOF FDC NDA patient population (which includes population-PK derived PK exposure data from adult Phase 2 and 3 studies) by carrying out an analysis of variance (ANOVA) for log-transformed AUC_{tau} of GS-331007 and LDV as the primary endpoint and C_{max} of GS-331007 and LDV as a secondary endpoint. Geometric Mean Ratio and its 90% confidence interval will be provided.

8.2. Population PK Analysis

Population PK modeling will be applied on the combined data from both intensive PK samples collected in PK Lead-in Phase and sparse PK samples collected in the Treatment Phase to characterize the pharmacokinetics of SOF, GS-331007 and LDV using mixed-effect modeling techniques. Estimated PK parameters using the population PK model will be presented in a separate Population PK report.

9. REFERENCES

Centers for Disease Control and Prevention (CDC). Division of Nutrition, Physicial Activity, and Obesity> Nutrition: Growth Chart Training: A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years). Available at: http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. 2016a.

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Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Dec. Biometrika 1934;26 (4):pp. 404-13.

Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Archives of disease in childhood 1969;44 (235):291-303.

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Tanner JM, Goldstein H, Whitehouse RH. Standards for Children's Height at Ages 2-9 Years Allowing for Height of Parents. Archives of disease in childhood 1970;45:755-62.

10. SOFTWARE

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

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

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Study Procedures Table

Appendix Table 1. PK Lead-in Phase: Screening and On-Treatment Study Visits

	Screening (-28 days)	On-treatment		
		Day 1[b]	Day 3	Day 10 (+ 3 days)
Clinical Assessments				
Informed Consent / Assent	X			
Determine Eligibility	X	X		
Medical History	X [j]			
Complete Physical Examination	X	X		
Symptom-directed Physical Examination			X	X
Tanner Pubertal Stage Assessment		X		
Vital Signs[a]	X	X	X	X
Bone Age Assessment		X		
AEs and Concomitant Medications	X	X	X	X
Pregnancy Prevention Counseling[f]		X		
LDV/SOF FDC Swallowability Assessment	X	X[h]		
Quality of Life Survey		X[i]		
Review of Study Medication Compliance			X	X
Study Drug Dispensing[b]		X		
Subject Dosing Diary		X	X	X

	Screening (-28 days)	On-treatment		
		Day 1[b]	Day 3	Day 10 (+ 3 days)
Laboratory Assessments				
Hematology, Chemistry	X	X	X	X
Coagulation Tests	X	X		X
HCV RNA	X	X	X	X
Viral Sequencing [c]		X	X	X
Serum or Urine Pregnancy Testing[e]	X	X		X
Urinalysis	X	X		X
Urine Drug Screen	X			
PPD				
Intensive PK				X [d]
HCV Genotyping, IL28B	X			
HCV antibody, HIV antibody, HBs antigen, HBs antibody, HBc antibody, and HAV antibody	X			
HbA1c	X			
TSH	X			
Alpha fetoprotein	X			
Alpha-1 anti-trypsin	X			
HBV DNA[k]		X		

a Vital signs include blood pressure, pulse, respiratory rate and temperature, body weight, and height

b Day 1 assessments must be performed prior to dosing

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

d For Cohorts 1 and 2, plasma samples will be collected for PK analyses following dosing of study drug on Day 10 at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 5, 8, and 12 hours post-dose. For Cohort 3, plasma samples for PK analyses will be collected at the following time points: 0 (predose), 0.5, 2, 4, 8, and 12 hours post-dose.

e Females of childbearing potential only. Serum pregnancy test performed at screening and for confirmation of positive urine pregnancy test.

f Including partner pregnancy prevention for male participants (all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the Investigator based on subject's pubertal status).

g PPD

h Swallowability, for subjects on tablet formulation, can occur at Day 1 if not completed during screening.

i Quality of life survey will be completed by all subjects if a site is approved to use the survey. Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire.

j Parental height will be collected (if available)

k Only subjects HBcAb positive at Screening

Appendix Table 2. Treatment Phase: Screening and On-Treatment Study Visits

	Screening[c] (-28 days)	Day 1[c]	Visit identified by on-treatment study week								
			1[c]	2	4	8	12	16[k]	20[k]	24[k]	Early Termination
Clinical Assessments											
Informed Consent / Assent	X										
Determine Eligibility	X	X									
Medical History	X[i]										
Complete Physical Examination	X	X					X[j]			X	X
Symptom-Directed Physical Examination			X	X	X	X	X[k]	X	X		
Tanner Pubertal Stage Assessment		X					X[j]			X	X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X
Bone Age Assessment		X									
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling [g]		X					X[j]			X	X
LDV/SOF FDC Swallowability Assessment	X	X[h]									
Quality of Life Survey [e]		X					X[j]			X	X
Review of Study Medication Compliance					X	X	X	X	X	X	X
Study Drug Dispensing[b]		X			X	X	X[k]	X	X		
Palatability Assessment of Oral Granules as applicable		X									
Laboratory Assessments											
Hematology, Chemistry, Coagulation	X	X	X	X	X	X	X	X	X	X	X
HCV RNA	X	X	X	X	X	X	X	X	X	X	X
Viral Sequencing [d]		X	X	X	X	X	X	X	X	X	X

	Screening[c] (-28 days)	Day 1[c]	Visit identified by on-treatment study week								
			1[c]	2	4	8	12	16[k]	20[k]	24[k]	Early Termination
Serum or Urine Pregnancy Testing[l]	X	X			X	X	X	X	X	X	X
PPD											
Urinalysis	X	X									
Urine Drug Test	X										
HCV Genotyping, IL28B	X										
HCV antibody, HIV antibody, HBs antigen, HBs antibody, HBc antibody, and HAV antibody	X										
HbA1c	X										
TSH	X						X[j]			X	X
Alpha fetoprotein, Alpha-1 anti-trypsin	X										
HBV DNA[m]		X			X	X	X	X	X	X	X
Single PK collected at any time point			X	X			X	X	X	X	X
Single PK Sample collected between 15 minutes to 4 hours post-dose[n]					X	X					
PPD											

a Vital signs include blood pressure, pulse, respiratory rate and temperature, and body weight and height

b The IWRS will provide direction on the specifics of each subject's study drug dispensing.

c Subjects rolling over from PK Lead-in phase will not be required to repeat screening, Day 1 or Week 1 visits during the on Treatment Phase

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

e Quality of life survey will be completed by all subjects if a site is approved to use the survey. Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire.

f PPD

g Including partner pregnancy prevention for male participants (all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the Investigator based on subject's pubertal status).

h Swallowability, for subjects on tablet formulation, can occur at Day 1 if not completed during screening.

i Parental height will be collected (if available)

j Subjects on 12 Week Treatment regimen only

k Subjects on 24 Week Treatment regimen only

l Females of childbearing potential only. Serum pregnancy test performed at screening and for confirmation of positive urine pregnancy test

m Only subjects with positive HBcAb at Screening

n A single PK sample will be collected at Weeks 4 and 8 between 15 minutes to 4 hours post dose as applicable, PPD

o PPD

Appendix Table 3. Treatment Phase: Post Treatment Visits Following Primary Study

	4 Weeks Post Treatment	12 Weeks Post Treatment	24 Weeks Post Treatment
Clinical Assessments			
Vital Signs, Body weight and Height	X	X	X
Symptom-directed Physical Exam	X	X	X
AEs	X	X[c]	X[c]
Concomitant Medications	X		
Quality of Life Survey [a]		X	X
Tanner Pubertal Stage Assessment		X	X
Bone Age Assessment			X
Pregnancy Prevention Counseling[d]	X	X[f]	X[f]
Laboratory Assessments			
Hematology, Chemistry	X	X	
HCV RNA	X	X	X
Viral Sequencing [b]	X	X	X
Urine Pregnancy Test	X	X[e]	X[e]
HBV DNA[g]	X	X	X

a Quality of life survey will be completed by all subjects at 12-Week and 24-Week Post Treatment visits if a site is approved to use the survey. Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire.

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

c At Post Treatment Week 12 and 24, only SAEs will be captured

d Including partner pregnancy prevention for male participants (all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the Investigator based on subject's pubertal status).

e GT-3 subjects only: Female subjects of childbearing potential should be provided with Urine Pregnancy Test Kits, instructed on their use and requested to continue to self-monitor for pregnancy for 6 months after their last dose of RBV. If required by regulations, additional pregnancy tests beyond 6 months may be added. The subject should be contacted every 4 weeks and asked to report results of the urine pregnancy tests. If a positive urine pregnancy test is reported, the subject should return to the clinic for a serum pregnancy test.

f GT-3 subjects only

g Only subjects HBcAb positive at Screening

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.