CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed Dose Combination in the Treatment of Hepatitis C Virus (HCV) Infection in Pediatric Subjects Undergoing Cancer Chemotherapy	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA USA	
Indication:	Hepatitis C virus infection	
Protocol ID:	GS-US-337-1904	
Gilead Study Director/Medical Monitor:	Name: Telephone: Fax:	PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1:	06 October 2015 16 June 2017

CONFIDENTIALITY STATEMENT

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

Study Title:	A Phase 2, Open-label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed Dose Combination in the Treatment of Hepatitis C Virus (HCV) Infection in Pediatric Subjects Undergoing Cancer Chemotherapy
Study Centers Planned:	Single center in Egypt
Objectives:	The primary objectives of this study are as follows: • To evaluate the efficacy of ledipasvir/sofosbuvir (LDV/SOF) in treating HCV infection in pediatric subjects who are undergoing cancer chemotherapy, as measured by the proportion who achieve a sustained virologic response 12 weeks after the end of HCV treatment (SVR12) • To evaluate the safety and tolerability of treatment with LDV/SOF for 12 weeks The secondary objectives of this study are as follows: • To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of HCV treatment (SVR4 and SVR24) • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of HCV treatment The exploratory objectives of this study are: PPD [redacted]

Study Design:	Single-center, open-label study. Approximately 40 treatment naïve or experienced pediatric subjects with chronic HCV who are receiving a maintenance cancer chemotherapy regimen will be enrolled. All subjects will receive LDV/SOF FDC once daily for 12 weeks.
Number of Subjects Planned:	Approximately 40 pediatric subjects
Duration of Treatment:	LDV/SOF FDC daily for 12 weeks
Diagnosis and Main Eligibility Criteria:	Male and female treatment naïve or experienced children aged 12 to <18 years, with genotype 1 or 4 HCV infection, and are on a maintenance cancer chemotherapy regimen Refer to Section 4.2 and 4.3 for detailed Inclusion and Exclusion Criteria
Study Procedures/ Frequency:	Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. All subjects will complete the following study visits: Screening, Baseline/Day 1, on-treatment visits at the end of Weeks 1, 4, 8, and 12. All subjects will complete the post treatment Weeks 4, 12 and 24 visits. Screening assessments will include physical examination, medical history, body height and weight, vital signs, adverse events related to screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), HCV RNA, HCV genotype, serology (HIV antibody, HAV antibody, HCV antibody, hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb]), assessment of the presence or absence of cirrhosis and fibrosis stage, serum β-hCG (females of child bearing potential only), urinalysis, and LDV/SOF swallowability assessment (may be done up until Day 1). Fibrosis will be assessed via Fibrotest,® APRI, and Fibroscan; liver biopsy may be performed if necessary. Baseline/Day 1 assessments include medical history and host IL28B genotyping. Additional Baseline/Day 1 and on-treatment assessments include adverse events (AEs), concomitant medications, study medication pill count, physical examination, height, weight, vital signs, laboratory tests for safety and fibrosis assessments (by Fibrotest at Day 1, Week 12, and ESDD as applicable and APRI at Week 12 and ESDD as applicable), HCV RNA, HBV DNA for subjects HBcAb positive at Screening, PPD pregnancy prevention counseling, and urine pregnancy tests (females of child bearing potential only).

	Post-treatment assessments include AEs, concomitant medications, vital signs and physical examination (at 4 weeks post treatment), safety laboratory tests, HCV RNA, HBV DNA for subjects HBcAb positive at Screening, fibrosis assessments (by Fibrotest and Fibroscan at 12 and 24 weeks post treatment, by APRI at Post Treatment Week 4), PPD pregnancy prevention counseling (if applicable), and urine pregnancy tests (females of child bearing potential only). PPD
Test Product, Dose, and Mode of Administration:	LDV/SOF is manufactured as a FDC tablet, consisting of 90 mg LDV and 400 mg SOF, for oral administration. Subjects will take 1 tablet daily with or without food. Subjects unable to swallow the LDV/SOF FDC 90 mg/400 mg tablets and who are able to swallow LDV/SOF 22.5 mg/ 100 mg tablets (as determined by LDV/SOF FDC Swallowability Assessment at Screening or at any time up until Day 1) will be assigned to 4 LDV/SOF FDC 22.5 mg/ 100 mg tablets once daily with or without food. Placebo tablets to match LDV/SOF FDC 90 mg/400 mg tablets and placebo tablets to match LDV/SOF 22.5 mg/ 100 mg tablets will be used for swallowability assessment.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	AEs and laboratory tests will be collected throughout the study.
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA.

Statistical Methods:

The primary efficacy endpoint for the study is SVR12 in all enrolled and treated subjects. A point estimate with a 2-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate. No hypothesis testing will be performed.

Secondary efficacy endpoints include:

- SVR4 and SVR24
- HCV viral kinetics

Exploratory endpoints include:

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum). All categorical endpoints will be summarized by the 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, SD, median, Q1, Q3, minimum, maximum) for continuous data.

With a sample size of 40 subjects, a 2-sided 95% exact confidence interval will extend at most 26.6% in length.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
β-hCG	β-human chorionic gonadotropin
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APRI	AST platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BID	twice a day
BLQ	below the lower limit of quantification
BMI	body mass index
BW	body weight
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)
CI	confidence interval
CL_{cr}	creatinine clearance
COPD	chronic obstructive pulmonary disease
CRF	case report form(s)
CRO	contract (or clinical) research organization
CSR	clinical study report
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)
EDC	electronic data capture
ESA	erythropoiesis stimulating agent
Emax	maximal effect
EOT	End of Treatment
ESDD	Early Study Drug Discontinuation
EU	European Union
FAS	full analysis set

FDA	(United States) Food and Drug Administration
FDC	Fixed-dose combination
GCP	Good Clinical Practice (Guidelines)
GCSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
GT	genotype (viral)
HAV	Hepatitis A Virus
Hb	Hemoglobin
HBsAb	hepatitis B surface antibody
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	interferon
IL28B	IL28B gene
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio of prothrombin time
IRB	Institutional Review Board
IUD	intrauterine device
IV	Intravenous
IWRS	interactive web response system
Kg	Kilogram
kPa	Kilopascal
L	Liter
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LDV	Ledipasvir
LLN	lower limit of the normal range
LOD	lower limit of detection
LLOQ	lower limit of quantification

LLT	lower-level term
PPD	
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MH	Mantel-Haenszel
mL	Milliliter
Min	Minute
mmHg	millimeters mercury
NIAID	National Institute of Allergy and Infectious Disease
NS (3/4A/5A/5B)	[HCV] non-structural protein
PCR	polymerase chain reaction
PEG	pegylated interferon
PHAC	Public Health Agency of Canada
PI	protease inhibitor
PK	Pharmacokinetic
PTT	Partial thromboplastin time
QD	once daily
QTcF	QT interval corrected using Fridericia' formula
RBC	red blood cell count
RBV	Ribavirin
RDRP	RNA-dependent RNA polymerase
RNA	ribonucleic acid
RVR	rapid virologic response
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	standard deviation
SOC	standard of care
SOF	sofosbuvir (GS-7977; formerly PSI-7977)
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	sustained virologic response
TND	target not detected
TPO	Thrombopoietin
ULN	upper limit of the normal range
US	United States
vRVR	very rapid virologic response
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% {Esteban 2008}. In Egypt, it is estimated that approximately 15% of the population has been infected with chronic hepatitis C, with genotype 4 accounting for approximately 90% of the infections and genotype 1 for the remainder {Nakano 2012}, {Ray 2000}. The proportion of children in Egypt with HCV antibodies was found to be 4% in those aged 15 to 19 years in a 2008 national population survey {El-Zanaty 2009} while earlier studies found 3% and 9% of screened subjects who were 19 years of age or younger had HCV antibodies {El-Raziky 2007}. Reports from other countries indicate the natural history of chronic HCV in children is relatively benign, but approximately 4% to 6% 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 {Hu 2010}.

Chronic hepatitis C is highly prevalent in Egyptian children receiving cancer chemotherapy or following allogeneic bone-marrow transplantation. {El-Sayed 2011}, {El-Sayed 2004} In 1 study, 33 of 100 children with cancer at 2 centers in Egypt were HCV RNA positive. {Sharaf-Eldeen 2007} The progression of HCV-related liver disease in this population may be rapid and may be the main cause of death in Egyptian patients with allogeneic bone marrow transplantation {El-Sayed 2004}. Patients also may experience a flare in their HCV while receiving immunosuppressive chemotherapy; HCV flare, or "reactivation", has been defined as an increase of ALT to >3x baseline level and/or increase of HCV RNA by 1 log10 IU/mL) {Mahale 2012}. HCV flares were found to have resulted in interruptions of cancer chemotherapy in approximately half of HCV-infected adult patients in a retrospective study by Mahale et al {Hu 1996}.

Although HCV flares may occur in patients with any tumor type, they are more common in those with hematological malignancies {Mahale 2012}; leukemias and lymphomas are among the most common childhood cancers {Ibrahim 2014}. The treatment of some of these such as acute lymphoblastic leukemia (ALL) and some types of non-Hodgkins lymphoma (NHL) include induction, consolidation, and maintenance phases of chemotherapy. The maintenance phase is less intensive and may continue for 2 – 3 years.

Pediatric treatment of HCV is controversial primarily because the current treatment option (pegylated interferon [Peg-IFN] plus ribavirin [RBV]) has relatively low and variable rates of success {Wirth 2012}, (SVR24 36-53% with genotype GT1and 55% in GT4 and > 80% in GT2 or GT3) and is limited by tolerability and severe side effects, including a potential effect on growth and development. HCV treatment is further complicated in patients receiving cancer chemotherapy.

Successful treatment of HCV infection would greatly impact liver disease outcomes and rates of liver decompensation and hepatocellular carcinoma in these pediatric patients and may facilitate treatment of their cancer.

1.2. Ledipasvir/Sofosbuvir Fixed-dose combination (LDV/SOF FDC)

Ledipasvir/sofosbuvir fixed-dose combination (LDV/SOF FDC; Harvoni®) combines two HCV specific DAA agents into a single tablet for the treatment of chronic HCV infection. Sofosbuvir is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed HCV replication, irrespective of HCV genotype. Ledipasvir is a novel HCV NS5A inhibitor. LDV/SOF FDC has been approved in US, Europe, Japan, and other countries. It is also being evaluated in a study in Egypt in adult patients with chronic genotype 4 HCV infection (GS-US-337-1643).

Please refer to the latest version of the Investigator's Brochure (IB) for additional information on the LDV/SOF FDC, and the individual components, including:

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

1.2.1. Additional Clinical Trial of LDV/SOF in Pediatric Patients with Chronic HCV Infection

Study GS-US-337-1116 is an ongoing Phase 2 study being conducted in multiple countries to assess the pharmacokinetics, safety and efficacy of LDV/SOF in pediatric subjects with chronic HCV infection. Three cohorts of up to 10 subjects each will be sequentially enrolled in a stepwise manner, following review of safety and PK data in the preceding cohort:

- 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

Steady state pharmacokinetics following 7 days of dosing will be assessed in a lead-in group in each cohort prior to enrolling subjects in the treatment phase.

Preliminary safety and PK data are available from adolescent subjects (N=10) who enrolled in the PK lead-in phase of Cohort 1 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). Review

of safety data supported expansion of enrolment into the treatment phase of Cohort 1 and initiation of enrollment in to the PK lead-in group of Cohort 2.

No serious adverse events or treatment discontinuations due to adverse events have been reported in the study as of 25 September 2015.

Table 1-1. Steady-state PK and Statistical Comparisons of LDV, SOF and GS-331007 PK in Adolescent Subjects (GS-US-337-1116; 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

1.3. Rationale for Study GS-US-337-1904

LDV/SOF FDC is approved for use in HCV-infected adults in Europe, North America and other countries and is currently in clinical development for the treatment of chronic HCV infection in pediatric patients. The current standard of care for the treatment of children infected with HCV is Peg-IFN and RBV and these regimens are long in duration, relatively toxic, not well tolerated, and may be contraindicated in patients receiving chemotherapy. Consequently, there is a need for new treatments for HCV that combine potent and sustained efficacy with improved tolerability and safety.

1.4. Risk/Benefit Assessment for the Study GS-US-337-1904

GS-US-337-1904 is being conducted in Egypt where the prevalence of HCV infection in pediatric patients receiving chemotherapy is high. This study will enroll subjects who are 12 to <18 years old, a group that is already being studied in another clinical trial and for whom pharmacokinetic data support use of the planned doses of LDV and SOF (GS-US-337-1116). Eligible patients will also be limited to those with hematological malignancies who are receiving maintenance chemotherapy, in order to the mitigate side effects associated with more intensive chemotherapy regimens used in induction and consolidation phases.

The combination of LDV plus SOF is anticipated to offer greater antiviral efficacy and avoid the adverse events associated with Peg-IFN+RBV. The improved tolerability may also result in fewer interruptions to cancer chemotherapy and may impact fibrosis progression in these patients.

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

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of ledipasvir/sofosbuvir (LDV/SOF) in treating HCV infection in pediatric subjects who are undergoing cancer chemotherapy, as measured by the proportion who achieve a sustained virologic response 12 weeks after the end of HCV treatment (SVR12)

- To evaluate the safety and tolerability of treatment with LDV/SOF for 12 weeks

The secondary objectives of this study are:

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

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

The exploratory objectives of this study are:

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- SVR12 in all enrolled and treated subjects. No hypothesis testing will be performed.

The secondary endpoints of this study are:

- SVR4 and SVR24
- HCV viral kinetics

Exploratory endpoints include:

3.2. Study Design

This is a phase 2 single-center open-label study investigating the efficacy and safety of LDV/SOF FDC in treating pediatric subjects with chronic HCV who are receiving maintenance cancer chemotherapy.

3.3. Study Treatments

All subjects will receive LDV/SOF FDC once daily with or without food. Subjects will peform a swallowability assessment (Sections 6.1.1 and 6.7.9) and will be assigned to receive 1 LDV/SOF FDC 90 mg/ 400 mg tablet daily or 4 LDV/SOF FDC 22.5 mg/ 100 mg tablets once daily or will be excluded from the study based on which tablet size they are able to swallow.

3.4. Duration of Treatment

Subjects will be treated for a total of 12 weeks.

3.5. HCV Virologic Response-Based Treatment Stopping Criteria

The following on-treatment HCV 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 and must occur no later than 2 weeks after an initial observation indicating virologic failure. All subjects who terminate treatment early will complete an Early Study Drug Discontinuation (ESDD) Visit, and should complete Post-Treatment Weeks 4, 12, and 24 Visits.

3.6. Discontinuation Criteria

When medically feasible, the Medical Monitor must be consulted prior to subject discontinuation.

Study drug must be discontinued in the following instances:

- Unacceptable toxicity, as defined in Section 7.5 of the protocol, 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
- Efficacy failure as defined in Section 3.5
- Significant protocol violation
- 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)

If a subject meets discontinuation criteria during treatment, an ESDD visit will be required (Section 6.5). All subjects should complete a 4-week, 12-week, and 24-week Post Treatment visit regardless of the treatment duration.

3.7. 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 40 treatment naïve or experienced pediatric subjects will be enrolled in this study. Male and female children 12 to < 18 years of age, with genotype 1 or 4 HCV infection, and who are receiving a maintenance cancer chemotherapy regimen will be enrolled.

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 must be able to provide written informed consent prior to any screening evaluations and willing to comply with study requirements. A subject will provide assent if possible; written assent will be provided if the subject has the ability to read and write, as determined by the Ethics Committee and the Investigator's assessment.

2) Male or female, 12 to <18 years of age (consent of parent or legal guardian required)

3) Weight ≥ 35 kg

4) Chronic HCV infection (≥ 6 months) documented by medical history or, if available, liver biopsy

5) HCV genotype 1 or 4 at screening

6) Receiving a protocol-approved maintenance chemotherapy regimen for a hematological malignancy (see Section 5.3.1)

7) HCV RNA ≥ 1000 IU/mL at screening

8) Adequate hematologic function (absolute neutrophil count ≥ 500/mm^3, hemoglobin ≥ 10 g/dL)

9) Treatment naïve or experienced, where treatment-experienced is defined as prior treatment failure or intolerance to a regimen including interferon with or without ribavirin that was completed at least 8 weeks prior to Baseline/Day 1

10) Females of childbearing potential (as defined in Appendix 4) must have a negative pregnancy test at Screening and Baseline/Day 1.

11) 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) Co-infection with HIV, acute hepatitis A virus (HAV) infection or chronic HBV coinfection (HBsAg positive [HBsAg+] at screening)

2) Decompensated liver disease defined as INR > 1.2 x ULN, platelets < 50,000/mm^3, serum albumin < 3.0 g/dL, or prior history of clinical hepatic decompensation (eg, ascites, jaundice, encephalopathy, variceal hemorrhage)

3) Evidence of a gastrointestinal malabsorption syndrome that may interfere with absorption of orally administered medications

4) Chronic liver disease of non-HCV etiology (eg, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency)

5) Evidence of hepatocellular carcinoma (HCC) or other non-hematologic malignancy (with the exception of certain resolved skin cancers)

   Note: liver imaging within 6 months of baseline/Day 1 is required in patients with cirrhosis to exclude HCC

6) History of solid organ or bone marrow transplantation

7) Active or recent history (≤ 1 year) of alcohol or drug abuse

8) Serum creatinine > 1.5 mg/dL

9) Estimated glomerular filtration rate < 90 mL/min/1.73m^2, as calculated by the Schwartz formula

10) Investigational agents taken within the past 28 days (except with the prior written approval of the Sponsor)

11) Use of any prohibited concomitant medications as described in Section 5.3

12) Pregnant or lactating subjects

13) Sexually-active males or females of childbearing potential who are not willing to use an effective method of contraception during the study (see Appendix 4 for further details)

14) Unable to swallow the LDV/SOF FDC 90mg/400mg and the LDV/SOF FDC 22.5mg/100mg placebo tablets

15) Known hypersensitivity to LDV, SOF, metabolites, or formulation excipients

16) Subject unable to comply with the dosing instructions for study drug administration and/or unable to complete the study schedule of assessments

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Description and Handling of LDV/SOF FDC

5.1.1. 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 SOF/LDV 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 Aluminium 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.

5.1.2. Packaging and Labeling

LDV/SOF FDC tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 or 30 tablets, 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 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.

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All LDV/SOF FDC and placebo to match LDV/SOF FDC bottles to be distributed to centers 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 (Feb 2010) and/or other local regulations as applicable.

5.1.3. Storage and Handling

LDV/SOF FDC tablets (both 90 mg/400 mg and 22.5 mg/100 mg strength) and placebo to match LDV/SOF FDC tablets (for both both 90 mg/400 mg and 22.5 mg/100 mg strengths), 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).

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug 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 tabletsand placebo tablets will be shipped to the investigator or qualified designee from Gilead Sciences (or its designee).

5.2. Dosage and Administration of LDV/SOF FDC

LDV/SOF FDC 90 mg/ 400 mg tablet is to 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. Each subject must be given instructions to maintain approximately the same daily dosing interval between study drug doses. In order to maintain compliance with the treatment regimen, LDV/SOF FDC should be administered at approximately the same time each day.

For a missed dose of LDV/SOF FDC tablet, subjects should be instructed to take the missed dose of study drug as soon as possible during the same day. Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

5.3. 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).

Investigational agents or devices for any indication are prohibited during the screening period and for a minimum of 28 days prior to the Baseline/Day 1 visit through the end of treatment.

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters ie, 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 Baseline/Day 1** through the end of treatment are listed below. 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[b]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials[b]	Rifabutin, Rifapentine, Rifampin	
Cardiac Medications	Amiodarone[c]	Digoxin[d]
Herbal/Natural Supplements[b]	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[e]	Rosuvastatin	

a It is recommended to separate antacid and LDV/SOF administration by 4 hours. H2-receptor antagonists may be administered simultaneously with or staggered from LDV/SOF 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. Proton-pump inhibitors should not be taken before LDV/SOF.
b May result in a decrease in the concentrations of study drug.
c 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.
d May result in an increase in the concentration of study drug and/or concomitant medications. Co-administration of LDV/SOF with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with LDV/SOF.
e Use with study drug may result in an increase in the concentration of rosuvastatin. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

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

5.3.1. Allowed Maintenance Chemotherapy Medications

Acceptable maintenance chemotherapy medications allowed in this study include the following:

- Vincristine
- Methotrexate
- 6-mercaptopurine (6-MP)

L-aspariginase and aracytine and/or short courses of steroids such as prednisone may also be used.

Administration of these medications should be staggered relative to dosing of LDV/SOF to minimize any potential for drug-drug interactions. For example, if subjects receive their maintenance chemotherapy in the morning, LDV/SOF should be taken in the evening.

Additional chemotherapy medications may be used after review and agreement by Gilead.

5.4. Accountability for LDV/SOF FDC

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

LDV/SOF FDC accountability records will be provided to each study site to:

- Record the date received and quantity of study drug kits
- Record the date, subject number, subject initials, the study drug kit number dispensed
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information.

Subjects must be instructed to bring back all study drug in the original container at every post-Day 1 study visit through the end of treatment.

5.4.1. Investigational Medicinal Product Return or Disposal

Please refer to Section 9.1.7 for Investigational Medicinal Product Accountability and Return.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

6.1.1. Screening Visit

Subjects will be screened within 28 days of Day 1 to determine eligibility for participation in the study. The screening window can be extended to 42 days prior to Day 1 in extenuating circumstances with sponsor approval.

The following assessments will be done at screening:

- Obtain parent or guardian consent and assent from the child; written assent should be provided if applicable
- Collect medical history, demographics, and concomitant medications
- Ask subject and/or parent/legal guardian if the subject is able to swallow and tolerate taking pills.
- Perform LDV/SOF FDC swallowability assessment
- Perform physical exam (PE) including vital signs (VS), body weight, and height
- Collect blood samples for
  - HCV antibody, HAV antibody, HIV antibody, HBsAg, HBsAb, HBcAb
  - HCV RNA
  - HCV genotype
  - Clinical chemistry (including Fibrotest), hematology (including APRI calculation) , and coagulation
  - Pregnancy test (females of childbearing potential only)
- Fibrosis assessment with Fibroscan; liver biopsy may be done if required

— For patients with cirrhosis, diagnostic imaging (CT or ultrasound) if results not available from imaging done within 6 months of Day 1 that excludes the presence of hepatocellular carcinoma (HCC)

- Collect urine sample for urinalysis
- Review of all inclusion and exclusion criteria

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 28 days after screening for enrollment into the study.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.1.2. Baseline Assessments

Day 1 tests and procedures must be completed prior to enrollment and dosing/dispensing of study drug.

At the Day 1 visit, complete the following:

- Confirm subject eligibility
- Review medical history since screening visit including adverse events and concomitant medications
- Perform symptom-directed PE including VS, body weight, and height
- Collect blood samples for clinical chemistry including Fibrotest, hematology, coagulation , HCV RNA, HBV DNA for subjects HBcAb positive at Screening, IL28B genotyping, PPD
- Collect urine sample for pregnancy testing for females of childbearing potential
- Pregnancy prevention counseling, if applicable
- Perform LDV/SOF FDC swallowability (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
- Dispense study drug(s) as directed by IWRS

- Instruct the subject on the packaging, storage and administration of study drug
- Subjects will be administered a dosing diary with instructions.

6.2. Treatment Assessments (± 3 days)

Treatment procedures/assessments are to be completed at the end of Weeks 1, 4, 8, and 12, and ESDD as applicable, for all subjects as outlined in Appendix 2.

At all visits:

- Perform symptom-directed PE and VS measurement
- Assess adverse events and concomitant medications since previous visit
- Collect blood samples for HCV RNA measurement PPD
- Assess study drug accountability
  - Dispense study medication at Weeks 4 and 8
- Review subject dosing diary

At Weeks 4, 8, and 12, and ESDD if applicable:

- Obtain height and body weight
- Collect blood samples for clinical chemistry and hematology
- Collect blood samples for HBV DNA only in subjects HBcAb positive at Screening
- Collect urine sample for pregnancy testing (females of childbearing potential)

At Weeks 4 and 12, and ESDD if applicable:

PPD

At Week 12 or ESDD:

- Pregnancy prevention counseling, if applicable
- Collect blood samples for Fibrotest and coagulation
- APRI Calculation

6.3. Post-treatment Assessments (± 5 days)

All subjects will complete the Post-Treatment Week 4, 12 and 24 visits, regardless of treatment duration.

Assessments at the Post-Treatment Week 4 visit include:

- Obtain height and body weight
- Symptom directed PE and VS
- Adverse events and concomitant medications
- Blood samples for clinical chemistry and hematology including APRI calculation, HCV RNA, HBV DNA only in subjects HBVAb positive at Screening, PPD
- Urine sample for pregnancy testing (females of childbearing potential)
- Pregnancy prevention counseling, if applicable

Assessments at the Post-Treatment Week 12 and 24 visit include:

- Collect any serious adverse events
- Obtain height and body weight
- For those who achieved SVR at the preceding visit (ie, achieved SVR4 or SVR12): Collect blood samples for HCV RNA PPD
- Collect blood samples for Fibrotest PPD
- Perform Fibroscan

6.4. Unscheduled Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments are at the investigator's discretion as clinically indicated, but the investigator should at a minimum collect AE and concomitant medication information.

If a subject has a chemotherapy interruption due to elevated ALT, a blood sample for HCV RNA measurement should be collected as soon as possible.

PPD

The Sponsor (e.g. Medical Monitor and Clinical Program Manager)/CRO must be informed, as soon as possible, when a subject discontinues treatment.

6.5. Assessments for Premature Discontinuation from Treatment and From the Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to perform the ESDD assessments (Section 6.2 and Appendix 2) and continue the subject in the study to complete the Weeks 4, 12, and 24 Post-Treatment Visits (Section 6.3 and Appendix 2). If this is not possible or acceptable to the subject or investigator, the subject may be prematurely discontinued (ie, withdrawn) from the study.

Discontinuation from study drug dosing and discontinuation from the overall study including follow-up will be collected as two separate events.

The sponsor (eg, Medical Monitor and Clinical Program Manager)/CRO must be informed as soon as possible when a subject discontinues from the study.

6.6. End of Study

Subjects are considered to have completed the study after the Post-Treatment Week 24 follow-up visit, regardless of treatment duration and early study drug discontinuation.

6.7. Procedures and Specifications

6.7.1. 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 (non-fasting), potassium, sodium; gamma-glutamyl transferase (GGT)
- Fibrotest
- APRI
- Virological Tests: Serologies for HCV, HBV (HBsAg, HBsAb, HBcAb), HAV, and HIV. HCV RNA will be measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. HBV DNA testing will be performed only in subjects HBcAb positive at Screening. Alternate assays may be used if the above assays are not available or are not definitive.

- IL28B genotype will be determined by polymerase chain reaction (PCR) amplification of the SNP, rs12979860. Alternate assays may be used if this assay is not available.

- Pregnancy Tests: Serum β-hCG or urine β-hCG (if positive, requires immediate confirmation with serum β-hCG).

6.7.2. 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.

6.7.3. 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.

6.7.4. Vital Signs

Vital sign collection 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 mm Hg mark on the manometer or to the nearest whole number on an automatic device.

6.7.5. Creatinine Clearance

Creatinine clearance is calculated by the Schwartz formula using actual height in cm (Ht).

CRCL (mL/min/1.73m^2) = k * height (cm) / serum creatinine (mg/dL)
where k, proportionality constant, is:
0.70: for adolescent males ≥ 12 years old
0.55: for adolescent females ≥ 12 years old
0.55: for children (>=2 and <12 years old)

6.7.8. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every month during the dosing period and for a minimum of 30 days following last dose of study drug. 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.

6.7.9. 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, the subject will be screen failed and excluded from the study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal 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 specified 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 7.6.1)
- 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.

7.1.2. 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 a 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.

7.1.3. 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 (eg, 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 (eg, 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 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator 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 IMP. For SAEs, an alternative causality must be provided (eg, 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 adverse event reporting.

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

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

7.2.2. Assessment of Severity

Severity should be recorded and graded according to the Gilead Sciences, Inc. (GSI) Grading Scale for Severity of AEs and Laboratory Abnormalities (see 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.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

7.3.1. 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.

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days 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.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated 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 drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined 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 study drug, he/she should promptly document and report the event to Gilead DSPH.

7.3.4. Electronic Serious Adverse Event (eSAE) Reporting Process

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

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, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:.

Gilead DSPH:	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.

- 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 eCRF and the event description section of the SAE form.

7.4. 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 drug. 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.

7.5. Toxicity Management

7.5.1. Subject Stopping Rules

The Gilead Medical Monitor must 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.

Due to a clinical or laboratory event, administration of study drug may be discontinued. If LDV/SOF FDC is stopped due to toxicity, it must not be restarted, and the subject must complete an ESDD visit. If possible, all subjects who terminate treatment early will complete the Early Study Drug Discontinuation (ESDD) Visit, and Post-Treatment Weeks 4, 12, and 24 Visits.

Subjects who meet any of the following laboratory criteria must stop study drug:

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

7.6. Special Situations Reports

7.6.1. 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.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH by transmitting electronically and also by sending paper pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the 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 (eg, 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 Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported 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: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject 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 PPD or email PPD

Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the electronic special situations report form and transmitted to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. If for any reason it is not possible to record the special situation report (SSR) information electronically, ie, the eCRF database is not functioning, record the SSR on the paper special situation reporting form and submit within 24 hours to:

Gilead DSPH: Fax: PPD
Email: PPD

As soon as it is possible to do so, any SSR reported via paper must be transcribed into the eCRF

Database according to instructions in the eCRF completion guidelines.

These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications do 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 7.3 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 CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To evaluate the efficacy of ledipasvir/sofosbuvir (LDV/SOF) in treating HCV infection in pediatric subjects who are undergoing cancer chemotherapy, as measured by the proportion of subjects who achieve a sustained virologic response 12 weeks after the end of HCV treatment (SVR12)
- To evaluate the safety and tolerability of treatment with LDV/SOF for 12 weeks

The secondary objectives of this study are:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of HCV treatment (SVR4 and SVR24)
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of HCV treatment

The exploratory objectives of this study are:

8.1.2. Primary Endpoint

The primary efficacy endpoint is SVR12 (HCV RNA <LLOQ 12 weeks after discontinuation of therapy) in the Full Analysis Set (FAS) population.

8.1.3. Secondary Endpoint

Secondary efficacy endpoints include the following:

- The proportion of subjects with HCV RNA < LLOQ at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)
- The proportion of subjects with HCV RNA < LLOQ while on treatment
- HCV RNA change from Baseline/Day 1
- The proportion of subjects with virologic failure

8.1.4. Safety Endpoints

The primary safety endpoint is any AE leading to permanent discontinuation of the study drug.

8.1.5. Other Endpoints of Interest

PPD

8.2. 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).

The study drug in this study is LDV/SOF. Last dose of study drug will be used in the definition of treatment emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various post-treatment time points.

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The analysis set for efficacy analyses will be the FAS which includes all enrolled subjects who took at least 1 dose of the study drug.

8.2.1.2. Safety

The analysis set for safety analyses will include all subjects who took at least 1 dose of the study drug.

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

8.3. Data Handling Conventions

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

For the analyses of categorical HCV RNA data, missing post-treatment HCV RNA data will have the missing data imputed. Missing on-treatment HCV RNA will have the missing data imputed up to the time of the last dose.

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

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

- If a subject took at least 1 dose of study drug, the subject will be included in a summary of AEs 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 the summary statistics for that time point. If the subject is missing a predose value, then the subject will be excluded from the calculation of the summary statistics for the predose value and the change from predose values.

Values for missing safety laboratory data will not be imputed; however, a missing Baseline/Day 1 result will be replaced with a screening result, if available. If no pretreatment laboratory value is available, the Baseline/Day 1 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/Day 1 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 the 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).

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

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

Baseline characteristic data will include body mass index, presence or absence of cirrhosis, HCV RNA level ($\log_{10}$ IU/mL), HCV genotype, IL28B genotype, prior HCV treatment experience, and additional endpoints as necessary.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is SVR12 (HCV RNA < LLOQ 12 weeks after cessation of therapy) in the FAS population. The primary analysis will be performed after all subjects have been followed through 12 weeks post-treatment or discontinued from study.

A point estimate with a 2-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) {Clopper 1934} will be constructed for the SVR12 rate. No statistical hypothesis testing will be performed.

8.5.2. Secondary Analyses

The proportion of subjects with HCV RNA below the LLOQ over time (including SVR endpoints) will be presented in tabular and graphical form.

Descriptive summaries and listings will be provided for additional efficacy evaluations of HCV RNA actual values, and change from baseline.

PPD

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

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

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

8.6.1. Extent of Exposure

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

8.6.2. 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 AE will be defined as any AE with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of the study drug; or any AE leading to premature discontinuation of the study drug.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by SOC and PT) will be provided for:

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- All treatment-related SAEs
- All AEs leading to premature discontinuation of the study drug
- Deaths

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

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by study visit along with corresponding change from baseline/day 1.

Graded laboratory abnormalities will be defined using the laboratory toxicity grading defined in Appendix 3 of this protocol. The incidence of treatment-emergent laboratory abnormalities, defined as values that increase by at least one toxicity grade from baseline/day 1 at any time post-baseline up to the date of last dose of study drug plus 30 days will be summarized.

Values for missing safety laboratory data will not be imputed; however, a missing baseline/day 1 result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the baseline/day 1 value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities.

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

8.6.4. Other Safety Evaluations

Individual data for vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistical summaries (n, mean, SD, median, Q1, Q3, minimum, and maximum), as appropriate.

8.7. Sample Size

With approximately 40 subjects enrolled into the study, a 2-sided 95% confidence interval of the SVR12 rate will extend at most 26.6% in length, assuming the expected SVR12 rate is 80%.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. 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 Harmonisation (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. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to 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.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

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

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, 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) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from a parent or legal guardian and assent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any

study-related procedures. The investigator must use the most current IRB or IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC local requirements.

9.1.4. 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, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC or laboratory. Laboratory specimens must be labeled in such as way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead 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. 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.

9.1.5. 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 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, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study 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 IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned 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 specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead 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 must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source

data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB or IEC, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB or IEC in accordance with local requirements and receive documented IRB or IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. Gilead 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.

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 in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years

The investigator will submit to Gilead 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.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's 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.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF 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 eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead 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 medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. 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 and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 2, Open-label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed Dose Combination in the Treatment of Hepatitis C Virus (HCV) infection in Pediatrics Undergoing Cancer Chemotherapy

GS-US-337-1904, Amendment 1, 16 June 2017

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

PPD

PPD
Study Director/Medical Monitor

PPD

June 21, 2017
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

Appendix Table 1. Screening, On-Treatment Visits

	Screening	Treatment					
	Day -28 to Day -1	Baseline/ Day 1[a]	Week 1 (±3 days)	Week 4 (±3 days)	Week 8 (±3 days)	Week 12 (±3 days)	ESDD
Consent /Assent	X						
Demographics	X						
Medical History	X	X					
Physical exam (PE)	X						
Symptom directed PE		X	X	X	X	X	X
Height and weight	X	X		X	X	X	X
Vital signs[b]	X	X	X	X	X	X	X
Swallowability Assessment	X						
AEs and Con-Meds	X	X	X	X	X	X	X
HBsAg, HBsAb, HBcAb, HIV antibody, HAV antibody, HCV antibody	X						
HCV RNA	X	X	X	X	X	X	X
HCV genotype	X						
HBV DNA[c]		X		X	X	X	X
IL28B genotype		X					
Urinalysis	X						
Hematology and Blood Chemistry (including ALT)	X[d]	X		X	X	X	X

	Screening	Treatment					
	Day -28 to Day -1	**Baseline/ Day 1[a]**	**Week 1 (±3 days)**	**Week 4 (±3 days)**	**Week 8 (±3 days)**	**Week 12 (±3 days)**	**ESDD**
PPD							
Fibrotest	**X**	**X**				**X**	**X**
FibroScan	**X**						
APRI Calculation	**X**					**X**	**X**
Coagulation	**X**	**X**				**X**	**X**
Pregnancy test[e]	**X**	**X**		**X**	**X**	**X**	**X**
Pregnancy prevention counseling[f]		**X**				**X**	**X**
Dispense drug		**X**		**X**	**X**		
Review subject dosing diary		**X**	**X**	**X**	**X**	**X**	
Review of Study Drug Adherence and Drug Accountability			**X**	**X**	**X**	**X**	**X**

a Baseline/Day 1 assessments must be performed prior to dosing.
b Vital signs include resting blood pressure, pulse, respiratory rate, and temperature. SAE and study procedure related AEs are to be collected form informed consent. Other AEs are to be collected from Baseline/Day1.
c HBV DNA testing done only when subjects are HBcAb positive at Screening
PPD
e For females of childbearing potential only: serum β-hCG at Screening, urine test thereafter. If urine is positive, confirm immediately with serum β-hCG
f If applicable

Appendix Table 2. Post-Treatment Study Visits

	4 Weeks Post-Treatment (±5 days)	12 Weeks Post-Treatment[a] (±5 days)	24 Weeks Post-Treatment (±5 days)
Clinical Assessments			
Symptom-directed PE	X		
Height and Weight	X	X	X
Vital Signs	X		
AEs	X	X[a]	X[a]
Concomitant Medications	X		
Fibrosis assessment[b]		X	X
Pregnancy prevention counseling[c]	X		
Laboratory Assessments			
Hematology and Blood Chemistry	X		X
APRI Calculation	X		
HCV RNA	X	X	X
HBV DNA[d]	X	X	X
PPD			
Urine Pregnancy Test[f]	X		

a All SAEs, including deaths, regardless of cause or relationship, must be reported after patient signs the informed consent through the end of the study

b Fibroscan and Fibrotest

c If applicable

d HBV DNA testing done only when subjects are HBcAb positive at Screening

PPD

f Females of childbearing potential

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

Antiviral Toxicity Grading Scale Version: 25 August 2015 modified for Pediatric Studies

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
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months#**	1000 to 1300/mm^3	750 to < 1000/mm^3	500 to < 750/mm^3	< 500/mm^3
	1.00 to 1.30 GI/L	0.75 to < 1.00 GI/L	0.50 to < 0.75 GI/L	< 0.50 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	— —	— —
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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	2.5 to < 3.0 mg/dL	2.0 to < 2.5 mg/dL	< 2.0 mg/dL
	0.74 mmol/L to < LLN	0.62 to < 0.74 mmol/L	0.49 to < 0.62 mmol/L	< 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[**] **Adult**	> 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
Pediatric < 18 Years	1.1 – 1.3 x ULN[†]	>1.3 – 1.8 x ULN[†]	>1.8 – 3.4 x ULN[†]	>3.4 x ULN
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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	>130 to 190 mg/dL	> 190 mg/dL	NA
	2.84 to 3.37 mmol/L	>3.37 to 4.92 mmol/L	>4.92 mmol/L	
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**	-	2.0 to < LLN g/dL 20 to < LLN g/L	< 2.0 g/dL < 20 g/L	NA
≥ 16 years	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)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	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. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following menarche until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Data from clinical pharmacokinetic interaction studies of SOF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical toxicity studies of SOF have demonstrated no adverse effect on fertility or embryo-fetal development.

Data from clinical pharmacokinetic interaction studies of LDV have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical toxicity studies of LDV have demonstrated no adverse effect on fertility or embryo-fetal development.

However, the risks of treatment with LDV/SOF during pregnancy in human have not been evaluated. Please refer to the latest version of the IB for additional information.

b. Contraceptive Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. A pregnancy test will be performed at the Post Treatment Week 4 visit. They must also agree to one of the following from Screening until 30 days of the last dose of LDV/SOF.

- Complete abstinence from intercourse of reproductive potential. Abstinence is acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle. Periodic abstinence (eg, 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:
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Tubal sterilization
  - bilateral tubal occlusion
  - Vasectomy in male partner
  - Barrier methods (one female barrier and one male barrier must be used in combination)
    - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
    - Male barriers: Male condom (with or without spermicide)
  - Hormonal methods
    - Implants of levonorgestrel
    - Injectable progesterone
    - Oral contraceptives (either combined or progesterone only)
    - Contraceptive vaginal ring
    - Transdermal contraceptive patch

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the last dose of LDV/SOF.

3) Contraceptive Requirements for Males Subjects

During the study, male subjects with female partners of childbearing potential should use condoms until 30 days after the last dose of LDV/SOF treatment when engaging in intercourse of reproductive potential. 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 30 days after the last dose of study drug.

Male subjects must agree to refrain from sperm donation for at least 30 days after the last dose of study drug.

4) Procedures to be Followed in the Event of Pregnancy

Subjects should be instructed to notify the investigator if they (or their partner) become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study 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 7.6.2.1.