CLINICAL STUDY PROTOCOL

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	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA	
IND No.:	115268	
EudraCT Number:	2014-003578-17	
Indication:	Hepatitis C Virus Infection	
Protocol ID:	GS-US-337-1116	
Gilead Sciences Medical Monitor:	Name:	Bittoo Kanwar, MD
	Telephone:	PPD
	Mobile:	PPD
	Fax:	PPD
	E-mail:	PPD
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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

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
IND Number: **EudraCT Number:**	115268 2014-003578-17
Study Centers:	Approximately 30 sites in the United States, Europe, Australia, and New Zealand
Number of Subjects:	Approximately 200 subjects
Target Population:	Adolescents and children (aged 3 to < 18) chronic hepatitis C virus (HCV) infection
Treatment Duration:	PK Lead-in – 10 days Treatment Phase – 12 or 24 weeks
Objectives:	The primary objective of the PK Lead-in Phase of this study is: • To evaluate the steady state pharmacokinetics (PK) and confirm the dose of LDV/SOF FDC in chronic HCV-infected pediatric subjects The secondary objective of the PK Lead-in Phase of this study is: • To evaluate the safety, tolerability, and antiviral activity of 10 days of dosing of LDV/SOF FDC in chronic 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 +/- RBV for 12 or 24 weeks in chronic 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 virological response (SVR) 12 weeks after completion of treatment (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 SVR 4 and 24 weeks after completion of treatment (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 effect of growth and development on pediatric subjects during and after treatment

The exploratory objective of this study is:

- PPD

Study Design:

Open-label, multi-cohort, two-part study evaluating the PK, safety, and antiviral activity of LDV/SOF FDC +/- RBV in chronic HCV-infected pediatric subjects.

The study will be divided into 2 parts and will commence with GT-1, -3, and -4 HCV-infected pediatric subjects as follows (subjects with GT-2, -5, and -6 will be included once adult data are available, if appropriate):

PK Lead-in Phase: PK Lead-in will evaluate and/or confirm age appropriate LDV/SOF FDC doses by analyzing PK, safety, and antiviral activity of LDV/SOF FDC through 10 days of dosing for each of the three cohorts. Children aged 3 to < 6, children aged 6 to < 12 years, and adolescents aged 12 to < 18 years with evidence of chronic HCV and HCV RNA ≥ 1000 IU/mL at study entry will be evaluated. Subjects must be treatment naïve without history of cirrhosis to participate in the PK Lead-in Phase.

Three cohorts of at least 10 subjects each will be sequentially enrolled:

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

The study will start with Cohort 1. Subjects will receive LDV/SOF FDC (90 mg/ 400 mg fixed dose combination tablet or 4 x 22.5 mg/ 100 mg based on LDV/SOF FDC swallowability assessment) for 10 days with intensive PK conducted on Day 10.

Once Cohort 1 data is analyzed and a Cohort 2 dose is determined, Cohort 2 will open for screening. Cohort 2 subjects will receive 45 mg/ 200 mg LDV/SOF FDC (2 x 22.5 mg/ 100 mg tablets or subject enrollment will be deferred until oral granulate formulation is available, if determined necessary based on the LDV/SOF FDC swallowability assessment) for 10 days with intensive PK conducted on Day 10.

PK Lead-in subjects in each cohort (Cohorts 1, 2 and 3) will immediately enroll in the Treatment Phase as they complete Day 10 of the PK Lead-in Phase. They will continue dosing with LDV/SOF FDC with no interruption of study drug administration. Subjects rolling over from the PK Lead-in will not be required to perform Treatment Phase Screening, Day 1, or Week 1 visits in the Treatment Phase.

Following completion of study treatment in the PK Lead-in of each Cohort, intensive PK and safety results of study treatment will be reviewed to confirm the appropriateness of the evaluated LDV/SOF FDC dose for the Treatment Phase of that Cohort as well as to determine the age-appropriate dose to be evaluated in the PK Lead-in of the next Cohort.

Treatment Phase: Treatment Phase will be initiated sequentially by cohort after confirmation of age-appropriate LDV/SOF FDC dosage levels. Subjects who participate in PK Lead-in Phase will immediately rollover into 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. Additional subjects will be enrolled in the Treatment Phase of each Cohort upon confirmation of the appropriateness of the dose.

Children aged 3 to < 12 years and adolescents aged 12 to < 18 years with chronic HCV-infection and a HCV RNA ≥ 1000 IU/mL at study entry (those who were dosed in the PK Lead-in Phase will have met these criteria prior to enrollment) will be evaluated. The study will commence with GT-1, -3, and -4 HCV infected pediatric subjects and will subsequently enroll subjects with GT-2, -5, and -6 once adult data is available, if appropriate.

Subjects enrolled in the study will receive the following regimen:

- United Kingdom:
  - GT-1 and GT-4 treatment-naïve with or without cirrhosis: LDV/SOF FDC for 12 weeks
  - GT-1 and GT-4 treatment-experienced without cirrhosis: LDV/SOF FDC for 12 weeks
  - GT-1 and GT-4 treatment-experienced with cirrhosis (as determined by liver biopsy): LDV/SOF FDC for 24 weeks
  - GT-3 treatment-experienced with or without cirrhosis: LDV/SOF FDC + RBV for 24 weeks
- United States/Australia/New Zealand (GT-1 only):
  - GT-1 treatment-naïve with or without cirrhosis: LDV/SOF FDC for 12 weeks
  - GT-1 treatment-experienced without cirrhosis: LDV/SOF FDC for 12 weeks
  - GT-1 treatment-experienced with cirrhosis (as determined by liver biopsy): LDV/SOF FDC for 24 weeks

The study will enroll both treatment-naïve and treatment experienced pediatric subjects, with up to 40 subjects allowed to be treatment experienced. Approximately 200 total subjects, including subjects that participated in the PK Lead-in Phase, will be enrolled in Treatment Phase as follows:

- Group 1: Approximately 100 adolescent subjects (12 to < 18 years of age)
- Group 2: Approximately 100 pediatric subjects (3 to < 12 years of age)

The following definitions will be used for treatment experienced subjects:

- Interferon intolerant: Subject who discontinued therapy (≤ 12 weeks total) due to ≥ 1 adverse event
- Interferon non-responder: Subject who did not achieve undetectable HCV RNA levels while on treatment

Relapse/breakthrough: Subject who achieved undetectable HCV RNA during treatment or within 4 weeks of the end of treatment but did not achieve a sustained virologic response (SVR)

The study schedule contains the following visits: Screening, Day 1, Weeks 1, 2, 4, 8, and 12 (and Weeks 16, 20, and 24 for subjects requiring 24 weeks of treatment) during the treatment phase followed by post-treatment visits 4, 12 and 24 weeks after discontinuation of therapy.

All subjects who do not attain SVR or have viral relapse will be encouraged to discuss treatment with standard-of-care (SOC) therapy with their healthcare provider.

Substudy and Long-Term Follow-Up Study:

Pharmacogenomics (PG) Substudy

PPD

Long-Term Follow-up

Subjects who attain SVR24 or those who do not attain SVR24 and do not initiate other experimental or approved anti-HCV therapy will be followed every 6 months for the first 2 years followed by every 12 months for assessments of growth, quality of life, and long-term viral suppression (if applicable) in a separate protocol (GS-US-334-1113). This follow-up will continue for 5 years.

Diagnosis and Main Eligibility Criteria:

Chronic HCV-infected, treatment-naïve and treatment experienced (up to 40 subjects); male and female subjects aged 3 to < 18 as determined at Day 1. The study will commence with GT-1, -3, and -4 HCV-infected pediatric subjects and will subsequently enroll subjects with GT-2, 5 and -6 once adult data are available, if appropriate.

Inclusion Criteria:

- Chronic HCV infection documented by either:
  - A) positive anti-HCV antibody test or positive HCV RNA or positive HCV genotyping test at least 6 months prior to the Day 1 visit, or

B) liver biopsy performed prior to the Day 1 visit with evidence of chronic HCV- infection

- HCV RNA ≥ 1000 IU/mL at Screening
- PK Lead-in Only: subjects in Cohort 1 (age 12 to < 18 years of age) must weigh ≥ 45 kg
- PK Lead-in Only: subjects in Cohort 2 (age 6 to < 12 years of age) must weigh ≥ 17 kg and < 45 kg
- Females of childbearing potential (as defined in Appendix 5) must have a negative pregnancy test at Screening and Day 1.
- Hematologic or biochemical parameters at screening within the protocol-specified requirements

Exclusion Criteria:

- HIV, acute hepatitis A virus (HAV) or chronic HBV infection
- History of or current decompensated liver disease
- Hepatocellular carcinoma or other malignancy (with exception of certain resolved skin cancers)
- Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency)
- Systemic corticosteroid use for > 2 weeks (pulmonary/nasal administration is permitted)
- Active or recent history (≤ 1 year) of drug or alcohol abuse
- History or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of the study, or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate.
- Sexually active subjects who are not willing to use 2 forms of an effective method of contraception , as referenced in Appendix 5

See Sections 4.2 and 4.3 of the protocol for full eligibility criteria.

Study Procedures/ Frequency:

Screening assessments will be completed within 28 days of the Day 1 visit.

Screening assessments will include: medical history (including parental height, if available), complete physical examination, vital signs (including body height and weight), concomitant medications, LDV/SOF FDC Swallowability Assessment (may be performed at

screening up to Day 1), hematology, safety laboratory tests, coagulation tests, HCV RNA, serum β-human chorionic gonadotropin (hCG - females of childbearing potential only), urinalysis, and urine drug screen, IL28B genotyping, serology (HIV, HAV, HCV, and HBV, HCV genotyping), HbA1c, thyroid stimulating hormone (TSH), alpha fetoprotein, alpha-1 anti-trypsin.

For subjects continuing from PK Lead-in into the Treatment Phase, a screening visit for the Treatment Phase will not be required.

PK Lead-in Phase:

Study Visits will occur at Day 1, Day 3, and Day 10.

On-Treatment assessments include physical examination, Tanner Pubertal Stage Assessment (Day 1 only), vital signs (including body height and weight), bone age assessment (Day 1 only), adverse events (AEs), concomitant medications, pregnancy prevention counseling (Day 1 only; all subjects ≥ 12 years of age and subjects < 12 years of age at the discretion of the Investigator based on subject's pubertal status), quality of life survey (Day 1 only), safety laboratory tests, HCV RNA, viral sequencing sampling and urinalysis. Coagulation testing and urine pregnancy tests (females of child bearing potential only) will be performed at Day 1 and Day 10 only. LDV/SOF FDC swallowability assessment with placebo will be performed (if not performed at Screening) on Day 1 to assess a subject's ability to swallow the 90 mg/ 400 mg or 22.5 mg/ 100 mg FDC tablet (only subjects administered LDV/SOF FDC in tablet form).

Subjects (at least 10 subjects per cohort) enrolled in the PK Lead-in Phase will participate in an intensive PK evaluation on Day 10. Following completion of the Day 10 intensive PK visit, subjects will then return for scheduled study visits outlined in the Treatment Phase and will continue dosing with LDV/SOF FDC with no interruption of study drug administration. Subjects will be administered a dosing diary with instructions.

Treatment Phase:

Study visits will occur at Day 1, and at the end of Weeks 1, 2, 4, 8, and 12 (and Weeks 16, 20, and 24 for subjects requiring 24 weeks of treatment). All Treatment Phase subjects will then return for follow-up visits at 4, 12 and 24 weeks after discontinuation of therapy.

On-treatment assessments will include physical examination, vital signs (including body height and weight), AEs, concomitant medications, pregnancy prevention counseling (all subjects

≥ 12 years of age and subjects < 12 years of age at the discretion of the Investigator based on subject's pubertal status), safety laboratory tests, coagulation tests, HCV RNA, viral sequencing, urine pregnancy tests (females of childbearing potential only), PK samples, a quality of life survey, and urinalysis. Tanner Pubertal Stage assessment will be performed at Day 1 and end of treatment visits; parental heights will be recorded at Day 1. The Bone Age Assessment will be performed at the Day 1 visit. LDV/SOF FDC swallowability assessment will be performed (if not performed at Screening) on Day 1 to assess a subject's ability to swallow a placebo to match the 90 mg/ 400 mg or 22.5 mg/ 100 mg LDV/SOF FDC tablet (only subjects administered LDV/SOF FDC in tablet form). For subjects continuing from the PK Lead-in, the screening, Day 1, and Week 1 visits of the Treatment Phase will not be required. Samples for viral RNA sequencing/phenotyping will be collected at Day 1 and every visit thereafter.

Post-treatment assessments will include vital signs (including body weight and height), symptom-directed physical examination, AEs (only SAEs will be captured at post-treatment Week 12 and post-treatment Week 24), concomitant medications (only post-treatment Week 4), safety laboratory tests, HCV RNA, Tanner Pubertal Stage assessment (only post-treatment Week 12 and post-treatment Week 24), Bone Age Assessment (only post-treatment Week 24) and urine pregnancy tests (as defined in Appendix 5).

PPD

Test Product, Dose, and Mode of Administration:

PK Lead-in:

(Cohort 1) LDV/SOF FDC is manufactured as a tablet, consisting of 400 mg SOF and 90 mg LDV, for oral administration. LDV/SOF FDC tablets will be administered once daily. Subjects unable to swallow the LDV/SOF FDC 90 mg/ 400 mg adult tablets (as determined by LDV/SOF FDC Swallowability Assessment at Screening or at any time during the study) will be re-assigned to 4 x 22.5 mg/ 100 mg LDV/SOF FDC tablets daily.

(Cohort 2) LDV/SOF FDC 45 mg/ 200 mg (2 x 22.5 mg/ 100 mg) will be administered once daily. Subjects unable to swallow the LDV/SOF FDC 22.5 mg/ 100 mg tablets (as determined by LDV/SOF FDC Swallowability Assessment) will be deferred until oral granulate formulation is available.

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

Treatment Phase:

Subjects who participated in PK Lead-in of each Cohort will continue in 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. Additional subjects will be enrolled in the Treatment Phase of each Cohort upon confirmation of the appropriateness of the dose.

RBV Weight-Based Dosing (GT-3 Subjects only):

The RBV dose is:

Body Weight kg (lbs.)	RBV Daily Dose	RBV Number of Capsules
<47 (<103)	15 mg/kg/day	Use Oral Solution. Divided dose in the morning and evening.
47-49 (103-108)	600 mg/day	1 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
50-65 (110 – 143)	800 mg/day	2 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
66-80 (145 – 176)	1000 mg/day	2 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
81-105 (178-231)	1200 mg/day	3 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
>105 (>231)	1400 mg/day	3 x 200-mg capsules A.M. 4 x 200-mg capsules P.M.

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

The morning dose of RBV will be taken with food with an age-appropriate dose of LDV/SOF FDC. The evening dose of RBV will be taken with food.

Reference Therapy: None

Evaluation Criteria:

Safety: AEs, laboratory tests, physical examinations, and vital sign measurements will be collected throughout the study.

Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® AmpliPrep/COBAS® TaqMan® HCV Test.
PK:	For subjects in the PK Lead-in, the steady-state PK of LDV, SOF, and its major metabolites (GS-331007 and GS-566500) will be assessed at Day 10. 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 postdose (with predose also serving as t= 24). 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 (with predose also serving as t = 24). Plasma PK parameters such as C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, AUC_{tau}, and $t_{1/2}$ will be estimated. For all subjects in the Treatment Phase, a single PK blood sample will be collected at all visits while on treatment. The PK of GS-331007, SOF and LDV will be assessed. The effect of age and LDV/SOF FDC dose on PK (GS-331007, SOF, and LDV) will be explored.
Statistical Methods:	For the PK Lead-in, plasma PK parameters C_{max}, T_{max}, C_{last}, T_{last}, $C_{tau,}$ AUC_{tau}, AUC_{last}, and $t_{1/2}$ will be estimated. The PK parameters will be summarized by cohort. The effect of age and LDV/SOF FDC dose on PK (GS-331007, SOF, and LDV) will be explored. For the Treatment Phase, the primary safety endpoint is any AE leading to permanent discontinuation of study drug and will be summarized by the 4 regimens based on treatment-experience, cirrhosis status and genotype, by age group, by regimen and age group, and overall. The key efficacy endpoint is SVR12 in all enrolled and treated subjects and will be summarized the 4 regimens based on by treatment-experience, cirrhosis status and genotype, by age group, by regimen and age group, and overall. Point estimate and its 95% confidence interval will be provided. Subgroup analysis on SVR12 will be performed by treatment-experience and cirrhosis status, by IL28B genotype, and by GT. Other clinically relevant subgroup analyses may be conducted as appropriate (i.e., assuming that adequate numbers of patients in these subsets are available for analysis).

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum). All categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data by the 4 regimens based on treatment-experience, cirrhosis status and GT, by age group, by regimen and age group, and overall.

With approximately 100 subjects enrolled into each age group of Treatment Phase, 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%.

This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BLQ	below the lower limit of quantification
BMI	body mass index
CK	creatine kinase
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CRF	case report form(s)
CRO	Contract (or clinical) research organization
DAA	Direct acting antiviral
dL	Deciliter
DNA	deoxyribonucleic acid
DMC	Data Monitoring Committee
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
ESA	Erythropoiesis stimulating agent
ESPGHAN	European Society for Paediatric Gastroenterology
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	Fixed-Dose Combination
FEV_1	forced expiratory volume in one second
GCP	Good Clinical Practice (Guidelines)
GCSF	Granulocyte colony stimulating factor
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
GT	Genotype (viral)
GSI	Gilead Sciences, Inc.
GT	Genotype (viral)
HAV	Hepatitis A Virus

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

Hb	Hemoglobin
HbA_{1c}	Hemoglobin A_{1c}
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	high-density polyethylene
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL28B	IL28B gene
IND	Investigational New Drug (Application)
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
kg	Kilogram
L	Liter
LDV	Ledipasvir
LLN	lower limit of the normal range
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MH	Mantel-Haenszel
mL	Milliliter
Min	Minute
mmHg	millimeters mercury
NS (3/4A/5A/5B)	Non-structural Protein
PBMC	peripheral blood mononuclear cell(s)
PEG	peginterferon alfa-2a
P-gp	P-glycoprotein
PI	Protease inhibitor
PK	Pharmacokinetic
QD	once daily (use only in tables)
RBC	Red blood cell count
RBV	ribavirin
RNA	ribonucleic acid
SADR	Serious adverse drug reaction

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

SAE	serious adverse event
SD	Standard deviation
SOC	Standard-of-Care
SOF	Sofosbuvir
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
t_{max}	The time (observed time point) of C_{max}
TSH	Thyroid stimulating hormone
t½	An estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
ULN	upper limit of the normal range
US	United States
WBC	white blood cell count

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) is responsible for a large proportion of chronic liver disease worldwide and accounts for 70% of cases of chronic hepatitis in industrialized countries. The global prevalence of chronic hepatitis C is estimated to average 3% {19705}.

The natural history of chronic HCV-infection in children differs from that in adults since HCV-infection in children is relatively benign. Most children chronically infected with HCV are asymptomatic or have mild nonspecific symptoms. Clinical symptoms are present in approximately 20% of children in the first 4 years of life, with hepatomegaly being the most frequent sign (10%). Many, but not all, perinatally infected children will have intermittently or persistently abnormal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, particularly in the first 2 years of life. In children with vertical HCV-infection who have undergone liver biopsy, the histological spectrum is usually mild, although severe liver disease is encountered {19801}. Despite the overall more favorable prognosis compared to adults, approximately 4% to 6% of children with chronic HCV-infection have evidence of advanced fibrosis or cirrhosis and some children eventually require liver transplantation for end-stage liver disease as a consequence of HCV-infection {19799}.

The goal of HCV treatment in both pediatric and adult populations is eradication of the virus, thereby preventing hepatic inflammation, hepatic fibrosis, cirrhosis, and liver failure resulting in either death or need for liver transplantation. This goal, however, is limited by the nature of the disease and the fact that not all patients are suitable candidates for currently approved treatments. In addition, pediatric treatment is controversial as the current treatment options are limited and severe side effects and tolerability can significantly limit or preclude their use. Despite well-established guidelines for the treatment of HCV in adults, there is no universal consensus on when or if to treat chronic HCV-infection in children. In 2010, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) issued guidance for clinical trial development for chronic HCV-infection in children {20286}. In the guideline, the ESPGHAN suggested that the primary goal of treatment in children is to eradicate the infection to prevent late complications. Hence, the goal is not the treatment of an ongoing liver disease, but rather the prevention of a future one.

PEG and weight-based RBV are currently considered the SOC for the treatment of HCV-infection in children. Current recommendations are that patients with GT-2 or GT-3 be treated with PEG+RBV for 24 weeks and those with GT-1 or GT-4 should receive 48 weeks of therapy. Successful treatment of GT-1, however, has proved very difficult to achieve in spite of additional therapy or increased duration of treatment. A number of pediatric studies have reported that despite 48 weeks of treatment, sustained virologic response (SVR24) was observed in only 36% to 53% of subjects with GT-1, while response rates were > 80% in subjects with GT-2 or GT-3 {20285}.

Most children treated with PEG+RBV experience at least 1 adverse event due to treatment {20285}. Although most of these events are mild to moderate in severity, many of them result in dose reductions of 1 or both of the drugs. The most common adverse events have consisted of influenza-like illness (91%), headache (62%), and injection site reactions (45%), often leading to poor compliance and/or discontinuation from treatment.

Additionally, the concern for growth and development in this age group and the role that both PEG and RBV potentially play in reducing growth rates has initiated significant debate among pediatric hepatologists as to whether these treatments should even be considered in the pediatric population {20282}. Many pediatricians currently advocate delay of treatment past adolescence or even into adulthood when options with DAAs are possible {20282}. Unfortunately, in the 25% of pediatric patients who do meet the criteria for treatment (elevated transaminases and viral loads), the option of PEG+RBV therapy remains inadequate in regard to both efficacy in GT-1 and safety due to the many risks associated with this treatment.

1.2. Ledipasvir/Sofosbuvir Fixed-Dose Combination

Ledipasvir/Sofosbuvir fixed-dose combination (LDV/SOF FDC) combines two HCV specific direct acting antiviral (DAA) agents into a single tablet for the treatment of chronic HCV-infection. SOF is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed HCV replication with demonstrated activity against GT 1-6 HCV-infection. Ledipasvir (LDV) is a novel HCV NS5A inhibitor that has demonstrated potent anti-HCV activity, with the highest activity against GT1 HCV-infection. Harvoni® (LDV/SOF FDC) has been approved in the United States by the Food and Drug Administration (FDA) for treatment of HCV infection GT-1 adult patients. Harvoni® is indicated for both treatment-naïve and treatment-experienced subjects with or without cirrhosis with a 12 week treatment duration. For treatment-experienced subjects with cirrhosis a 24 week treatment duration is recommended. Harvoni® is also approved in the EU for treatment of HCV infection GT-1 and GT-4 adult patients as outlined above and for GT-3 treatment-experienced adults with cirrhosis and/or prior treatment failure subjects for 24 weeks treatment duration with ribavirin (RBV).

1.2.1. Summary of Additional Clinical Experience with Ledipasvir/Sofosbuvir Fixed-Dose Combination

The LDV/SOF FDC phase 3 program consisted of 3 clinical studies: GS-US-337-0102 {28583}, GS-US-337-0109 {28585}, and GS-US-337-0108 {28587}. Studies GS-US-337-0102 and GS-US-337-0109 evaluated treatment with LDV/SOF FDC ± RBV for 12 or 24 weeks in treatment-naïve and treatment experienced subjects, respectively, infected with GT-1 HCV. Both studies enrolled up to 20% of HCV-infected subjects who had documented compensated cirrhosis. GS-US-337-0108 evaluated LDV/SOF FDC ± RBV treatment for 8 weeks and LDV/SOF FDC treatment for 12 weeks in non-cirrhotic treatment-naïve subjects with GT-1 HCV-infection. Across these 3 clinical studies, LDV/SOF FDC demonstrated a high degree of efficacy (> 93%) for treatment-naïve and treatment experienced subjects with GT-1 HCV-infection in subjects with and without cirrhosis and achieved their primary efficacy endpoints {28583}; {28585}; {28587}. Additionally, treatment with LDV/SOF FDC ± RBV was safe and well tolerated in the Phase 3 studies {28583}; {28585}; {28587}. The inclusion of RBV to the treatment regimen was associated with an increase in the total incidence of adverse events and in graded laboratory abnormalities of anemia and increased bilirubin.

LDV/SOF FDC indication in GT-3 HCV infection is supported by the Phase 2 Study GS-US-337-0122 (ELECTRON-2). In this Phase 2 open-label study, the safety and efficacy of LDV/SOF FDC were evaluated with or without RBV in 51 treatment-naïve patients with GT-3 HCV infection, with or without cirrhosis. Subjects were treated with LDV/SOF FDC (n = 25) or LDV/SOF FDC + RBV (n = 26) for 12 weeks. SVR12 rates were 64% (16/25) and 100% (26/26) in the LDV/SOF FDC and LDV/SOF FDC + RBV treatment groups, respectively. The relative efficacy of a 12-week regimen consisting of ledipasvir/sofosbuvir + ribavirin, compared to a 24-week regimen of sofosbuvir + ribavirin has not been investigated. Therefore, 24 weeks of therapy is advised in all treatment-experienced GT3 patients and those treatment-naïve GT3 patients with cirrhosis to maximize therapeutic benefit to achieve SVR.

Both nonclinical and clinical data support the inclusion of GT-4 HCV-infected subjects in the Study GS-US-337-1116.

LDV displays potent antiviral activity against GT-4. In the replicon system the EC50 value of LDV for GT-4d HCV was 0.60 nM and 0.39 nM for GT-4a HCV (final report in preparation). For reference, the EC50 values of LDV for GT-1a and GT-1b is 0.031 nM and 0.004 nM, respectively.

In the Phase 3 Study GS-US-337-0102 (ION-1), 2 subjects with GT-4d HCV infection were inadvertently randomized in violation of the protocol inclusion/exclusion criteria. Both subjects achieved SVR12. Subject PPD was treated for 12 weeks with LDV/SOF FDC and Subject PPD was treated for 24 weeks with LDV/SOF FDC + RBV.

In Study GS-US-337-1119, a European study investigating the efficacy and safety of LDV/SOF FDC in treatment-naive and treatment-experienced subjects with chronic GT-4 or GT-5 HCV infection, a total of 44 subjects with GT-4 HCV infection, of whom 10 (23%) have cirrhosis and 22 (50%) are treatment experienced, have been enrolled to receive LDV/SOF FDC for 12 weeks. SVR12 has been achieved by 41/44 (93%) subjects, with 21/22 treatment naïve subjects and 20/22 treatment-experienced subjects having achieved SVR12.

In addition, preliminary data are available from Group E of the NIAID/NIH collaborative Study CO-US-337-0117. In this group, 21 subjects with GT-4 HCV infection are receiving 12 weeks of LDV/SOF FDC treatment. In total, 6 subjects have cirrhosis. Post-treatment week 12 data is available for 20 subjects. 20 of 21 subjects have achieved SVR12.

Preliminary data are also available for Cohort 1 adolescent subjects (N=10) who enrolled in the PK lead-in and received adult clinical doses of LDV/SOF 90 mg/400 mg. Mean exposures of LDV, SOF and GS-331007 in these subjects were comparable to observed exposures in the adult subjects in the Phase 2/3 LDV/SOF clinical program; thereby confirming the appropriateness of adult dose in the adolescent population (12 to < 18 years of age) Table 1-1.

Safety data available for Cohort 1 adolescent subjects (N=10) who enrolled in the PK lead-in and received adult clinical dose of LDV/SOF FDC 90 mg/ 400 mg resulted in no significant safety concerns.

Table 1-1. Steady-state PK and Statistical Comparisons of LDV, SOF and GS-331007 PK in Adolescent Subjects (PK Lead-in) and Adult Subjects (Phase 2/3 Population PK Analysis)

Mean (%CV)	Adolescents (N=10)	Phase 2/3 (N=2113)	GMR% (90% CI)
LDV			
AUC_{tau} (ng*hr/ml)	10200 (50.9)	8530 (60.8)	127 (94.9, 170)
C_{max} (ng/ml)	564 (41.2)	364 (51.4)	162 (125, 209)
C_{tau} (ng/ml)	319 (71.5)	247 (59.2)	128 (95.2, 172)
SOF*			
AUC_{tau} (ng*hr/ml)	2180 (26.6)	1380 (34.0)	160 (138, 185)
C_{max} (ng/ml)	1140 (57.2)	659 (34.0)	156 (127, 190)
GS-331007			
AUC_{tau} (ng*hr/ml)	12700 (13.7)	12500 (29.2)	105 (90.6, 122)
C_{max} (ng/ml)	1010 (21.5)	736 (28.2)	139 (120, 161)

Data reported to 3 significant figures; *N=1542

Please refer to the Investigator's Brochure (IB) for additional information on the LDV/SOF FDC including:

- In Vitro Anti-Hepatitis C Virus Activity
- Nonclinical Pharmacokinetics and In Vitro Metabolism
- Nonclinical Pharmacology and Toxicology
- Clinical Experience

1.3. Ribavirin (RBV)

Ribavirin is a guanosine analogue that inhibits the in vitro replication of a wide range of RNA and DNA viruses {15572}, {15668}. Ribavirin monotherapy has little or no effect on the replication of HCV but can result in normalization of serum ALT activity and improvement in liver histology. When combined with interferon or PEG therapy, RBV decreases substantially the relapse rate seen after cessation of interferon therapy {12557}, {12558}.

Ribavirin is a known teratogen (FDA category X). Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 7 months following completion of treatment. A comprehensive review of RBV is contained in the package insert/SmPC.

1.4. Rationale for the Current Study

This clinical study is designed to evaluate the efficacy and safety of treatment with LDV/SOF FDC +/- RBV for adolescents and children with chronic HCV-infection.

Currently PEG and weight-based RBV are considered the SOC for the treatment of HCV-infection in children. Therefore, there is a need for new treatments for HCV in the pediatric population that combine potent and sustained efficacy with improved tolerability and safety. The primary aim for new treatments of pediatric patients with HCV is to eliminate the need to use PEG. In this way, pediatric patients would be able to avoid the necessity of weekly injections which can be traumatic and burdensome, and significantly reduce the serious adverse events seen with PEG administration. The secondary aim is to eliminate RBV and the adverse events seen with its administration within GT-1 and GT-4 HCV infected subjects.

Harvoni® (LDV/SOF FDC) is approved in the US and EU for the treatment of adults with chronic HCV infection. LDV/SOF FDC +/- RBV would provide an all-oral, IFN-free regimen with a shorter treatment duration (12 or 24 weeks of LDV/SOF FDC +/- RBV treatment versus standard-of-care 24 to 48 weeks of treatment) for GT-1, -3, and -4 HCV infection subjects and would offer another important option in the treatment of HCV infection in the pediatric population.

In vitro viral replicon assay has data demonstrating LDV has potent, picomolar antiviral activity against GT-1a and GT-1b HCV-infection. In the LDV/SOF FDC phase 3 program, LDV/SOF FDC without RBV has been shown to have good efficacy and safety in adults infected with GT-1 HCV-infection. In the GS-US-337-0102 (ION-1), GS-US-337-1119, and CO-US-337-0117, LDV/SOF FDC without RBV has been shown to have good efficacy and safety in adults infected with GT-4 HCV-infection. In study GS-US-337-0122, a phase 2 open-label study of GT-3 treatment-naïve adult subjects with and without cirrhosis, LDV/SOF FDC for 12 weeks resulted in an SVR12 of 64% whereas LDV/SOF + RBV for 12 weeks resulted in an SVR of 100% {29292}. The clinical data to support the use of Harvoni in patients infected with HCV GT3 are limited. As a result, the current study will include a 24-week RBV treatment regimen for only treatment experienced pediatric subjects who enroll with GT-3 HCV-infection.

Considering that SOF has pan-genotypic activity and LDV has in vitro, picomolar to nanomolar antiviral activity against certain subtypes within GT 4-6 and sub-micromolar antiviral activity against certain subtypes within GT-2, studies have been planned and/or initiated with LDV/SOF FDC in adult subjects with GT-2, -5, and -6. If emerging LDV/SOF FDC data in these additional GTs support treatment in these genotypes in adults, pediatric subjects with GT-2, -5 and -6 will be enrolled in the current study. Of note, there is an ongoing study enrolling GT-2 and -3 pediatric patients, GS-US-334-1112, for treatment with SOF + RBV for 12 and 24 weeks, respectively.

1.5. Rationale for Dose Selection of LDV/SOF FDC

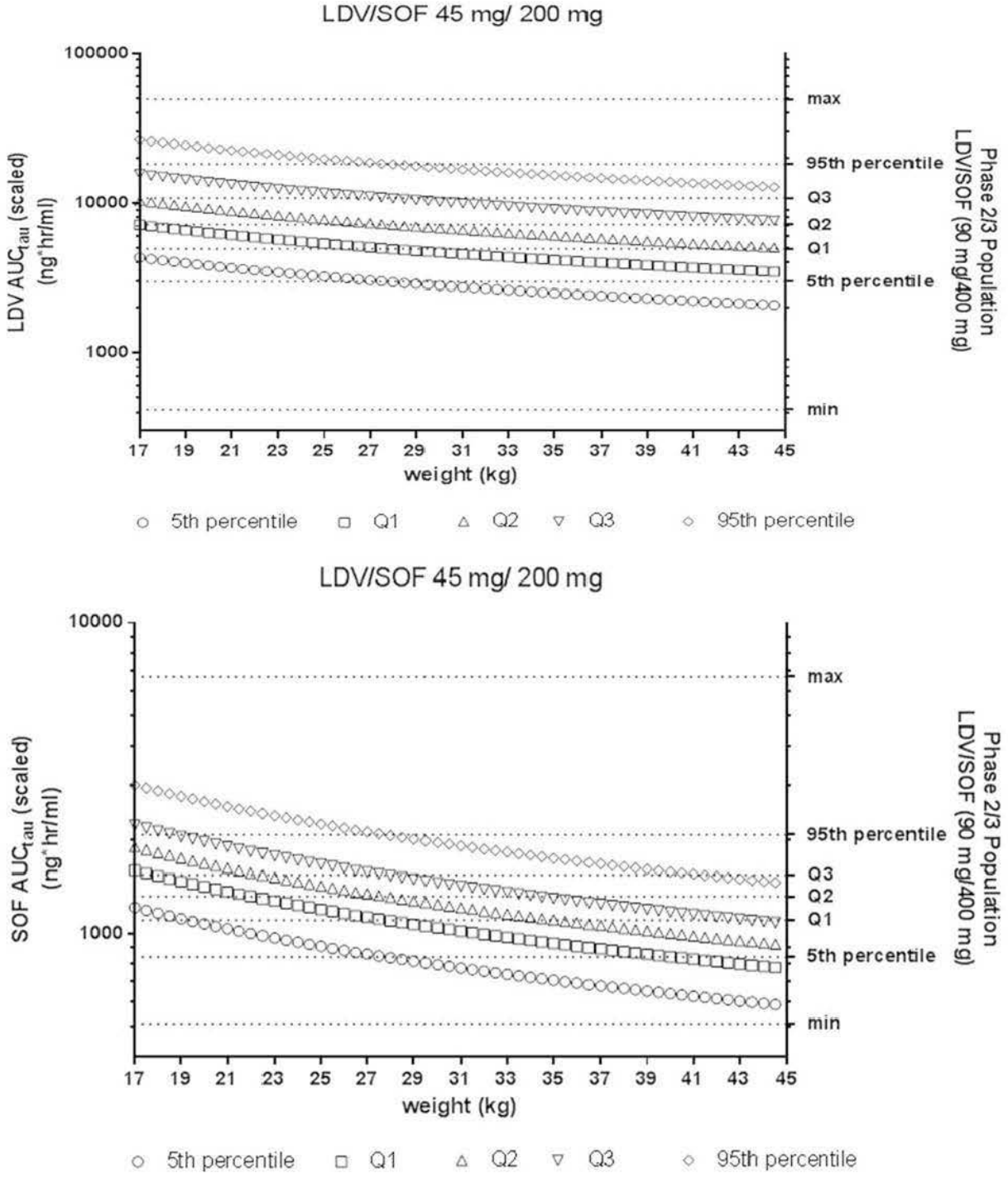
Ledipasvir /Sofosbuvir (90 mg/400 mg) fixed-dose combination tablet +/- RBV has demonstrated favorable safety and efficacy profiles in over 3000 HCV-infected subjects across different patient populations in phase 2 and 3 clinical trials. These doses represent the marketed dose of a ledipasvir/sofosbuvir fixed-dose combination tablet for the treatment of HCV-infection in adults.

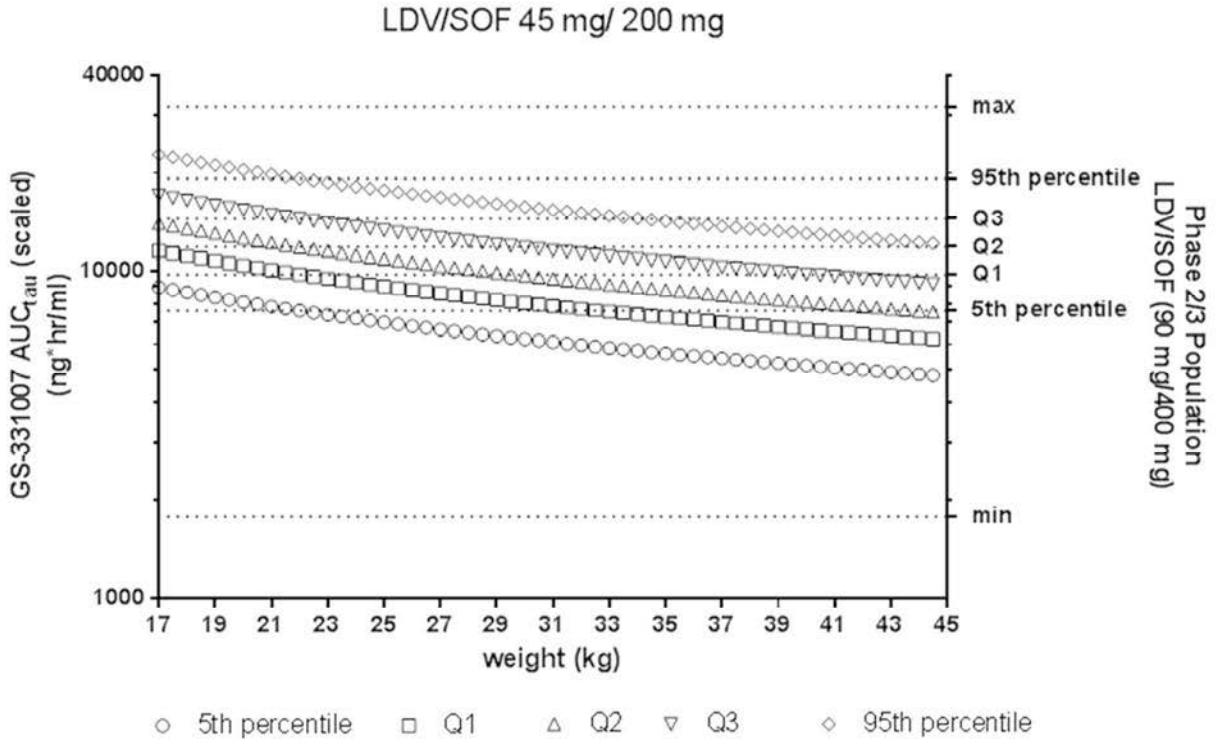
Selection of doses of LDV/SOF FDC +/- RBV for adolescents and younger age groups will target systemic exposures similar to those observed in adults at the proposed marketed dose. LDV and SOF are substrates for efflux drug transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). LDV is also a subject to slow oxidative metabolism via an unknown mechanism. SOF is extensively metabolized to the pharmacologically active nucleoside analog phosphate. The activation pathway involves hydrolysis by intestinal and hepatically expressed carboxylesterase (CES1) and Cathepsin A (CatA) enzymes {20287}, {20288}. SOF is also converted to GS-331007, an inactive circulating metabolite, which is eliminated renally by active tubular secretion and glomerular filtration. Available data suggest comparable hepatic expression of CES1 in adolescents and adults with modestly decreased expression in children. However, little is known about the developmental regulation of Pgp, CES, and CatA. When adjusted for BSA, the processes of active secretion and glomerular filtration approximate adult activity by 6 to 12 months of age {5914}.

The adult clinical dose of LDV/SOF FDC (90 mg/ 400 mg) is being evaluated in adolescent subjects (12 to <18 years old, weighing ≥ 45 kg). The appropriateness of adult dose for this age range is supported by data from the Cohort 1 PK Lead-in subjects which demonstrated comparable LDV, SOF and GS-331007 exposures in adolescent subjects and in adult subjects in Phase 2/3 population PK analyses.

LDV/SOF FDC (45 mg/ 200 mg) dose is proposed for an evaluation in children (6 to < 12 years of age, weighing ≥ 17 kg and < 45 kg). This proposed dose was supported by scaling of adult exposures based on correlations between body weight and clearance capacity (liver volume/size for LDV and SOF, and renal capacity for GS-331007) for the expected body weight range in childen (6 to < 12 years of age) as demonstrated in Figure 1-1 {34882}, {5914}. Additionally, the dose of LDV/SOF FDC 45 mg/ 200 mg provides comparable dosing to the clinical adult dose on mg/kg basis (LDV range: 0.5 to 2.1 mg/kg; SOF range: 2.3 to 9.5 mg/kg) in Phase 2/3 program. Based on these scaling approaches, the dose of LDV/SOF FDC 45 mg/ 200 mg is expected to achieve mean systemic exposures of LDV, SOF and GS-331007 that as observed in the Phase 2/3 population. Safety and PK data in children (6 to < 12 years of age) who enroll in the PK-lead will be evaluated to confirm the appropriatness of the dose for this age group and inform dose selection for children < 6 years old.

Figure 1-1. Predicted LDV, SOF and GS-331007 AUC_{tau} following administration of LDV/SOF FDC 45 mg/ 200 mg in Children (6 to < 12 years of age)





Age-appropriate formulations of LDV/SOF FDC (a smaller, 22.5 mg/ 100 mg strength tablet and a non-tablet formulation currently under development) that offer an important option in the treatment of HCV-infection in the pediatric population are planned for evaluation in children below 12 years of age or children who are unable to swallow the adult dose tablet formulation.

1.6. Overall Risk/Benefit Assessment

Although the majority of pediatric patients infected with HCV exhibit minimal hepatic sequelae despite active viral replication and inflammation, a subset of children and adolescents will require treatment. Studies suggest that 3 major categories of disease can occur within 10 years after putative HCV exposure: (1) undetectable viremia and normal ALT, (2) persistent yet uncomplicated mild liver disease, and (3) progression to end-stage liver disease {20273}. It is the last two groups of children in whom therapy may be indicated to prevent end-stage disease, either during childhood/adolescence or in early adulthood.

Given that the current SOC for the treatment of children infected with HCV is PEG and RBV and these regimens are long in duration, relatively toxic, and not well tolerated, there continues to be a need for new treatments for HCV that combine potent and sustained efficacy with improved tolerability and safety.

The combination of LDV plus SOF is anticipated to offer greater antiviral efficacy which could result in a shorter treatment duration and/or lead to a regimen without RBV or interferon. These in turn could result in reduction in adverse events. LDV/SOF FDC could also potentially be of benefit in patients who have failed prior treatment with SOF+/-RBV+/- PEG.

If high rates of SVR can be obtained with short, well-tolerated regimens, the anticipated improvements in safety and tolerability would offer a favorable risk-benefit determination for individuals with chronic HCV-infection.

2. OBJECTIVES

The primary objective of the PK Lead-in Phase of this study is:

- To evaluate the steady state pharmacokinetics (PK) and confirm the dose of LDV/SOF FDC in chronic HCV-infected pediatric subjects

The secondary objective of the PK Lead-in Phase of this study is:

- To evaluate the safety, tolerability, and antiviral activity of 10 days of dosing of LDV/SOF FDC in chronic 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 +/- RBV for 12 or 24 weeks in chronic 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 SVR 12 weeks after completion of treatment (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 SVR 4 and 24 weeks after completion of treatment (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 effect of growth and development on pediatric subjects during and after treatment

The exploratory objective of this study is:

- PPD

3. STUDY DESIGN

3.1. Treatment Plan and Regimen

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

3.1.1. PK Lead-in

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 for each cohort. Children aged 3 to < 6 years, children aged 6 to < 12 years, and adolescents aged 12 to < 18 years with chronic HCV-infection and a HCV RNA ≥ 1000 IU/mL at study entry will be evaluated. Subjects must be treatment naïve without history of cirrhosis to participate in the PK Lead-in Phase. Three cohorts of at least 10 subjects each will be sequentially enrolled:

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

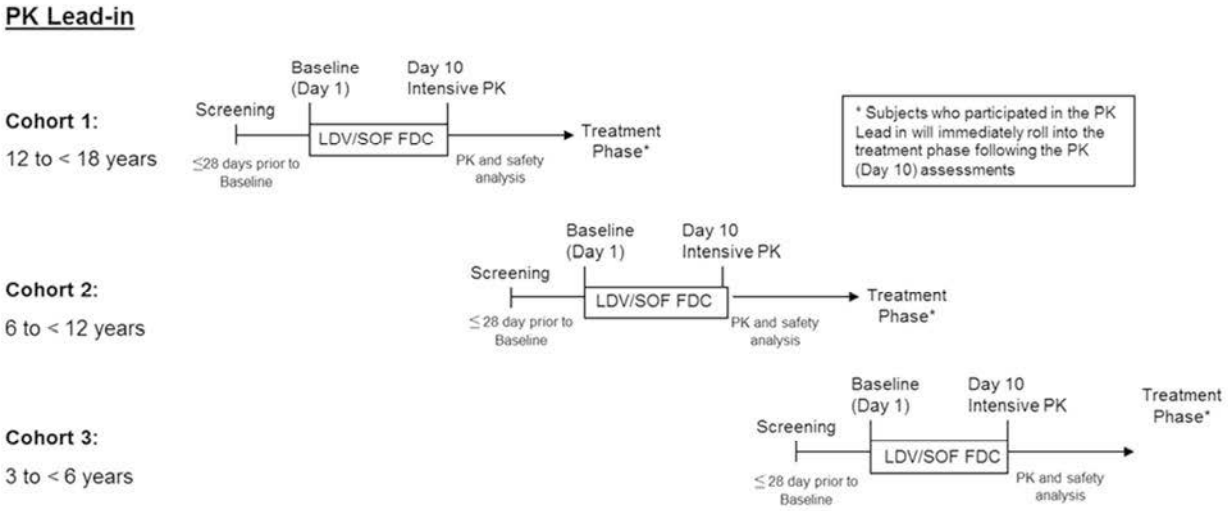
The study will start with Cohort 1. Subjects will receive LDV/SOF FDC (90 mg/ 400 mg adult tablet or 4 x 22.5 mg/100 mg tablets if determined necessary based on LDV/SOF FDC swallowability assessment) for 10 days with intensive PK conducted on Day 10.

Cohort 2: Subjects will receive LDV/SOF FDC 45 mg/ 200 mg (2 x 22.5 mg/ 100 mg tablets or subject will be deferred until oral granulates formulation is available, if determined necessary based on LDV/SOF FDC swallowability assessment).

Following completion of study treatment in the PK Lead-in of Cohort 2 and pending PK and safety results, the PK Lead-in of Cohort 3 will initiate and receive study treatment (age-appropriate dose and formulation).

Subjects enrolled in the PK Lead-in of each cohort (Cohorts 1, 2 and 3) 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. Subjects rolling over from the PK Lead-in Phase will not be required to perform the screening, Day 1, or Week 1 visit of the Treatment Phase.

Figure 3-1. PK Lead-in Phase Study Schema



3.1.2. Treatment Phase

The Treatment Phase will be initiated sequentially by age group as defined in Cohort 1, 2, and 3 of the PK Lead-in. Subjects who participated in PK Lead-in will immediately rollover into 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. The first visit in the Treatment Phase for these subjects will be the Week 2 visit. Additional subjects will be enrolled in the Treatment Phase of each Cohort upon confirmation of the appropriateness of the dose from the PK Lead-in.

Children aged 3 to < 12 years (Group 2) and adolescents aged 12 to < 18 years (Group 1) with chronic HCV-infection and a HCV RNA ≥ 1000 IU/mL at study entry (those who were dosed in the PK Lead-in will have met this criteria prior to enrollment) will be evaluated.

Subjects enrolled in the Treatment Phase will receive the following regimen:

a) United Kingdom:

— GT-1 & GT-4 treatment-naïve subjects with or without cirrhosis: LDV/SOF FDC for 12 weeks

— GT-1 & GT-4 treatment-experienced subjects without cirrhosis: LDV/SOF FDC for 12 weeks

— GT-1 & GT-4 treatment-experienced subjects with cirrhosis: LDV/SOF FDC for 24 weeks

— GT-3 treatment-experienced subjects with or without cirrhosis: LDV/SOF FDC + RBV for 24 weeks

b) United States/Australia/New Zealand:

— GT-1 treatment-naïve subjects with or without cirrhosis: LDV/SOF FDC for 12 weeks

— GT-1 treatment-experienced subjects without cirrhosis: LDV/SOF FDC for 12 weeks

— GT-1 treatment-experienced subjects with cirrhosis: LDV/SOF FDC for 24 weeks

Table 3-1. Subject Enrollment by HCV Genotype, Country and Treatment Duration

	GT-1			GT-4			GT-3
	Cirrhotic or Non-cirrhotic Subjects (TN)	**Non-cirrhotic Subjects (TE)**	**Cirrhotic Subjects (TE)**	**Cirrhotic or Non-cirrhotic Subjects (TN)**	**Non-cirrhotic Subjects (TE)**	**Cirrhotic Subjects (TE)**	**Non-cirrhotic or Cirrhotic Subjects (TE)**
United States	12 Weeks of treatment with LDV/SOF FDC	12 Weeks of treatment with LDV/SOF FDC	24 Weeks of treatment with LDV/SOF FDC	N/A	N/A	N/A	N/A
Australia	12 Weeks of treatment with LDV/SOF FDC	12 Weeks of treatment with LDV/SOF FDC	24 Weeks of treatment with LDV/SOF FDC	N/A	N/A	N/A	N/A
New Zealand	12 Weeks of treatment with LDV/SOF FDC	12 Weeks of treatment with LDV/SOF FDC	24 Weeks of treatment with LDV/SOF FDC	N/A	N/A	N/A	N/A
United Kingdom	12 Weeks of treatment with LDV/SOF FDC	12 Weeks of treatment with LDV/SOF FDC	24 Weeks of treatment with LDV/SOF FDC	12 Weeks of treatment with LDV/SOF FDC	12 Weeks of treatment with LDV/SOF FDC	24 Weeks of treatment with LDV/SOF FDC	24 Weeks of treatment with LDV/SOF FDC + RBV

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

Subjects with GT -1, -3, and -4 will be enrolled first. If emerging LDV/SOF FDC data in GT-2, -5, and -6 support treatment in these GTs in adults, pediatric subjects with GT-2, -5, and -6 will be subsequently enrolled.

The study will enroll both treatment naïve and treatment experienced pediatric subjects with up to 40 subjects allowed to be treatment experienced. Approximately 200 total subjects, including subjects from the PK Lead-in Phase, will be enrolled in the Treatment Phase as follows:

- Group 1: Approximately 100 adolescent subjects (12 to < 18 years of age)
- Group 2: Approximately 100 pediatric subjects (3 to < 12 years of age)

The following definitions will be used for treatment experienced subjects:

- Interferon intolerant: Subject who discontinued therapy (≤ 12 weeks total) due to ≥ 1 adverse event
- Interferon non-responder: Subject who did not achieve undetectable HCV RNA levels while on treatment
- Relapse/breakthrough: Subject who achieved undetectable HCV RNA during treatment or within 4 weeks of the end of treatment but did not achieve a sustained virologic response (SVR)

All subjects who do not attain SVR or have viral relapse will be encouraged to discuss treatment with SOC therapy with their healthcare provider.

3.2. Visit Schedule

3.2.1. PK Lead-in

Screening assessments will be completed within 28 days of the Day 1 visit.

Study Visits will occur at Screening, Day 1, Day 3, and Day 10.

Subjects (at least 10 subjects per cohort) enrolled in the PK Lead-in Phase will participate in an intensive PK evaluation on Day 10. Subjects will be administered a dosing diary with instructions.

Following completion of the Day 10 intensive PK visit, subjects will then return for scheduled study visits outlined in the Treatment Phase and continue dosing with LDV/SOF FDC with no interruption of study drug administration. Subjects rolling over from the PK Lead-in Phase will not be required to perform the screening, Day 1, or Week 1 visits of the Treatment Phase.

3.2.2. Treatment Phase

Screening assessments will be completed within 28 days of the Day 1 visit. Subjects continuing from the PK Lead-in Phase will not be required to complete Screening, Day 1, and Week 1 visits of the Treatment Phase.

- **Subjects requiring 12 weeks of treatment**: Study visits will occur at Screening, Day 1, and the end of weeks 1, 2, 4, 8, and 12.
- **Subjects requiring 24 weeks of treatment**: Study visits will occur at Screening, Day 1, and the end of weeks 1, 2, 4, 8, 12, 16, 20, and 24.

All subjects will then return for follow-up visits at 4, 12, and 24 weeks after discontinuation of therapy.

The total time to complete all study visits is approximately 40 or 52 weeks including:

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

The assessments performed at each visit are described in Section 6.

3.3. Virologic Response-Based Stopping Criteria

HCV RNA will be unblinded to the Investigator and Sponsor.

The following on-treatment virologic response-based treatment stopping criteria will be utilized:

- Confirmed HCV RNA ≥LLOQ after 2 consecutive HCV RNA <LLOQ
- Confirmed >1 $\log_{10}$ increase from nadir
- HCV RNA ≥LLOQ through 8 weeks of treatment

Confirmation should be performed as soon as possible but within 2 weeks after determination of initial observation. Subjects that meet the virologic response-based stopping criteria above will be notified of their eligibility to participate in the Long-Term Follow-Up Study (GS-US-334-1113).

3.4. Treatment Discontinuations Criteria

The Medical Monitor should be consulted prior to subject discontinuation when medically feasible. Study medication must be discontinued in the following instances:

- Unacceptable toxicity (as defined in Section 7) or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Pregnancy of female subject or female partner of male subject.
- Efficacy failure as defined in Section 3.3.
- Significant protocol violation including non-compliance with study assessments.
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason.
- Discontinuation of the study at the request of Gilead, regulatory agency, or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

3.5. Discontinuations

Subjects discontinuing treatment prior to completion of the assigned dosing period should complete an Early Termination visit as described in the Section 6.4.8.

Subjects who permanently discontinue the study drug for any reason including safety and/or tolerability concerns prior to completion of the assigned dosing period will be followed according to the post-treatment study assessments described in Section 6.5.

3.6. Pharmacogenomic Substudy

PPD

3.7. Long-Term Follow-Up

All subjects (those who attain SVR24 or those who do not attain SVR24) who do not initiate other experimental or approved anti-HCV therapy will be followed every 6 months for the first 2 years followed by every 12 months for assessments of growth, quality of life, and long-term viral suppression (if applicable) in a separate protocol (GS-US-334-1113). This follow-up study will continue for 5 years.

3.8. Breakthrough Futility Assessment

A futility assessment will be performed after the first 10 subjects complete Week 8 on study or have viral breakthrough at or prior to Week 8. If 3 or more of the first 10 subjects enrolled have viral breakthrough at or prior to Week 8 or are non-responders (HCV RNA $\geq$ LLOQ through 8 weeks of treatment) then further enrollment of subjects will be suspended. Virologic breakthrough is defined as confirmed HCV RNA $\geq$ LLOQ while on treatment after two consecutive visits with HCV RNA < LLOQ.

If a holding rule has been met and following an internal safety review it is deemed appropriate to restart enrollment, a request to restart enrollment with pertinent data will be submitted to the appropriate regulatory agencies. Enrollment will only resume after review by the appropriate regulatory agencies. Any subject on treatment when a holding rule has been met will be allowed to continue to treatment.

Subjects with known or suspected study drug non-adherence will not be considered to meet the definition of virologic breakthrough, relapse, or non-responder.

3.9. Reconsent

When a subject reaches the age of consent in their country/region, they will be invited to consent as adults to allow them to continue participating in the clinical trial.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 200 subjects will be enrolled in this study.

In order to manage the total study enrollment, Gilead Sciences, Inc. at its sole discretion, may suspend screening and/or discontinue the enrollment at any site at any time (upon written notice to the site). Discontinuation of the enrollment phase may result in the immediate ineligibility of all subjects screened but not yet enrolled, regardless of the progress or outcome of the screening assessments performed.

4.2. Inclusion Criteria

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

1. Parent or legal guardian able to provide written informed consent prior to any screening evaluations and willing to comply with study requirements. Subjects will provide assent if possible.
2. 3 years to < 18 years of age as determined at Day 1 (consent of parent or legal guardian required)
3. PK Lead-in only: subjects in Cohort 1 (age 12 to <18 years of age) must weigh ≥ 45 kg
4. PK Lead-in only: subjects in Cohort 2 (age 6 to <12 years of age) must weigh ≥ 17 kg and < 45 kg
5. PK Lead-in only: all subjects must be treatment naïve: no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific DAA agent
6. Treatment experienced subjects: prior treatment failure to a regimen including interferon either with or without RBV that was completed at least 8 weeks prior to Day 1.
   i. Interferon intolerant: Subject who discontinued therapy (≤ 12 weeks total) due to ≥ 1 adverse event
   ii. Interferon non-responder: Subject who did not achieve undetectable HCV RNA levels while on treatment
   iii. Relapse/breakthrough: Subject who achieved undetectable HCV RNA during treatment or within 4 weeks of the end of treatment but did not achieve a sustained virologic response (SVR)
7. Chronic HCV-infection documented by either:
   a) a positive anti-HCV antibody test or positive HCV RNA or positive HCV genotyping test at least 6 months prior to the Day 1 visit, or
   b) a liver biopsy performed prior to the Day 1 visit with evidence of chronic HCV-infection

8. Infection with HCV as determined at Screening:

   a) United Kingdom Only: The study will commence with GT-1, -3, and -4 HCV-infected pediatric subjects and will subsequently enroll subjects with GT-2, -5, and -6 once adult data is available, if appropriate.

   b) United States/ Australia/ New Zealand Only: The study will commence with GT-1, HCV-infected pediatric subjects and will subsequently enroll subjects with GT-2, -3, -4, -5, and -6 once adult data is available, if appropriate.

9. HCV RNA ≥ 1000 IU/mL at Screening

10. Adequate hematologic function (absolute neutrophil count ≥ 1,500/mm^3; hemoglobin ≥ 11 g/dL or ≥ 12 g/dL for GT-3 males only).

11. Negative serum β-HCG pregnancy test (for females of childbearing potential only, as defined in Appendix 5)

12. Subject able to provide written assent, if they have the ability to read and write, as determined by IRB/IEC/local requirements and Investigator's discretion

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1. Pregnant or lactating subjects

2. Sexually-active males or females of childbearing potential who are not willing to use an effective method of contraception during the study (see Appendix 5 for further details)

3. Treatment-naïve subjects with GT-3 HCV infection as determined at Screening. Treatment naïve is define by no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific DAA agent

4. Decompensated liver disease defined as INR > 1.2 × ULN, platelets < 50,000/mm^3, serum albumin < 3.5 g/dL, or prior history of clinical hepatic decompensation (e.g., ascites, jaundice, encephalopathy, variceal hemorrhage)

5. Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency)

6. α-fetoprotein > 50 ng/mL

7. Serum creatinine > 1.5 mg/dL

8. Estimated glomerular filtration rate < 90 mL/min/1.73m^2, as calculated by the Schwartz Formula

9. Evidence of hepatocellular carcinoma (HCC) or other malignancy (with the exception of certain resolved skin cancers)

10. Co-infection with HIV, acute HAV, or HBV

11. Significant cardiovascular, pulmonary, or neurological disease

12. Evidence of a gastrointestinal malabsorption syndrome that may interfere with absorption of orally administered medications

13. History of solid organ or bone marrow transplantation

14. Chronic daily non-steroidal anti-inflammatory drug therapy

15. Systemic corticosteroid use for > 2 weeks (pulmonary/nasal administration is permitted)

16. Investigational agents taken within the past 28 days (except with the expressed approval of the Sponsor)

17. Clinically-relevant alcohol or drug abuse within 12 months of screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator

18. Known hypersensitivity to the study drug, the metabolites, or formulation excipients

19. Any other condition (including alcohol or substance abuse) or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements

20. Use of any prohibited concomitant medications as described in Section 5.6

21. PK Lead-in only: subjects with history of cirrhosis (as determined by liver biopsy)

22. Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years. Subjects with psychiatric illness (without the prior mentioned conditions) that is well-controlled on a stable treatment regimen for at least 12 months prior to enrollment or has not required medication in the last 12 months may be included.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization and Blinding

Not applicable.

5.2. Ledipasvir/Sofosbuvir Fixed-Dose Combination

5.2.1. Description and Handling

5.2.1.1. Formulation

LDV/ SOF FDC tablets are orange, diamond-shaped, film-coated tablets containing 90 mg of LDV and 400 mg of SOF. The tablets are debossed with "GSI" on one side and "7985" on the other side. The LDV/SOF FDC tablets contain the following inactive ingredients: lactose monohydrate, copovidone, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol, FD&C yellow # 6 /sunset yellow FCF aluminum lake.

Placebo to match LDV/SOF FDC 90 mg/ 400 mg tablets for Swallowability Assessment are orange, diamond-shaped, film-coated tablets debossed with "GSI" on one side and "7985" on the other side. The tablets contain lactose monohydrate, copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol, FD&C yellow # 6 /sunset yellow FCF aluminum lake.

Age-appropriate formulations of LDV/SOF FDC have been developed for subjects who are unable to swallow the LDV/SOF FDC 90 mg/ 400 mg tablets which include a lower dose strength tablet (LDV/SOF FDC 22.5 mg/ 100 mg) formulation. LDV/ SOF FDC lower dose strength tablets are round, plain-faced, white film-coated tablets containing 22.5 mg of LDV and 100 mg of SOF. The LDV/SOF FDC lower dose strength tablets contain the following inactive ingredients: lactose monohydrate, copovidone, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc and polyethylene glycol.

Placebos to match LDV/SOF FDC 22.5 mg/ 100 mg tablets for Swallowability Assessment are round, plain-faced, white film-coated tablets. The placebo tablets contain the following inactive ingredients: lactose monohydrate, copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc and polyethylene glycol.

The non-tablet LDV/SOF FDC formulation will be based on the PK results obtained from cohorts 1 and/or 2 of this study. The formulation, composition, acceptability (including palatability) will be available and reflected in a protocol amendment which will be submitted for approval prior to dosing subjects who are unable to swallow tablets.

5.2.1.2. Packaging and Labeling

LDV/ SOF FDC 90 mg/ 400 mg tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 or 30 tablets, a silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child resistant screw cap with an induction-sealed, aluminum faced liner.

Placebo tablets to match LDV/SOF FDC 90 mg/ 400 mg tablets for Swallowability Assessment are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, a silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child resistant screw cap with an induction-sealed, aluminum faced liner.

LDV/SOF FDC 22.5 mg/ 100 mg tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, a silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child resistant screw cap with an induction-sealed, aluminum faced liner.

Placebo tablets to match LDV/SOF FDC 22.5 mg/ 100 mg tablets for Swallowability Assessment are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, a silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child resistant screw cap with an induction-sealed, aluminum faced liner.

The packaging and labeling of the non-tablet LDV/SOF FDC formulation will be based on the chosen formulation. The packaging and labeling will be available and reflected in a protocol amendment which will be submitted for approval prior to dosing subjects who are unable to swallow tablets.

All LDV/SOF FDC and placebo to match LDV/SOF FDC bottles to be distributed in the US, EU, and the rest of the countries shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA), Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (February 2010), and/or other local regulations as applicable.

5.2.2. Storage and Handling

LDV/ SOF FDC tablets, 90 mg/ 400 mg, should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F to 86 °F).

Placebo to match LDV/ SOF FDC tablets, 90 mg/ 400 mg, for Swallowability Assessment should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F to 86 °F).

LDV/SOF FDC tablets, 22.5 mg/ 100 mg, should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F to 86 °F).

Placebo to match LDV/ SOF FDC tablets, 22.5 mg/ 100 mg, for Swallowability Assessment should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F to 86 °F).

The storage and handling of the non-tablet LDV/SOF FDC formulation will be based on the chosen formulation. The storage and handling will be available and reflected in a protocol amendment implemented prior to dosing subjects who are unable to swallow tablets.

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the Investigational Medicinal Product (IMP) and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling LDV/SOF FDC.

Sufficient quantities of LDV/SOF FDC tablets, non-tablet LDV/SOF FDC formulation, and placebo tablets will be shipped to the investigator or qualified designee from Gilead Sciences (or its designee).

5.2.3. Dosage and Administration of LDV/SOF FDC

PK Lead-in:

Cohort 1: LDV/SOF FDC 90 mg/ 400 mg tablets will be administered once daily with or without food. Subjects determined unable to swallow the placebo to match the 90 mg/ 400 mg LDV/SOF FDC tablet (by LDV/SOF FDC Placebo Swallowability Assessment at Screening up to Day 1) will be re-assigned to 4 x 22.5 mg/ 100 mg tablets daily. Subjects who weigh < 45 kg will be excluded.

Cohort 2: LDV/SOF FDC 2 x 22.5 mg/ 100 mg tablets will be administered once daily with or without food. Subjects determined unable to swallow the placebo to match the 22.5 mg/ 100 mg LDV/SOF FDC tablet (by LDV/SOF FDC Placebo Swallowability Assessment) will be deffered until oral granulate formulation is available. Subjects must weigh ≥ 17 kg and < 45 kg.

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

Treatment Phase: Subjects who participated in the PK Lead-in of each Cohort will continue in 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. Additional subjects will be enrolled in the Treatment Phase of each Cohort upon confirmation of the appropriateness of the dose.

An additional age-appropriate formulation for LDV/SOF FDC Oral Granulates is currently under development. The dose for this formulation will be dependent on the PK results obtained from Cohorts 1 and/or 2 of this study. The strength, composition, and dosing administration will be available and reflected in a protocol amendment which will be submitted for approval prior to dosing subjects who are unable to swallow tablets.

Subjects should be instructed that if vomiting occurs within 5 hours of dosing an additional tablet should be taken. If vomiting occurs more than 5 hours after dosing, no further dose is needed.

If a dose is missed and it is within 18 hours of the normal time, subjects should be instructed to take the tablet as soon as possible and then subjects should take the next dose at the usual time. If it is after 18 hours then subjects should be instructed to wait and take the next dose at the usual time. Subjects should be instructed not to take a double dose.

5.3. Ribavirin (GT-3 Subjects Only)

5.3.1. Description and Handling of RBV

5.3.1.1. Formulation

REBETOL capsules consist of a white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate (40 mg), croscarmellose sodium, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide. The capsule shell imprint contains shellac, propylene glycol, ammonium hydroxide, coloring agent (E 132).The hard capsule is imprinted with blue ink.

REBETOL RBV Oral Solution 40 mg per mL is a clear, colorless to pale or light yellow bubble gum-flavored liquid. In addition to the active ingredient, RBV oral solution contains the following inactive ingredients: sucrose, glycerin, sorbitol, propylene glycol, sodium citrate, citric acid, sodium benzoate, natural and artificial flavor for bubble gum #15864, and water.

5.3.1.2. Packaging and Labeling

The RBV capsules are packaged in blisters. Each blister card contains 20 capsules and seven cards (140 capsules) per carton.

The RBV oral solution is packaged in 4-oz amber glass bottles (100 mL/bottle) with child-resistant closures.

RBV capsules and oral solution to be distributed to centers in the US, EU and the rest of the countries shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (February 2010) and/or other local regulations as applicable.

5.3.1.3. Storage and Handling

RBV capsules should not be stored above 30°C (86 °F).

RBV oral solution should not be stored above 30°C (86°F).

5.3.2. Dosage and Administration of RBV (GT-3 Subjects Only)

RBV dose will be administered by weight as follows:

Body Weight kg (lbs.)	RBV Daily Dose	RBV Number of Capsules
<47 (<103)	15 mg/kg/day	Use Oral Solution. Divided dose in the morning and evening.
47-49 (103-108)	600 mg/day	1 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
50-65 (110 – 143)	800 mg/day	2 x 200-mg capsules A.M. 2 x 200-mg capsules P.M.
66-80 (145 – 176)	1000 mg/day	2 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
81-105 (178-231)	1200 mg/day	3 x 200-mg capsules A.M. 3 x 200-mg capsules P.M.
>105 (>231)	1400 mg/day	3 x 200-mg capsules A.M. 4 x 200-mg capsules P.M.

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

The morning dose of RBV will be taken with food and LDV/SOF FDC. The evening dose of RBV will be taken with food.

RBV will be supplied by Gilead Sciences for all subjects.

5.4. Co-administration of LDV/SOF FDC and RBV (GT-3 Subjects Only)

In the Treatment Phase of the study, each subject will be given instructions to maintain approximately the same daily dosing interval between study drug doses.

For **morning doses**, subjects will be instructed to take study drugs as follows:

- LDV/SOF FDC
- Weight-based RBV (as per Section 5.3.2).

For **evening doses**, subjects will be instructed to take study drug as follows:

- Weight-based RBV (as per Section 5.3.2).

If a subject forgets to take the study medication at the correct time, it may be taken later in the day; however, no more than 90 mg/ 400 mg dose of LDV/SOF FDC should be taken on any calendar day. The subject should resume the standing dosing schedule on the next day. Study medications should not be cut or split.

5.5. Study Drug Compliance

Subjects will be instructed to return any unused LDV/SOF FDC and/or RBV in the original container on Day 3 (PK Lead-in), Day 10 (PK Lead-in), and/or at study treatment visits every 4 weeks (Treatment Phase).

Returned medication will be reconciled by the investigator in order to monitor the subject's compliance with the medication regimen.

5.6. Prior and Concomitant Medications

Concomitant medications taken within 30 days prior to screening, up to and including 30 days after the last dose of study drug, need to be recorded in the source documents and electronic case report form(s) (eCRFs).

The following medications are prohibited during the screening period and for a minimum of 28 days prior to the Day 1 visit through the end of treatment:

- Hematologic stimulating agents (e.g., erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)
- Chronic use of systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab)
- Investigational agents or devices for any indication
- Drugs disallowed per prescribing information of REBETOL® for GT-3 subjects only

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e., P-gp) with study drug(s) may result in PK interactions resulting in increases or decreases in exposure of study drug(s). **Examples of representative medications which are prohibited from 21 days prior to Day 1 through the end of treatment are listed below**. **In addition, the use of amiodarone is prohibited from 60 days prior to Baseline/Day 1 through the end of treatment.**

Table 5-1. Disallowed and Concomitant Medications to be Used with Caution

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing Agents[a]		Proton- Pump Inhibitors, H2-Receptor Antagonists, Antacids
Anticonvulsants[c]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials[c]	Rifabutin, Rifapentine, Rifampin	
Cardiac Medications	Amiodarone[e]	Digoxin[b], Dabigatran[b]
Herbal/Natural Supplements[c]	St. John's Wort, Echinaccea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[d]	Rosuvastatin	Atorvastatin, Simvastatin, Pravastatin, Pitavastatin, Fluvastatin, Lovastatin

a. It is recommended to separate antacid and LDV/SOF FDC administration by 4 hours. H2-receptor antagonists may be administered simultaneously with or staggered from LDV/SOF FDC at a dose that does not exceed doses comparable to famotidine 40 mg twice daily. Proton-pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with LDV/SOF FDC or up to 2 hours after taking LDV/SOF FDC. Proton-pump inhibitors should not be taken before LDV/SOF FDC.
b. May result in an increase in the concentration of study drug and/or concomitant medications. Co-administration of LDV/SOF FDC with digoxin or dabigatran may increase the concentration of digoxin or dabigatran. Caution is warranted and therapeutic concentration monitoring of digoxin or clinical monitoring of dabigatran is recommended when co-administered with LDV/SOF FDC.
c. May result in a decrease in the concentrations of study drug.
d. Use with study drug may result in an increase in the concentration of the HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.
e. May result in symptomatic bradycardia. Mechanism is not currently known. The use of amiodarone is prohibited from 60 days prior to Baseline/Day 1 through the end of treatment.

Medications for disease conditions **excluded** from the protocol (e.g., active cancer, transplantation) are not listed under this Concomitant Medication section and are disallowed in the study.

6. STUDY PROCEDURES

All subjects will complete screening, on-treatment, and post-treatment assessments. Screening assessments will be completed within 28 days of the Day 1 visit. The end of study will occur at the 24-week Post-Treatment visit. The schedule of assessments is described below.

Information on the specific laboratory parameters to be measured and clinical assessments to be performed are provided in Section 6.6.

6.1. Subject Enrollment

Each candidate's parent or legal guardian must sign an Informed Consent Form prior to the conduct of any screening procedures. Each study candidate who has the ability to read and write must sign an Assent Form, as required by IRB/IEC/local requirements, prior to the conduct of any study procedures. Screening evaluations will be used to determine the eligibility of each candidate for study enrollment. Candidates who fail to meet eligibility criteria by screening evaluations may be re-screened once ≥ 30 days after the initial screen if there is a reasonable expectation that the candidate will be eligible after repeat screening.

6.2. Screening Assessments

6.2.1. Screening Visit (Day –28 to Day 0)

Subjects will complete all screening assessments within 28 days of the Day 1 visit. The screening window can be extended to 42 days for subjects requiring additional HCV GT testing or for extenuating circumstances.

The following procedures will be performed and documented:

- Written informed consent from parent or legal guardian and assent from subject, if applicable (see above)
- Medical history, including:
  - Hepatitis C history
  - Hepatitis C treatment history
  - Family history (including height of parents, if known)
  - Liver biopsy results (if available)
- Complete physical examination
- Vital signs (temperature, blood pressure, pulse, respiratory rate) and body weight and height

- Obtain blood samples for tests as listed in Section 6.6.1:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Determination of HCV viral GT and subtype
  - HCV antibody, HIV 1/2 antibody, and HBs antigen, HAV antibody
  - HbA_{1c}
  - TSH
  - IL28B
  - Serum β-hCG pregnancy test for females of childbearing potential only
  - Alpha fetoprotein (AFP)
  - Alpha-1 anti-trypsin (ATT)
- Obtain urine sample for:
  - Urinalysis
  - Urine Drug Screen
- Review of concomitant medications
- Ask subject and/or parent/legal guardian if the subject is able to swallow and tolerate taking pills.
- Review of all inclusion and exclusion criteria
- Perform LDV/SOF FDC swallowability assessment

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the Day 1 visit assessments.

6.3. PK Lead-in: Treatment Assessments

6.3.1. Day 1

After confirmation of eligibility has been evaluated, the following tests and procedures must be completed prior to enrollment and dosing/dispensing on Day 1:

- Perform complete physical examination
- Tanner Pubertal Stage Assessment
- Vital signs, including body weight and height measurements
- A single X-ray of the left wrist, hand, and fingers for Bone Age Assessment
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling 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)
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - PPD
- Obtain urine samples for the following procedures:
  - Urinalysis
  - β-hCG pregnancy test for females of childbearing potential only
- Subject completes quality of life survey: Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire.

6.3.1.1. Drug Administration

- Dispense study drug(s) as directed by the IWRS
- Instruct the subject on the packaging, storage and administration of study drug
- Perform LDV/SOF FDC swallowability assessment (for subjects administered LDV/SOF FDC in tablet form only if not previously completed at screening). Observe the subject taking the first dose of study drug (with or without food) and record the time of first dose
- Subjects will be administered a dosing diary with instructions.

6.3.2. Day 3

The following procedures/assessments are to be completed on Day 3:

- Perform a symptom-directed physical examination as needed
- Vital signs, including body weight and height
- Assessment of AEs and concomitant medications
- Review medication compliance with subject and/or subject's parent/guardian
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing (archive)
- Review subject dosing diary

6.3.3. Day 10 – Intensive PK

The Day 10 Intensive PK visit should occur on the protocol-specified visit date based on the Day 1 visit. For the purposes of scheduling, the Day 10 Intensive PK visit may be performed within +3 days of the protocol-specified visit date (subjects will continue daily dosing through the Intensive PK Visit).

Subjects should come in a fasted state for the Day 10 Intensive PK visit (i.e., no food or drink except water at least 8 hours prior to the Day 10 Intensive PK visit). Subjects and/or parents/guardians should be instructed that the Day 10 dose of LDV/SOF FDC must **not** be taken until the evaluations listed below are completed.

If the subject has already dosed prior to the Day 10 clinic visit or is **not** in a fasted state, the Day 10 intensive PK assessments must not be completed. The subject and/or parents/guardians should be instructed to return in a fasted state within 3 days (Days 11, 12, or 13) for the intensive PK visit.

If dosing non-compliance is identified as per subject dosing diary and pill count on or prior to the Day 10 visit, the Day 10 intensive PK assessments must not be completed. The subject and/or parents/guardians should be counseled regarding proper dosing and be scheduled to return for the Day 10 intensive PK visit no sooner than 3 days following compliant dosing and no later than Day 14 (i.e., return on Day 13 or Day 14). If dosing non-compliance is due to an AE, consultation with the Gilead Medical Monitor is required regarding the potential of rescheduling the Day 10 intensive PK visit.

In both scenarios described above, the subject and/or parents/guardians should be reminded not to take the LDV/SOF FDC prior to arriving at the clinic on the day of the re-scheduled intensive PK visit. All Day 10 intensive PK assessments listed below should be completed when the subject returns.

The following evaluations are to be completed at the Day 10 Intensive PK visit:

- Perform a symptom-directed physical examination
- Vital signs, including body weight and height
- Assessment of AEs and concomitant medications
- Perform study drug accountability
- Review Subject Dosing Diary
- Review medication compliance with subject and/or parent/guardian.
- Obtain urine samples for the following procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, the Intensive PK sampling will not be completed. The positive result will be confirmed with a serum pregnancy test.
- Obtain blood samples for the following laboratory analyses:
  - Hematology
  - Chemistry

- Coagulation tests
- HCV RNA
- Viral sequencing (archive)

- Perform intensive PK sampling:
  - Blood samples will be collected at 0 (predose, ≤ 30 minutes prior to dosing). After collection of the predose sample, subjects will be provided a standardized meal. Within 5 minutes after consuming the standardized meal, subjects will be dosed with LDV/SOF FDC per dosing requirements.
  - Post-dose blood samples will be collected as follows:
    - For Cohorts 1 and 2: 0.5, 1, 2, 3, 4, 5, 8, and 12 hours post-dose (with predose also serving as t= 24).
    - For Cohort 3 only: 0.5, 2, 4, 8, and 12 hours post-dose (with predose also serving as t = 24).
  - Subjects will be restricted from food intake until after collection of the 4-hour post dose blood sample, except for subjects in Cohort 3. Please also refer to the PK manual for details about standardized meals and PK sample processing instructions.

After completing the Day 10 intensive PK visit subjects will then continue to the Week 2 visit in Treatment Phase (described in Section 6.4.2) with no interruption in dosing.

6.4. Treatment Phase: Treatment Assessments

6.4.1. Day 1

After confirmation of eligibility has been evaluated, the following tests and procedures must be completed prior to enrollment and dosing/dispensing on Day 1:

- Perform complete physical examination
- Tanner Pubertal Stage Assessment
- Vital signs, including body weight and height measurements
- A single X-ray of the left wrist, hand, and fingers for Bone Age Assessment
- Review of AEs and concomitant medications
- Pregnancy prevention counseling 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).

- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - PPD
- Obtain urine sample for:
  - Urinalysis
  - β-hCG pregnancy test for females of childbearing potential only
- Subject completes quality of life survey: Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire
- Perform LDV/SOF FDC swallowability assessment (for subjects administered LDV/SOF FDC in tablet form only if not previously completed at screening)

6.4.1.1. Drug Administration

- Dispense study drug as directed by the IWRS
- GT-3 subjects only: Instruct the subject on the appropriate RBV dose after weight-based dosage is calculated using Day 1 weight
- Instruct the subject on the packaging, storage, and administration of study drug
- Observe the subject taking the first dose of study drug (with or without food) and record the time of first dose

6.4.2. Weeks 1 and 2 (± 3 days)

Subjects who participated in the PK Lead-in will start study visits in the Treatment Phase at Week 2. The following procedures/assessments are to be completed at these visits:

- Vital signs, including body weight and height measurements
- Perform symptom-directed physical examination

- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - Single PK

6.4.3. Weeks 4 and 8 (± 3 days)

- Vital signs, including body weight and height measurements
- Perform symptom-directed physical examination
- Assessment of AEs and concomitant medications
- Obtain blood samples for
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - Single PK
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Review medication compliance with subject and/or parent/guardian (subject should return all study drug at these visits)
- Dispense study drug as directed by the IWRS

6.4.4. Week 12 (± 3 days) - Subjects on 12 Week Treatment Regimen Only

- Perform complete physical examination
- Tanner Pubertal Staging Assessment
- Vital signs, including body weight and height measurements
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling 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)
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - TSH
  - Single PK
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Subject completes quality of life survey: Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire.
- Review medication compliance with subject and/or parent/guardian.
- Subjects should return all bottles of study drug at the Week 12 Visit

6.4.5. Week 12 (± 3 days) - Subjects on 24 Week Treatment Regimen Only

- Perform symptom-directed physical examination
- Vital signs, including body weight and height measurements
- Assessment of AEs and concomitant medications

- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - Single PK
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Review medication compliance with subject and/or parent/guardian (subject should return all study drug at these visits)
- Dispense study drug as directed by the IWRS

6.4.6. Week 16 and 20 (± 3 days) – Subjects on 24 Week Treatment Regimen Only

- Vital signs, including body weight and height measurements
- Perform symptom-directed physical examination
- Assessment of AEs and concomitant medications
- Obtain blood samples for
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - Single PK
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Review medication compliance with subject and/or parent/guardian (subject should return all study drug at these visits)
- Dispense study drug as directed by the IWRS

6.4.7. Week 24 (± 3 days) – Subjects on 24 Week Treatment Regimen Only

- Perform complete physical examination
- Tanner Staging Assessment
- Vital signs, including body weight and height measurements
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling including partner pregnancy prevention for male participants (Subjects 12 to < 18 years of age and subjects < 12 years of age at the discretion of the Investigator based on subject's pubertal status)
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - TSH
  - Single PK
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Subject completes quality of life survey: Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire
- Review medication compliance with subject and/or parent/guardian.
- Subjects should return all bottles and blister cards (if applicable) of study drug at the Week 24 Visit

6.4.8. Unscheduled Visit/Early Termination Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments are at the investigator's discretion.

The Sponsor/CRO should be informed when a subject comes off treatment due to an adverse event. If a subject discontinues treatment then the assessments outlined below should be performed.

- Perform complete physical examination
- Tanner Pubertal Stage Assessment
- Vital signs, including body weight and height measurements
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling 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)
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing (archive)
  - TSH
  - Single PK
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Subject completes quality of life survey: Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire.
- Review medication compliance with subject and/or parent/guardian.
- Subjects should return all bottles and/or blister cards (if applicable) of study drug at the Early Termination Visit

All subjects should complete Post-Treatment assessments after early termination, as described in Section 6.5.

6.5. Post-Treatment Assessments

6.5.1. 4-Week Post-Treatment Visit (± 5 days)

- Vital signs, including body weight and height measurements
- Perform symptom-directed physical examination
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing (archive)
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Pregnancy prevention counseling 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)

Female subjects of childbearing potential on treatment with LDV/SOF FDC + RBV 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 local 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.

6.5.2. 12-Week Post-Treatment Visit (± 5 days)

- Vital signs, including body weight and height measurements
- Perform symptom-directed physical examination
- Assessment of SAEs
- Perform Tanner Pubertal Stage assessment

- Obtain blood samples for
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing (archive)
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Pregnancy prevention counseling 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)
- Subject completes quality of life survey: Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire

6.5.3. 24-Week Post-Treatment Visit (± 5 days)

- Vital signs, including body weight and height measurements
- Perform symptom-directed physical examination
- Assessment of SAEs
- Tanner Pubertal Stage Assessment
- A single X-ray of the left wrist, hand, and fingers for Bone Age Assessment
- Obtain blood samples for
  - HCV RNA
  - Viral sequencing (archive)
- GT-3 subjects only: Obtain urine sample for β-hCG pregnancy test for females of childbearing potential only
- GT-3 subjects only: Pregnancy prevention counseling 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)
- Subject completes quality of life survey: Subject is to review questionnaire with a parent/guardian and write/mark answers directly onto the questionnaire.

All subjects (those who attain SVR24 or those who do not attain SVR24) who do not initiate other experimental or approved anti-HCV therapy will be followed every 6 months for the first 2 years followed by every 12 months for assessments of growth, quality of life, and long-term viral suppression (if applicable) in a separate protocol (GS-US-334-1113). This follow-up will continue for 5 years.

6.6. Procedures and Specifications

6.6.1. Clinical Laboratory Analytes

Hematology: Hematocrit, Hemoglobin (Hb), Platelet count, Red blood cell count (RBC), White blood cell count (WBC) with differential (absolute and percentage) including Lymphocytes, Monocytes, Neutrophils, Eosinophils, Basophils, Reticulocyte count and MCV.

Coagulation: INR, Prothrombin time (PT), Activated partial thromboplastin time (APTT)

Chemistry Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatinine, Total Bilirubin (reflex to Direct Bilirubin), Glucose, Lipase, Potassium, Sodium, Gamma-glutamyl transferase (GGT), alpha fetoprotein (AFP), alpha-1 anti-trypsin, creatine kinase (CK) and amylase.

Urinalysis: Appearance, Blood, Color, Glucose, Leukocyte esterase, pH, Protein, Urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal.

Virological Tests: Serologies for HCV, HBV and HIV. HCV RNA will be measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 for Use with the High Pure System. HCV GT and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV GT should the above assays become unavailable.

IL28B genotype will be determined by polymerase chain reaction (PCR) amplification of the SNP, rs12979860, with sequence specific forward and reverse primers and allele specific fluorescently labeled TaqMan® MGB probes. Gilead reserves the rights to use alternate assays for IL28B determination should the above assay become unavailable.

Pregnancy Tests: Serum β-hCG, Urine β-hCG (if positive, requires immediate confirmation with Serum β-hCG)

Additional Tests: Urine Drug Screen (for amphetimines, cocaine, methadone, opiates), Hemoglobin A1c (HbA1c), TSH (reflex Free T4), Alfa fetoprotein (AFP), Alpha-1 anti-trypsin (AAT).

6.6.2. Medical History

Medical history including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history will be collected on all subjects during screening. Parental heights will be recorded at Screening.

6.6.3. Complete Physical Examination

A complete physical examination must include source documentation of general appearance, and the following body systems: Head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; neurological.

6.6.4. Tanner Pubertal Stage Assessment

The Tanner Stage scale is available in Appendix 4. All subjects will receive a baseline Tanner Pubertal Stage Assessment. If the assessment determines that the subject is at a Tanner 5 at Day 1, no further Tanner Pubertal Stage Assessments are to be completed. Date of first menses will be documented.

6.6.5. Height & Weight Measurement

Height and weight measurement will be collected at each study visit. The difference in body weight and height measurements between Day 1 and End of Treatment, post-treatment Week 12, and post-treatment Week 24 will be calculated.

6.6.6. 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 bone age from x-ray.

6.6.7. Swallowability Assessment

A LDV/SOF FDC swallowability assessment will be performed at screening up to Day 1. Subjects who have indicated that they can take pills will be observed taking a placebo to match the 90 mg/ 400 mg LDV/SOF FDC tablet. This will confirm the swallowability of the 90 mg/ 400 mg tablet size. If a subject is unable to swallow the 90 mg/ 400 mg LDV/SOF FDC tablet size, he/she will repeat the assessment with a placebo for the 22.5 mg/ 100 mg LDV/SOF FDC tablet. If unable to swallow the 22.5 mg/ 100 mg LDV/SOF FDC tablet, enrollment of the subject will be deferred until the granule formulation is available.

6.6.8. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and temperature.

Blood pressure will be measured using the following standardized process:

- Subject should sit for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
- Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

6.6.9. Estimated Glomerular Filtration Rate (GFR)

Estimated Glomerular Filtration Rate (GFR) 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; and for adolescent males ≥ 12 years old is 0.70); L is height in centimeters (cm); and S_{cr} is serum creatinine (mg/dL)]

6.6.10. Viral Sequencing (Archive)

Plasma samples will be collected at Day 1 and each subsequent visit for viral sequence analysis. Unused samples may be archived.

6.6.11. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period and for a minimum of 6 months following the last dose of RBV or for a minimum of 30 days following the last dose of LDV/SOF FDC if not taking RBV. If required by local regulations, additional pregnancy tests beyond 6 months for RBV or 30 days for subjects not taking RBV may be added. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drug immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

GT-3 subjects only: Pregnancy test kits will be dispensed to female subjects of child bearing potential at the 4 Week Post-Treatment visit. The subject will be contacted by telephone monthly to confirm that urine pregnancy testing has been performed post-treatment and to record the outcome. Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine pregnancy tests.

6.6.12. Quality of Life Survey (PedsQL™)

The **PedsQL** ™ Pediatric Quality of Life Inventory V4.0 Short Form (SF15) will be completed at Day 1, End of Treatment, Early Termination (if applicable), 12-Week Post-Treatment, and 24-Week Post-Treatment visits.

The **PedsQL** ™ has separate survey instruments administered by age group, including the Teen Report (ages 13-18), Child Report (ages 8-12), Young Child Report (ages 5-7), and Toddlers (ages 2-4). Each survey accompanied by the respective parent proxy survey will be administered to the subject and their parent/legal guardian (with the exception of the Toddlers Report which will only be completed by the parent/legal guardian) for the current age group at the time of survey administration.

7. TOXICITY MANAGEMENT

7.1. Modification of Dose/Schedule Due to Toxicity

Dose reduction of RBV (GT-3 subjects only) due to toxicity should be performed according to the product label. Information is provided in Table 7-1.

Table 7-1. RBV Dose Reduction Guidelines

Laboratory Values	Reduce RBV Dose by 200 mg/day[a] if:	Discontinue RBV if:
Hemoglobin in subjects with no cardiac disease	<10 g/dL	<8.5 g/dL
Hemoglobin in subjects with history of stable cardiac disease	≥2 g/dL decrease in hemoglobin during any 4 week period treatment	<12 g/dL despite 4 weeks at reduced dose

a. Dose reduction in pediatric patients taking the oral solution is accomplished by modifying the recommended RBV dose from original starting dose of 15 mg/kg daily in a two-step process to 12 mg/kg/day, then to 8 mg/kg/day, if needed.

7.2. Subject Stopping Rules for LDV/SOF FDC and RBV

The Gilead Medical Monitor should be consulted prior to dose discontinuation of LDV/SOF FDC unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject.

Administration of LDV/SOF FDC may be discontinued due to a clinical or laboratory event. There is no option for LDV/SOF FDC dose reduction. If LDV/SOF FDC is stopped for toxicity, it should not be restarted, RBV should be stopped (GT-3 subjects only), and the subject should complete an Early Termination Visit.

Subjects who meet any of the following laboratory criteria must stop treatment with LDV/SOF FDC:

- Elevation of ALT and/or AST >5x Day 1 or nadir, confirmed by immediate repeat testing
- Abnormal elevation of ALT >3x Day 1 and total bilirubin >2 x ULN, confirmed by immediate repeat testing
- Confirmed elevation of ALT >15 x ULN, confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 event or lab abnormality assessed as related to treatment with LDV/SOF FDC

8. ADVERSE EVENTS MANAGEMENT

8.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

8.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post- treatment complications that occur as a result of protocol-mandated procedures, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (see Section 8.5.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF

8.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

8.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 8.1.1 and 8.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

8.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

8.2.1. Assessment of Causality for Study Drug and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the investigational medicinal product. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures (e.g.., venipuncture)

8.2.2. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 3).

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

8.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead or CRO

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 4 weeks after last administration of study drug must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of causal relationship, that occurs after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required 24-week post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-mandated procedures performed after informed consent is signed

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported. Investigators are not obligated to actively seek SAEs after the 24 week post-treatment follow-up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event directly to Gilead DSPH.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead Sciences, Drug Safety and Public Health:	Fax:	+1 650 522-5477
	E-mail:	Safety_FC@gilead.com
Gilead Sciences, Medical Monitor:	Name:	Bittoo Kanwar, MD
	Phone:	PPD
	Mobile:	PPD
	Fax:	PPD
	E-mail:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE report form.

8.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

8.5. Special Situations Reports

8.5.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging or distribution of the medicinal product.

8.5.2. Instructions for Reporting Special Situations

8.5.2.1. Instructions for Reporting Pregnancies

The investigator should report all pregnancies that are identified after the subject first consents to participate in the study (i.e., signs the informed consent) and throughout the study, including the post-treatment follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 8.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 8.1 and 8.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported directly to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com or Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drug must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy report form and pregnancy outcome report forms within 24 hours. Monitoring of the partner pregnancy should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 (650) 522-5477 or email Safety_FC@gilead.com.

Clinical staff should also report any pregnancies to the Ribavirin Pregnancy Registry at 1 800-593-2214 (see also http://www.ribavirinpregnancyregistry.com).

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

8.5.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 8.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Objectives and Endpoints

9.1.1. Analysis Objectives

The primary objective of PK Lead-in Phase of this study is:

- To evaluate the steady state pharmacokinetics (PK) and confirm the dose of LDV/SOF FDC in chronic HCV-infected pediatric subjects

The secondary objective of PK Lead-in Phase of this study is:

- To evaluate the safety, tolerability, and antiviral activity of 10 days of dosing of LDV/SOF FDC in chronic HCV-infected pediatric subjects

The primary objective of Treatment Phase of this study is:

- To evaluate the safety and tolerability of LDV/SOF FDC +/- RBV for 12 or 24 weeks in chronic HCV-infected pediatric subjects

The secondary objectives of Treatment Phase of this study are:

- To determine the antiviral efficacy of 12 and 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 SVR 12 weeks after completion of treatment (SVR12)
- To determine the antiviral efficacy of 12 and 24 weeks of LDV/SOF FDC +/- RBV treatment in chronic HCV-infected subjects, as assessed by the proportion of subjects with SVR 4 and 24 weeks after completion of treatment (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 effect of growth and development on pediatric subjects during and after treatment

The exploratory objective of this study is:

- PPD [redacted]

9.1.2. Primary Endpoints

For the PK Lead-in Phase, the appropriateness of the LDV/SOF FDC dose will be assessed by evaluating the steady-state PK of the LDV/SOF FDC. The primary endpoint for determining steady state PK is AUC_{tau} of GS-331007, SOF, and LDV. Additional steady-state PK parameters of GS-331007, SOF, and LDV (e.g., AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λz, CL/F, Vz/F and $t_{½}$) will be estimated and summarized as described in Section 9.4.

For the Treatment Phase, the primary safety endpoint is any AE leading to permanent discontinuation of study drug (s).

9.1.3. Secondary Endpoints

For the PK Lead-in Phase, the secondary endpoint will include antiviral activity measurements, including assessment of HCV RNA. AEs leading to permanent discontinuation of study drug will be evaluated as a secondary safety endpoint.

For the Treatment Phase, the key efficacy endpoint is SVR12 and secondary efficacy endpoints include SVR4, SVR24, breakthrough and relapse. Additional efficacy evaluations may include HCV RNA change from Day 1; ALT normalization; and viral kinetic parameters. Secondary safety endpoints of growth and development measurements will be assessed (e.g. height, weight, and Tanner Stage Assessment).

9.2. Analysis Conventions

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

9.2.1. Analysis Sets

9.2.1.1. Pharmacokinetics (PK) Analysis Sets

Intensive PK Analysis Set

The intensive PK analysis set will include all PK Lead-in subjects who received at least one dose of study drug and for whom at least one non-missing PK concentration data, during the intensive sampling period, reported by PK lab. The PK analysis set will be used for detailed pharmacokinetic analysis of LDV, SOF, and metabolites.

Sparse PK Analysis Set

The PK analysis set will include all enrolled subjects who received at least one dose of study drug and for whom at least one observed concentration data of LDV, SOF, or GS-331007 are available. The PK analysis set will be used for analysis of general PK and single sample plasma concentrations.

9.2.1.2. Safety Analysis Set

The primary analysis set for safety analyses will include subjects who were enrolled and have received at least one dose of study drug.

Treatment-emergent data will be analyzed and defined as data collected from the first dose of study drug through the date of last dose of study drug plus 30 days.

9.2.1.3. Efficacy Analysis Set

The analysis set for antiviral activity analyses will be the Full Analysis Set (FAS) which includes HCV-infected subjects who were enrolled and have received at least one dose of study drug.

9.2.2. Data Handling Conventions

Natural logarithm transformation for key PK parameters, such as C_{max} and AUC_{tau}, will be applied for pharmacokinetic analysis.

The PK concentration values below the limit of quantitation (BLQ) will be treated as zero for the determination of summary and order statistics. Individual values that are BLQ will be presented as "BLQ" in the concentration data listing 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 BLQ for the time point, then the minimum value will be displayed as "BLQ". If more than 50% of the subjects have a concentration data value BLQ for the time point, then the minimum and median values will be displayed as "BLQ". If all subjects have concentration data values BLQ for the time point, then all order statistics (minimum, first quartile [Q1], median, third quartile [Q3], maximum) will be displayed as "BLQ".

Missing data can have an impact upon the interpretation of the trial data. Other than the endpoints discussed below, in general, values for missing data will not be imputed.

For the analysis of post-baseline categorical efficacy endpoints, if a data point is missing and is preceded and followed in time by values that are deem successes, then the missing data point will be termed a success; otherwise the data point will be termed a failure.

Any subject with missing data due to premature discontinuation of the study medication will be considered a failure at the time points subsequent to the date of discontinuation. If no HCV RNA values are obtained after the last dose of study medication, the subject will be considered a treatment failure for the SVR endpoints.

Where appropriate, safety data for subjects that did not complete the study will be included in summary statistics. For example,

- If a subject received study medication, the subject will be included in a summary of adverse events according to the treatment received; otherwise, if the subject is not dosed then they will be excluded from the summary.
- If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a pre-dose value, then the subject will be excluded from the calculation of summary statistics for the pre-dose value and the change from pre-dose values.

Values for missing safety laboratory data will not be imputed; however, a missing baseline result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the baseline value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities.

Values for missing vital signs data will not be imputed; however, a missing baseline result will be replaced with a screening result, if available.

HCV RNA values below the LLOQ for the assay will be set to the lower limit minus 1 for calculation of summary statistics for the actual HCV RNA values and the change from baseline values by study visit. The reported values will be provided in the HCV RNA listing.

For selected analyses of early time point data, HCV RNA data (IU/mL) may be transformed to the logarithmic (base 10) scale (log_{10} IU/mL).

9.2.3. Interim Analysis

No formal interim analyses are planned for this study.

9.3. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by age group and overall for PK Lead-in and by the 4 regimens based on treatment-experience, cirrhosis status and genotype, by age group, by regimen and age group, and overall for Treatment Phase respectively.

Demographic data will include sex, self-identified race/ethnicity, and age.

Baseline characteristic data will include body weight, height, body mass index, HCV RNA level (log_{10} IU/mL), HCV GT, prior treatment experience, and additional endpoints as necessary.

9.4. Pharmacokinetic Analysis

PK analysis will be performed for PK Lead-in using the intensive PK analysis set. The concentration data of LDV, SOF, and metabolites (GS-331007 and GS-566500) over sampling time will be listed and summarized by nominal time and cohort. Pharmacokinetic parameters (e.g., AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λz, CL/F, Vz/F and $t_{½}$) will be listed and summarized for LDV, SOF, and metabolites (as applicable) using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean and its 95% confidence interval, coefficient of variation %, standard deviation, median, Q1, Q3, minimum, and maximum) by cohort and overall. Plasma concentrations over time will be plotted in semilogarithmic and linear formats as mean ± standard deviation and median (Q1, Q3).

To evaluate if the steady-state PK of GS-331007, SOF, and LDV achieved in pediatric subjects of this study are similar to the exposures observed in adult subjects (Table 9-1), the GS-331007, SOF, and LDV exposure data from this study will be compared to the integrated adult data. The primary endpoint of this analysis will be evaluated by carrying out an analysis of variance

(ANOVA) for log-transformed GS-331007, SOF, and LDV AUC_{tau}. The 90% confidence intervals will be constructed for the ratio of geometric means of each PK parameters. The equivalence boundary is set as 50% to 200%.

Given that dose ranging studies for SOF established that a dose of 200 mg results in suboptimal exposure compared to the 400 mg dose, and the lack of clinically significant exposure-safety relationships observed across a broad range of GS-331007 and SOF exposure, bounds of 50% to 200% for GS-331007 and SOF AUC_{tau} will allow identification of a clinically relevant difference in exposure in the pediatric population.

A phase 2 study evaluating LDV doses of 30 or 90 mg LDV in combination with DAAs VDV+TGV+RBV suggested LDV exposure may be suboptimal at the 30 mg dose based on the incidence of virologic breakthrough being approximately half in the 90 mg arm; as such the 90 mg dose was selected for further development. In the 90 mg LDV arm of this study, the LDV AUC_{tau} at the 25 percentile was 3230 hr*ng/mL. While this value is 62% lower than the mean LDV AUC_{tau} (8530 hr*ng/mL) observed in adult HCV-infected subjects in the LDV/SOF FDC Phase 2/3 population, it provides ~99.8% of maximal viral load reduction (exposure-response model established in the monotherapy proof of concept study). In the Phase 2/3 population when administered the LDV/SOF FDC, there was a lack of clinically significant exposure-efficacy or safety relationships observed across the broad range of LDV exposure. Taken together these data support the utility of bounds of 50% to 200% for LDV AUC_{tau} to identify a clinically relevant difference in LDV exposure in the pediatric population.

In all pediatric age groups, the targeted exposures for GS-331007, SOF, and LDV are the adult equivalent for which safety and efficacy has been established. In the absence of any pediatric PK information (i.e., variability and exposure of GS-331007, SOF, or LDV is unknown) assuming a 2-fold higher variability, or a 30 % difference in GS-331007, SOF, or LDV AUC_{tau} in the pediatric population compared to adults, the predicted 90% CIs of the geometric mean ratio (GMR) will be contained within the bounds of 50% to 200%.

Individual patient management will be performed by maintaining exposures comparable to adults. In the event more than one subject in each cohort exhibits GS-331007, SOF, or LDV exposures (AUC_{tau}) less than the 2.5th percentile of adult values, a dose assessment may be require for the cohort as appropriate.

The effect of age and LDV/SOF FDC dose on PK (LDV, SOF and GS-331007) will be assessed.

Table 9-1. GS-331007, SOF, and LDV PK Parameters after Once-Daily Administration of SOF/LDV FDC in HCV-Infected Adults Subjects (Population PK Analysis from Phase 2 and 3 Studies)

Mean (%CV) PK Parameter[a]	GS-331007 (N=2113)	SOF (N=1542)	LDV (N=2113)
AUC_{tau} (ng•h/mL)	12,500 (29.2)	1380 (34.0)	8530 (60.8)
C_{max} (ng/mL)	736 (28.2)	659 (34.0)	364 (51.4)
C_{tau} (ng/mL)	N/A	N/A	247 (59.2)

a. Pharmacokinetic parameters are presented as mean (%CV) and are shown to 3 significant digits.

9.5. Safety Analysis

Safety analysis will be performed for PK Lead-in and overall study Treatment Phase respectively. Safety data will be summarized by age group and overall for PK Lead-in Phase and by the 4 regimens based on treatment-experience, cirrhosis status and genotype, by age group, by regimen and age group, and overall for the Treatment Phase respectively.

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements, and by the documentation of AEs.

All safety data collected while on or after the first dose of study drug administration up to 30 days after the last dose of study drug will be summarized by cohort according to the study drug received.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data.

9.5.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the CRF. Exposure data will be summarized.

9.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any new or worsening adverse event that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC and preferred term) will be provided by cohort:

- All AEs,
- All study drug-related AEs,
- Combined Grade 2, 3 and 4 AEs,
- Combined Grade 3 and 4 AEs,
- Combined Grade 2, 3 and 4 study drug-related AEs,

- Combined Grade 3 and 4 study drug-related AEs,
- All AEs that caused permanent discontinuation from study drug,
- All AEs that caused change in dose or temporary interruption of study drug,
- All SAEs (including death), and
- All study drug-related SAEs

All AEs collected during the course of the study will be presented in data listings.

9.5.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Absolute values and changes from baseline at all scheduled visits will be summarized. Graded laboratory abnormalities will be defined using the grading scheme in Grading of Laboratory Abnormalities provided in Appendix 3. Incidence of treatment-emergent laboratory abnormalities, defined as values that increase by at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by age group and overall. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment emergent.

All laboratory abnormalities will be included in the listings of laboratory data.

9.5.4. Other Safety Evaluations

9.5.4.1. Tanner Pubertal Stage Assessment

Tanner Stages (Appendix 4) will be summarized by baseline Tanner Stage using frequency and percentage. Age of first menses will be summarized descriptively.

9.5.4.2. Vital Signs (including Body Weight and Height)

Vital signs including body weight and height and change from baseline will be summarized at each visit.

9.6. Efficacy Analysis

Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® TaqMan® HCV Test, v2.0 for use with the High Pure System.

Efficacy analysis will be performed by the 4 regimens based on treatment-experience, cirrhosis status and genotype, by age group, by regimen and age group, and overall for Treatment Phase.

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum). All categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition.

9.6.1. Key Efficacy Analysis

The key efficacy endpoint is SVR12 (HCV RNA < LLOQ 12 weeks after completion of treatment) in the FAS population. Point estimate and its 95% confidence interval will be provided.

9.6.2. Secondary Efficacy Analysis

For the PK Lead-in Phase, serum HCV RNA actual values and change from baseline will be summarized at each visit.

For the Treatment Phase, the proportion of subjects with HCV RNA below LLOQ over time (including SVR endpoints SVR4 and SVR24) will be presented in tabular and graphical form. In addition, descriptive summaries and listings will be provided for additional efficacy evaluations including serum HCV RNA actual values and change from baseline, proportion of subjects with virologic failures, and other endpoints of interest including ALT normalization.

PPD

9.6.3. Subgroup Analysis

Subgroup analysis on SVR12 will be performed by treatment experience and cirrhosis status, by IL28B genotype, and by GT. Other clinically relevant subgroup analyses may be conducted as appropriate (i.e., assuming that adequate numbers of subjects in these subsets are available for analysis).

Details on efficacy analyses will be described in the statistical analysis plan.

9.7. Quality of Life Analysis

The data from PedsQL ™ Pediatric Quality of Life survey will be summarized by visit and age group and overall.

9.8. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety 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.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9.9. Sample Size

With approximately 100 subjects enrolled into each age group of Treatment Phase, 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%.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonization (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States IND, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to.

Since this is a "covered" clinical trial, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with Gilead Sciences, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify Gilead Sciences of any change to reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

This study is also subject to and will be conducted in accordance with 21 CFR, part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

10.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent/assent) will be submitted by the investigator to an IRB (for studies conducted in the United States) or IEC (for studies conducted outside of the United States). Approval from the IRB or IEC must be obtained **before** starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation. Additionally, modifications should be submitted to competent authorities, as necessary.

10.1.3. Informed Consent/Assent

The investigator is responsible for obtaining written informed consent from the parent/legal guardian of the subject participating in this study after adequate explanation to the parent/legal guardian and subject of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. Written assent should be obtained from the subject as required by IRB/IEC/local requirements for this age population. The investigator must utilize an IRB- or IEC-approved consent/assent form for documenting written informed consent/assent. Each informed consent/assent will be appropriately signed and dated by the subject or the subject's parent/legally authorized representative and the person obtaining consent/assent.

10.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from Gilead Sciences, including but not limited to the Investigator Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of Gilead Sciences during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead Sciences. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data are listed in the Source Data verification Plan, and should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in trial (including trial number);

- Trial discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- Record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity);
- Concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- Date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with Gilead Sciences. The investigator must notify Gilead Sciences before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead Sciences must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead Sciences to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 15 years for purposes of this study.

10.1.6. Case Report Forms

For each subject enrolled, a CRF (or eCRF) must be completed and signed by the principal investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a pre-randomization screening period if a CRF was initiated). If a subject

withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.7. Drug Accountability

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product, and comparators. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Gilead Sciences and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with Gilead Sciences requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet Gilead Sciences' requirements for disposal, arrangements will be made between the site and Gilead Sciences or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead Sciences. All protocol modifications must be submitted to the IRB, IEC, or competent authorities in accordance with local requirements. Approval must be obtained before changes can be implemented.

10.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). Gilead Sciences will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from Gilead Sciences, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met:***

- the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead Sciences in an abstract, manuscript, or presentation form; or
- the study has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include Gilead Sciences' confidential information (see Section 10.1.4).

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead Sciences' request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice (ICH GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead Sciences may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead Sciences medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead Sciences access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead Sciences and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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12. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

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

GS-US-337-1116, Protocol Amendment 3.0, 28 May 2015

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

BITTOO KANWAR
Bittoo Kanwar, MD (Printed)
Medical Monitor

28 MAY 2015
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) _____ Signature _____

Date _____ Site Number _____

Appendix 2. Study Procedures Table

Appendix Table 1. PK Lead-in: 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
Laboratory Assessments				
Hematology, Chemistry	X	X	X	X
Coagulation Tests	X	X		X

	Screening (-28 days)	On-treatment		
		Day 1[b]	Day 3	Day 10 (+ 3 days)
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 1/2 antibody, HBs antigen, HAV antibody	X			
HbA1c	X			
TSH	X			
Alpha fetoprotein	X			
Alpha-1 anti-trypsin	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 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)

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		
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

	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
Viral Sequencing [d]		X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing[l]	X	X			X	X	X	X	X	X	X
Single PK			X	X	X	X	X	X	X	X	X
PPD											
Urinalysis	X	X									
Urine Drug Test	X										
HCV Genotyping, IL28B	X										
HCV antibody, HIV 1/2 antibody, HBs antigen, HAV antibody	X										
HbA1c	X										
TSH	X						X[j]			X	X
Alpha fetoprotein, Alpha-1 anti-trypsin	X										

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 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 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

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	
Laboratory Assessments			
Hematology, Chemistry	X	X	
HCV RNA	X	X	X
Viral Sequencing[b]	X	X	X
Urine Pregnancy Test	X	X	X[e]

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.

Appendix 3. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months#**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric subjects. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Infant <1 Year	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 t o <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine[**]	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
LDL (Fasting) Adult	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
LDL (Fasting) Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

*Calcium should be corrected for albumin if albumin is < 4.0 g/dL
** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatrics <16 years** **≥ 16 years**	-	2.0 to < LLN g/dL 20 to < LLN g/L	< 2.0 g/dL < 20 g/L	NA
	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection **Adult and Pediatric ≥ 10 Years**	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weak-ness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **Necrosis (involving dermis and deeper tissue)**
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 4. 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 {34663}, {34664}

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1. Background

Ribavirin is contraindicated in pregnancy as significant teratogenic and embryocidal effects have been demonstrated in all animal species tested. Pregnancy must be excluded before the start of treatment with study drugs and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed regularly throughout this study. Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment (7 months for males). Please refer to the latest version of the product insert for additional information.

Non-clinical toxicity studies of LDV/SOF FDC demonstrated no adverse effect on fertility or embryo-fetal development. However, there are no clinical studies of LDV/SOF FDC in pregnant women. Please refer to the latest version of the investigator's brochure for additional information.

2. Definition of Female of Childbearing Potential and Contraceptive Requirements for Female Subjects (and their male partners)

For the purpose of this trial, all post-menarchal females will be considered to be of childbearing potential, unless there is documentation of irreversible ovarian failure or surgical sterilization.

Post-menarchal females must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Day 1 visit prior to dosing. They must also agree to one of the following from 3 weeks prior to Day 1 until 6 months after last dose of RBV or 30 days after last dose of LDV/SOF FDC if not taking RBV:

- Complete abstinence from intercourse. Abstinence is acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom, from the date of Screening until 6 months after last dose of RBV or 30 days after the last dose of LDV/SOF FDC if not taking RBV:

  — intrauterine device (IUD) with a failure rate of < 1% per year

  — female barrier method: cervical cap or diaphragm with spermicidal agent

  — tubal sterilization

— vasectomy in male partner

— implants of levonorgestrel

— injectable progesterone

— oral contraceptives (either combined or progesterone only)

— contraceptive vaginal ring

— transdermal contraceptive patch

3. Contraceptive Requirements for Male Subjects (and their female partners)

All male study participants must agree to consistently and correctly use a condom from Day 1 until 7 months after last dose of RBV or 90 days after the last dose of LDV/SOF FDC if not taking RBV. If their female partner is of childbearing potential (as defined above), their female partner must use 1 of the methods of birth control listed above from the date of Screening until 7 months after last dose of RBV or 90 days after last dose of LDV/SOF FDC if not taking RBV.

Male subjects must agree to refrain from sperm donation for at least 7 months after last dose of RBV or 90 days after the last dose of LDV/SOF FDC if not taking RBV.

4. Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 6 months (7 months for partners of male subjects) of last RBV dose or 30 days (90 days for partners of male subjects) of last LDV/SOF FDC dose if not taking RBV. Subjects who become pregnant or who suspect that they are pregnant must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 8.5.2.1.