GILEAD

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Ledipasvir/Sofosbuvir in Subjects with Genotype 1, 4, 5 and 6 Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	115268	
EudraCT Number:	2016-003489-25	
Clinical Trials.gov Identifier:	NCT03036839	
Indication:	Hepatitis C Virus Infection	
Protocol ID:	GS-US-337-4063	
Gilead Study Director:	Name: Telephone: Fax: Email address:	PPD PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax: Email address:	PPD PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1.0: Amendment 2.0: Amendment 3.0:	23 September 2016 29 November 2016 30 January 2017 02 March 2017

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Ledipasvir/Sofosbuvir in Subjects with Genotype 1, 4, 5 and 6 Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease
IND Number:	115268
EudraCT Number:	2016-003489-25
Clinical Trials.gov Identifier:	NCT03036839
Study Centers Planned:	Approximately 35 centers in, North America, Europe, and Asia Pacific
Objectives:	The primary objectives of this study are as follows: • To evaluate the antiviral efficacy of treatment with ledipasvir/sofosbuvir (LDV/SOF) for 8, 12, or 24 weeks in subjects with chronic hepatitis C virus (HCV) infection who are on dialysis for End Stage Renal Disease (ESRD), as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12) • To evaluate the safety and tolerability of each treatment regimen 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 each study treatment regimen (SVR4 and SVR24) • To evaluate the proportion of subjects with virologic failure • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment • To evaluate the emergence of viral resistance to LDV and SOF during treatment and after cessation of treatment • To evaluate the steady-state pharmacokinetics of LDV and SOF and its metabolites in subjects who are on dialysis for (ESRD)

The exploratory objectives of this study are:

[redacted]

Study Design:

Approximately 100 subjects with genotype 1, 4, 5, or 6 HCV infection will be enrolled to 1 of 3 groups and will receive treatment with LDV/SOF for 8, 12, or 24 weeks. The treatment group to which subjects are assigned will be determined by genotype, the absence or presence of cirrhosis and whether the subject is treatment naïve or treatment experienced.

Group 1: Treatment naïve genotype 1 subjects without cirrhosis will be treated with LDV/SOF for 8 weeks

Group 2: Treatment experienced genotype 1 subjects and treatment naïve or treatment experienced genotype 4, 5, and 6 subjects without cirrhosis will be treated with LDV/SOF for 12 weeks

Group 3: Subjects with compensated cirrhosis will be treated with LDV/SOF for 24 weeks

Substudies

[redacted]

CCI

CCI

CCI

Number of Subjects Planned:	Approximately 100 subjects
Target Population:	Adults with chronic hepatitis C virus (HCV) infection who are on dialysis for ESRD
Duration of Treatment:	Subjects will be treated for 8, 12, or 24 weeks.
Diagnosis and Main Eligibility Criteria:	Chronic HCV infected genotype 1, 4, 5, or 6 male and non-pregnant/ non-lactating female subjects aged 18 years or older who are on dialysis for ESRD, including subjects with HIV co-infection if they are suppressed on a stable, protocol-approved antiretroviral (ARV) regimens for ≥8 weeks prior to Screening.
Study Procedures/ Frequency:	For a list of assessments at each visit, refer to the Study Procedures Tables in Appendix 2: for subjects in Group 1 can be found in Appendix Table 1, for Group 2 in Appendix Table 2 and for Group 3 in Appendix Table 3. Subjects who achieve SVR12 will also complete the posttreatment week 24 visit. Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. The screening window can be extended up to 42 days in extenuating circumstances, with the approval of the medical monitor. Screening assessments will include physical examination, medical history, height, weight, vital signs, 12-lead electrocardiogram (ECG), adverse events (AEs) related to screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), HCV RNA, serology (HIV, HCV, HBV) hemoglobin A1c (HbA1c), assessment of the

presence or absence of cirrhosis, screening for hepatocellular carcinoma (HCC) for subjects with cirrhosis, serum β-hCG (females of child bearing potential only), HCV genotyping, IL28B genotyping, and serum drug screen. HIV/HCV co-infected subjects will have additional testing for CD4 T-cell count and HIV-1 RNA.

Study visits will occur at Day 1 and at the end of Weeks 2, 4, 6, and 8 for subjects in Group 1.

Study visits will occur at Day 1 and at the end of Weeks 2, 4, 6, 8, and 12 for subjects in Group 2.

Study visits will occur at Day 1 and at the end of Weeks 2, 4, 6, 8, 12, 16, 20, and 24 for subjects in Group 3.

On-treatment assessments include adverse events (AEs), concomitant medications, study medication pill count, physical examination, weight, vital signs, safety laboratory tests, HCV RNA, HBV DNA (for HBcAb+ subjects only), sparse PK sampling, and serum β-hCG (females of child bearing potential only). HIV/HCV co-infected subjects will have additional assessments, including CD4 T-cell count and HIV-1 RNA assessments.

Single 12-lead ECGs will be collected at Screening, Day 1 (prior to study drug administration), and at the on-treatment Week 8 (Group 1), Week 12 (Group 2) and Week 24 (Group 3) visits, or Early Termination (ET) visit (if applicable). At the time of collection, ECGs will be reviewed by qualified study staff (as determined by the investigator) for clinically significant abnormalities. End of treatment or ET results will be compared to the subject's Day 1 ECG as part of routine safety monitoring.

All subjects will complete posttreatment visits at Weeks 4 and 12 after completion of treatment. Subjects who achieve SVR12 will also complete the posttreatment Week 24 visit.

Post-treatment assessments include AEs, concomitant medications, vital signs, physical examination, safety laboratory tests, HCV RNA, HBV DNA (for HBcAb+ subjects only), and serum β-hCG (females of child bearing potential only). HIV/HCV co-infected subjects will have additional assessments including CD4 T-cell count and HIV-1 RNA assessments.

HRQoL surveys (SF-36, CLDQ-HCV, FACIT-F, and WPAI) will be conducted at Day 1, on-treatment Weeks 8 (Group 1), Week 12 (Group 2), Week 24 (Group 3), or (ET) (if applicable), and posttreatment Week 12.

Samples for HCV or HIV viral sequencing / phenotyping will be collected at Baseline/Day 1 and every visit thereafter.

	CCI [redacted]
Test Product, Dose, and Mode of Administration:	LDV/SOF fixed dose combination (FDC) is manufactured as a 90mg/400mg tablet for oral administration. Subjects will take 1 tablet daily with or without food. CCI [redacted]
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 performed using COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0.
Pharmacokinetics:	The PK of LDV and SOF (and metabolites) may be assessed.
Statistical Methods:	The primary efficacy endpoint for the study is SVR12 in all enrolled and treated subjects. In the primary efficacy analysis, the point estimate and the 2-sided 95% exact confidence interval of SVR12 rate will be provided for each treatment group and overall. With a sample size of 100 subjects, a 2-sided 95% exact confidence interval will extend at the most 20% in length. Secondary efficacy endpoints include SVR4, SVR24, and the proportion of subjects with virologic failure. Steady state PK plasma parameters will be listed by subject and summarized by treatment group and overall using descriptive statistics for each analyte (SOF [and its metabolites] and LDV, as appropriate).

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
Ab	antibody
ABW	Actual body weight
AE(s)	adverse event(s)
ALT	alanine aminotransferase (also SGPT)
ANC	Absolute Neutrophil Count
aPTT	activated partial thromboplastin time
ARV	antiretroviral
AST	aspartate aminotransferase (also SGOT)
AV	atrioventricular
BMD	Bone Mineral Density
BMI	Body Mass Index
BW	body weight
CD4+	cluster of differentiation 4+
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CLCr	creatinine clearance rate
CLDQ-HCV	Chronic Liver Disease Questionnaire
CM	concomitant medication
cm^2	square centimeter
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CRO	contract (or clinical) research organization
CSR	Clinical study report
CT	Computerized Tomography
DAA	direct-acting antiviral
dL	deciliter
DNA	deoxyribonucleic acid
DSPH	Gilead Drug Safety and Public Health
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eg	example given
ER	Emergency room
ESRD	End Stage Renal Disease
ET	Early Termination
EU	European Union

EudraCT	European Union Drug Regulating Authorities Clinical Trials
FACIT-F	Fatigue Index
FAS	full analysis set
FCF	yellow # 6 / sunset yellow FCF aluminum lake
FD&C	Federal Food, Drug and Cosmetic
FDA	(United States) Food and Drug Administration
FDC	Fixed-dose combination
FEV1	forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
g	grams
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	giga
GS-7977	formerly PSI-7977
GSI	Gilead Sciences, Inc.
GT	genotype
h	hour
H2	Histamine
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HBcAb+	Hepatitis B core antibody-positive
HBsAb	Hepatitis B surface antibody
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
HMG-CoA	3-hydroxy-3-methyl-glutaryl coenzyme A
HPF	high power field
HRQoL	Health Related Quality of Life
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IFN	Interferon
IL28B	Interleukin-28B gene

IMB	Intermenstrual Bleeding
IMP	Investigational Medical Product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio of prothrombin time
IRB	institutional review board
IU	International Units
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IWRS	interactive web response system
kg	Kilogram
kPa	kilopascal
L	liter
LAM	Lactational amenorrhea method
LDV	ledipasvir
LLN	lower limit of the normal range
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
m2	square meter
MCV	mean corpuscular volume or mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalents
mg	milligram
MGB	minor groove binder
mL	Milliliter
mm3	cubic millimeter
mmHg	millimeters mercury
mmol	millimole
n	number
NS (3/4A/5A/5B)	Non-structural Protein
PCR	Polymerase Chain Reaction
Peg-IFN	pegylated interferon
P-gp	P-glycoprotein
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPIs	Proton-pump inhibitor
PR	P and R waves (in electrocardiography)
PT	preferred term or prothrombin time
Q1	Quartile 1
Q3	Quartile 3

QA	Quality assurance
QTc	corrected QT
RAV	Resistance-associated variants
RBC	Red blood cell count
RBV	ribavirin
RNA	ribonucleic acid
SADR	Serious adverse drug reaction
SAE	serious adverse event
Scr	serum creatinine (mg/dL)
SD	Standard deviation
sec	seconds
SF-36	36-Item Short Form Health Survey
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SNP	Single nucleotide polymorphism
SOC	System Organ Class
SOF	sofosbuvir, formerly GS-7977
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
SVR12	Sustained Virologic Response 12 weeks after cessation of treatment
SVR24	Sustained Virologic Response 24 weeks after cessation of treatment
SVR4	Sustained Virologic Response 4 weeks after cessation of treatment
TEN	toxic epidermal necrolysis
TND	Target not detected
ULN	Upper limit of normal
US	United States
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment
β-hCG	β-human chorionic gonadotropin
µg	microgram
µL	microliter
µmol	micromole

1. INTRODUCTION

1.1. Background

Hepatitis C virus infection is a global health challenge with the estimated number of persons infected ranging from 80 to 150 million worldwide {Gower 2014, World Health Organization (WHO) 2014}. Hepatitis C virus has significant genetic (RNA sequence) variability and is classified on this basis into at least 6 genotypes. There is significant geographical variation in the distribution of HCV genotypes. In North America and Europe, genotype 1 HCV infection predominates. In Asia, genotype 1 and 3 HCV infections are the most prevalent. Genotype 4, 5, and 6 are highly prevalent in northern Africa, southern Africa, and southeast Asia, respectively.

The disease burden of HCV infection is due to progression of chronic liver disease, which can lead to cirrhosis, liver failure, HCC, and death. Globally, 27% of all subjects with cirrhosis and 25% of those who develop HCC are attributable to HCV infection {Perz 2006}. In addition to having a higher incidence of HCC, subjects with chronic HCV infection have a higher incidence and mortality of many types of non-liver cancers including pancreatic, rectal, kidney, non-Hodgkin's lymphoma, and lung cancers, compared with the general population {Allison 2015}. Curing HCV infection is associated with numerous health benefits including more than 70% reduction in the risk of HCC and a 90% reduction in the risk of liver-related mortality and liver transplantation {Morgan 2013, Poynard 2002, van der Meer 2012, Veldt 2007}.

Recently, there has been a transformation in the treatment of HCV infection with the development of direct-acting antiviral agents (DAAs) targeting viral proteins essential to viral replication. DAA based treatment regimens are generally well tolerated and result in high sustained virologic response (SVR) at 12 weeks following completion of all treatment (SVR12) rates across most patient populations {AbbVie Inc 2016, Bristol-Myers Squibb 2016, Gilead Sciences Inc 2015a, Gilead Sciences Inc 2015b, Gilead Sciences Inc 2016, Merck & Co Inc 2016}. SOF based regimens (Sovaldi® and Harvoni®) are the most widely prescribed treatments for HCV infection due to the efficacy, tolerability, and simplicity of the dosing regimens. In addition, SOF-based regimens offer the advantages of having relatively few drug-drug interactions, strong concordance between clinical trial and "real world" data, and absence of a requirement for baseline NS5A polymorphism testing {Arias 2016, Gilead Sciences Inc 2015a, Gilead Sciences Inc 2015b, Ioannou 2016}.

Despite the progress made in the development of effective treatments for HCV infection, many challenges remain. These include the evaluation of DAA based regimens in patient populations not evaluated in registration clinical studies, including subjects with advanced hepatic disease, or advanced renal disease and in pediatric populations. In addition, the treatment of populations with high HCV prevalence such as the incarcerated, or injection drug users will require the development of treatment models tailored to these specific populations. Finally, as the highest prevalence of HCV infection occurs in low and middle income countries, the development of treatment algorithms that can be implemented in resource limited settings will be necessary to decrease the global prevalence and burden of HCV infection.

1.2. Ledipasvir/Sofosbuvir Fixed Dose Combination

Ledipasvir is a HCV NS5A inhibitor with potent activity against genotype 1, 4, 5, and 6 HCV. Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor. LDV/SOF (Harvoni®) is a co-formulation of LDV 90 mg and SOF 400 mg that is approved in the US, EU, and other regions for the treatment of HCV infection in adults.

1.2.1. General Information

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

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

1.2.2. Additional Clinical Information; Study GS-US-334-0154

1.2.2.1. Study Design

Study GS-US-334-0154 is an ongoing Phase 2b, open-label study of SOF-based regimens in subjects with severe renal impairment. In Part A, subjects with genotype 1 or 3 HCV infection and severe renal impairment were randomized to SOF 200 mg + RBV 200 mg for 24 weeks (Cohort 1) or SOF 400 mg + RBV 200 mg (Cohort 2) for 24 Weeks. Based on data from Cohort 1 and 2, Cohort 3 was opened for enrollment and subjects with genotype 1 or 4 HCV infection and severe renal impairment were treated with LDV/SOF (90/400 mg) for 12 weeks. Final data is available for Cohort 1 and Cohort 2 and is presented below. Enrollment in Cohort 3 is ongoing and preliminary data is summarized in Section 1.2.2.8.

1.2.2.2. Disposition (Cohort 1 and 2)

A total of 20 subjects were enrolled and received at least 1 dose of study drug; 10 subjects in Cohort 1 [SOF 200 mg + RBV 200 mg] and 10 subjects in Cohort 2 [SOF 400 mg + RBV 200 mg]. The majority of subjects (80.0%) completed study treatment (8 subjects in each cohort). Four of the 20 enrolled and treated subjects, prematurely discontinued study treatment (20.0%, 2 subjects in each cohort). The reasons for premature discontinuation of study treatment were AEs (2 subjects from Cohort 2), noncompliance with study drug (1 subject from Cohort 1), and withdrawn consent (1 subject in Cohort 1).

1.2.2.3. Demographics and Baseline Characteristics (Cohorts 1 and 2)

Demographics and baseline characteristics were similar in both treatment groups. The majority of subjects were male (70.0%), 45.0% of subjects were black and 35.0% of subjects were white, the majority of subjects were non-Hispanic/Latino (85.0%), and the mean age was 60 years (range: 45−75). The mean (SD) baseline body mass index (BMI) for subjects was 27.3 (3.71) kg/m^2 and 70.0% of subjects had BMI < 30 kg/m^2.

The majority of subjects had genotype 1a HCV infection (65.0%, 13 subjects), 20.0% (4 subjects) had genotype 1b, and 15.0% (3 subjects) had genotype 3a. In Cohort 1, the majority of subjects had non-CC (CT or TT) IL28B alleles (80.0%); while 50.0% of subjects in Cohort 2 had non-CC (CT or TT) IL28B alleles. Overall, the majority of subjects had HCV RNA ≥ 6 log_{10} IU/mL (65.0%, 13 subjects), with a mean (SD) HCV RNA value of 6.4 (0.47) log_{10} IU/mL. A total of 4 subjects (20.0%, all in Cohort 2) had cirrhosis at screening. In Cohort 1, no subjects reported a known history of cirrhosis; however, 20.0% (2 subjects) had FibroTest scores corresponding to stage of F3-F4 (severe fibrosis). In Cohort 1, the median (range) estimated glomerular filtration rate using the Cockcroft-Gault equation was 20.0 (14.4−35.8) mL/min, and in Cohort 2 it was 25.4 (17.5−39.1) mL/min. The majority of subjects in Cohort 1 (70.0%) were treatment-naive; the 3 subjects who were treatment-experienced had failed prior treatment with a DAA + pegylated interferon (Peg-IFN) + RBV regimen (2 subjects) or interferon + RBV (1 subject). The majority of subjects in Cohort 2 (70.0%) were treatment-experienced; the majority of these subjects (71.4%, 5 of 7 subjects) had failed prior treatment with Peg IFN+RBV.

1.2.2.4. Efficacy (Cohort 1 and 2)

The SVR12 rates were as follows:

- Cohort 1 (SOF 200 mg + RBV 200 mg): 40.0% (95% CI: 12.2% to 73.8%) of subjects (4 of 10) achieved SVR12

- Cohort 2 (SOF 400 mg + RBV 200 mg): 60.0% (95% CI: 26.2% to 87.8%) of subjects (6 of 10) achieved SVR12

In Cohort 1, 6 of 10 subjects (60.0%) did not achieve SVR12: 5 subjects (50.0%) relapsed and 1 subject withdrew consent. In Cohort 2, 4 subjects (40.0%) did not achieve SVR12; all 4 subjects relapsed. Two of these subjects prematurely discontinued study treatment on Day 64 and Day 117, respectively, both due to an AE. No subjects in either cohort had on-treatment virologic failure (i.e., breakthrough, rebound, or nonresponse). The concordance observed between SVR12 and SVR24 was 100% in both cohorts. HCV RNA levels (log_{10} IU/mL) declined rapidly with similar decreases in HCV RNA observed in both treatment cohorts. After 1 week of treatment, the mean (SD) change from baseline in HCV RNA levels was −4.41 (0.826) log_{10} IU/mL in Cohort 1 and –4.68 (0.635) log_{10} IU/mL in Cohort 2. The decreases were maintained from Week 2 through the end of treatment at Week 24.

No nonstructural protein 5B (NS5B) nucleoside inhibitor (NI) resistance-associated variants (RAVs) were detected in any of the subjects at baseline. The NS5B NI RAV E237G was detected in 3 subjects at the time of relapse (2 with genotype 1a [1 subject from each cohort] and 1 with genotype 1b [Cohort 1]). E237G showed a small reduction in susceptibility to SOF (1.3-fold change) in a genotype 1a replicon assay, which was within assay variation, and was as susceptible as wild-type in the genotype 1b replicon assay (1.0-fold change).

1.2.2.5. Pharmacokinetics/Pharmacodynamics (Cohort 1 and 2)

SOF AUC_{tau} and C_{max} were modestly higher in subjects receiving the 400-mg dose compared with the 200-mg dose and AUC_{tau} was generally similar at Week 2 and Week 12 for both doses. Compared to historical reference data (SOF US NDA Phase 2/3 HCV-infected subjects without renal impairment [creatinine clearance CL_{cr}, ≥ 60 mL/min] administered SOF 400 mg + RBV ± Peg-IFN), dose-adjusted SOF AUC_{tau} and C_{max} were ~137% and ~221% higher, respectively, for the 200-mg SOF dose. SOF AUC_{tau} and C_{max} were ~36% and ~100% higher than historical reference data, respectively, for the SOF 400-mg dose. Changes in the PK of GS-566500 were generally similar to those observed with SOF, consistent with historical data. Higher SOF AUC and C_{max} (~503% and ~331%, respectively) were observed following the SOF 400-mg dose. No difference in GS-331007 exposure was observed between Week 2 and Week 12, suggesting subjects reached steady-state by Week 2. Overall, changes in SOF and GS-331007 PK were consistent with results of Phase 1 Study P7977-0915, which evaluated SOF PK in HCV-negative subjects with renal impairment.

Consistent with a long $t_{1/2}$, RBV exposures in both cohorts were higher at Week 12 compared with Week 2. The RBV AUC_{tau} and C_{tau} values at Week 12 for both cohorts were similar to those reported for the administration of RBV 1200 mg/day in subjects with normal renal function.

1.2.2.6. Safety (Cohort 1 and 2)

Most subjects (Cohort 1: 60.0%, Cohort 2: 80.0%) received study drug for the protocol-specified duration of 24 weeks. In Cohort 1, the proportion of subjects with ≥ 90% adherence to SOF (80.0%) was higher than to RBV (40.0%). The lower adherence rate to RBV in Cohort 1 was primarily due to intentional RBV dose reductions or interruptions instituted by site investigators for the management of AEs. In Cohort 2, the proportion of subjects with ≥ 90% adherence to SOF (80.0%) was similar to RBV (70.0%).

Most subjects experienced at least 1 AE (Cohort 1: 100.0%, Cohort 2: 90.0%). In Cohort 1, the most commonly reported AEs (i.e., those occurring in ≥ 2 subjects) were headache (40.0%); anemia (30.0%); and hemolytic anemia, hypoesthesia, insomnia, irritability, muscle spasms, pruritic rash, and rash (20.0%, each). In Cohort 2, the most commonly reported AEs were anemia (40.0%) and dizziness (20.0%). Most AEs were of Grade 1 or Grade 2 severity. Grade 3 AEs were reported in 2 subjects (20.0%) in Cohort 1 and 3 subjects (30.0%) in Cohort 2. Anemia was the only Grade 3 AE reported in > 1 subject (1 subject in Cohort 1 and 2 subjects in Cohort 2). No Grade 4 AEs, deaths, or pregnancies were reported during the study. A total of 4 subjects (20.0%, 2 subjects in each cohort) had at least 1 treatment-emergent serious adverse event (SAE), with no SAEs reported for more than 1 subject. All SAEs were considered by the

investigators to be not related to study drug. A total of 4 subjects (20.0%, 2 subjects in each cohort) had AEs leading to premature discontinuation of any study drug. The 2 subjects in Cohort 1 had AEs leading to premature discontinuation of RBV only (anemia in 1 subject and fatigue, irritability, and generalized rash in 1 subject; all of these AEs were considered to be related to study drug). Of the 2 subjects in Cohort 2 experiencing AEs that led to premature discontinuation of SOF and RBV, 1 subject had a Grade 2 AE of fatigue that was considered to be related to study drug and 1 subject had a Grade 3 AE of renal failure and an SAE of pneumonia that were considered to be not related to study drug.

All subjects had at least 1 laboratory abnormality reported. 60.0% of subjects in Cohort 1 and 70.0% of subjects in Cohort 2 had a Grade 3 or 4 laboratory abnormality. Across both cohorts, the observed Grade 3 or 4 hematology abnormalities were decreased hemoglobin and lymphocytes. Decreased hemoglobin and decreases in lymphocyte count are known effects of RBV therapy. Across both cohorts, the Grade 3 or 4 chemistry laboratory abnormalities were increased creatinine, decreased serum bicarbonate, increased serum glucose, and increased blood urea nitrogen. All 5 subjects with Grade 3 or 4 increases in creatinine (2 subjects in Cohort 1, 3 subjects in Cohort 2) had Grade 2 or 3 elevations of creatinine at baseline and throughout study treatment. The 2 subjects with Grade 3 decreases in serum bicarbonate (1 subject in each cohort) had graded decreases in serum bicarbonate at baseline. All 3 subjects with Grade 3 increased serum glucose had a medical history of diabetes. The 1 subject in Cohort 2 who had a Grade 3 increase in blood urea nitrogen had graded elevations in blood urea nitrogen at baseline and throughout study treatment.

Overall, there were 3 subjects (15.0%) with an AE under the Renal and Urinary Disorders system organ class (SOC): 1 subject in Cohort 1 and 2 subjects in Cohort 2. Of these, 1 subject (Subject PPD in Cohort 2 discontinued study treatment due to a Grade 3 AE of renal failure and an SAE of pneumonia. The other AEs in the Renal and Urinary Disorders SOC were Grade 1 or 2 (chronic kidney disease and nocturia) that did not lead to modification or interruption of study treatment. One subject (Subject PPD in Cohort 2 started dialysis during the study due to worsening of subject's chronic kidney failure from Stage 4 to Stage 5, which was considered by the investigator to be unrelated to study treatment.

No subjects had clinically significant ECG abnormalities during treatment with SOF+RBV. No meaningful change in systolic function measured by ejection fraction was observed in either treatment cohort. In addition, no subject had a decrease in ejection fraction below 50%. The median (Q1, Q3) change in ejection fraction from baseline to Week 24 for Cohort 1 was 0.09% (−0.97, 2.70), and in Cohort 2 was −0.73% (−4.28, 1.08). As compared to baseline echocardiograms, there were overall no significant changes in fractional shortening, left ventricular end diastolic volume (LVEDV), or left ventricular internal dimension in diastole (LVIDD) at Week 12 or Week 24.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse rate) were observed during the study.

1.2.2.7. Conclusions (Cohort 1 and 2)

The conclusions for Cohorts 1 and 2 were as follows:

- For subjects with severe renal impairment, the overall SVR12 rates following treatment with SOF (200 mg or 400 mg) in combination with RBV for 24 weeks were as follows:
  - In Cohort 1 (SOF 200 mg + RBV 200 mg), the SVR12 rate was 40.0%.
  - In Cohort 2 (SOF 400 mg + RBV 200 mg), the SVR12 rate was 60.0%.
- No subjects in either treatment cohort had on-treatment virologic failure (i.e., breakthrough, rebound, or nonresponse).
- Virologic relapse was associated with the emergence of the NS5B NI RAV E237G in 3 of 9 subjects (33.3%).
- SOF and GS-331007 exposures in HCV-infected subjects with severe renal impairment in this study were higher than exposures observed in the reference US Phase 2/3 population of HCV-infected subjects without renal impairment.
  - SOF AUC_{tau} and C_{max} were 36% and 100% higher, respectively, for the SOF 400-mg dose.
  - GS-331007 AUC_{tau} and C_{max} were 503% and 331% higher, respectively, for the SOF 400 mg dose.
  - The effect of severe renal impairment on SOF and GS-331007 exposures in HCV infected subjects administered the SOF 400 mg dose with RBV 200 mg was generally comparable with the results from a dedicated renal impairment study in HCV-negative subjects (Study P7977-0915).
- SOF was safe and well tolerated. The AE and laboratory safety profile observed was consistent with that reported for SOF+RBV in subjects without renal impairment. There were no new safety signals or toxicities observed in this study of subjects with severe renal impairment.

1.2.2.8. Preliminary Data from Cohort 3

As of August 2016, 10 subjects have been enrolled and treated in Cohort 3. Preliminary data suggest LDV/SOF has been well tolerated. No subjects have discontinued treatment. There have been 4 SAEs reported; hypoglycemia and syncope in one subject (Subject PPD and acute renal failure (Subject PPD in one subject, and acute kidney injury in one subject (Subject PPD The syncope experienced by Subject PPD was assessed as secondary to hypoglycemia. No SAE was assessed as related to study drugs. An analysis of echocardiogram data for 8 subjects demonstrates stable parameters from screening through the

end of treatment, and does not suggest an impact of LDV/SOF treatment on cardiac function. Eight subjects who have reached posttreatment Week 12 to date have achieved SVR12 (100%, 8/8).

1.2.3. Additional Non-Clinical Toxicology Information

In dogs, repeated administration of GS-9851 (the diastereomeric mixture of SOF and GS-491241) or SOF at exposures similar to those expected in ESRD patients may decrease erythropoiesis and lower the numbers of circulating red cells (reflected by the decrease in red blood cells, hemoglobin concentration, and/or hematocrit). In the 4- and 13-week studies in dogs, there were slightly lower average circulating red cell indices, and minimally decreased erythropoiesis (observed by bone marrow cytology) at 500 and ≥ 100 mg/kg/day, respectively. However, in the 39-week dog study, while minimally decreased erythropoiesis was observed in a few dogs, there were no SOF-related effects on circulating red cell indices at 500 mg/kg/day. In mice and rats, SOF did not affect hematology parameters at any dose level; specifically, there were no effects in mice dosed up to 1000 mg/kg/day for up to 13 weeks or in rats dosed up to 500 mg/kg/day for up to 26 weeks. There were also no bone marrow cytology findings in rats dosed up to 26 weeks. In vitro, the diastereomic mixture GS-9851 also showed low cytotoxicity to erythroid cell lines.

1.3. Rationale for This Study

The GS-US-337-4063 study is a Phase 2, open-label, multicenter study evaluating the efficacy and safety of treatment of LDV/SOF for 8, 12, or 24 weeks in subjects on dialysis for ESRD. Approximately 100 subjects will be enrolled.

LDV/SOF (Harvoni®) is approved in the US, EU, and other regions for the treatment of genotype 1, 3 (EU only), 4, 5, and 6 HCV infection. However, subjects with severe renal impairment were not eligible for the registration LDV/SOF clinical studies. There is therefore no dosing recommendation provided for HCV-infected subjects with severe renal impairment or those on dialysis in the prescribing information in the US, EU, and other regions.

There remains a medical need for highly effective treatment for HCV-infected subjects with ESRD on dialysis. Chronic HCV infection has a significant negative impact on morbidity and mortality in subjects on dialysis {Fabrizi 2007}. The Kidney Disease International Working Group (KDIGO) recommend that HCV infection be treated prior to kidney transplant as there is evidence that this leads to improved graft and patient outcomes {Kidney Disease: Improving Global Outcomes 2008}.

Although, some regions do have approved HCV treatment options for HCV-infected subjects with severe renal impairment including Viekira Pak® and Zepatier™ {AbbVie Inc 2016, Merck & Co Inc 2016}, both regimens have limitations. The use of Viekira Pak® is limited since many populations require the addition of ribavirin for optimal efficacy and RBV-induced toxicities are exacerbated in subjects with renal impairment. In addition, the components of Viekira Pak® (ombitasvir, paritaprevir, ritonavir, and dasabuvir) have drug-drug interaction potential which adds increasing complexity to the management of subjects with severe renal

impairment who frequently have multiple comorbid conditions and concomitant medications. The use of Zepatier is limited by the requirement for baseline resistance testing for subjects with genotype 1a infection and addition of RBV is required for some populations. Furthermore, both regimens carry the risk of alanine aminotransferase (ALT) elevations and/or hepatotoxicity and neither regimen is pangenotypic.

SOF-based regimens are currently the most widely prescribed treatments for HCV infection. Despite the lack of dosing recommendations for subjects with severe renal impairment in the prescribing information for SOF-based regimens, it is apparent from the number of publications of small cohort studies describing treatment of subjects with severe renal impairment with SOF-based regimens that such treatment is not uncommon {Bhamidimarri 2015, Desnoyer 2016, Hundemer 2015, Navarro-Millan 2013, Nazario 2016}. The simplicity of SOF-based dosing regimens, relative lack of drug-drug interactions, and absence of a requirement for baseline NS5A polymorphism testing or RBV use makes SOF-based regimens a viable option for physicians, even when considering the lack of dosing recommendations in this population.

The unmet medical need of the population and the ongoing off-label use of SOF-based regimens provide a strong rationale for the conduct of this study as the data obtained will address the gaps in knowledge regarding the use of SOF-based regimens in subjects with HCV infection who are on dialysis for ESRD.

1.4. Rationale for Dose Selection of LDV/SOF

Subjects in this study will be administered LDV/SOF, a co-formulation of LDV 90 mg and SOF 400 mg that is approved in the US, EU, and other regions as Harvoni® for the treatment of HCV infection in adults. The treatment durations evaluated are aligned with those outlined for RBV-free treatment in the EU prescribing information for subjects without cirrhosis or with compensated cirrhosis; specifically

- Subjects who are treatment naïve and without cirrhosis; LDV/SOF for 8 weeks
- Subjects who are treatment experienced and without cirrhosis: LDV/SOF for 12 Weeks
- Subjects who have compensated cirrhosis: LDV/SOF for 24 weeks

The results of a Phase 1 single dose study of LDV in subjects with severe renal impairment indicates that no relevant differences in LDV exposure were observed between subjects with normal renal function and subjects with severe renal impairment. In a Phase 1 study of the PK of SOF in subjects with renal impairment, the SOF and GS-331007 AUC were 171% and 451% higher, respectively, in subjects with severe renal impairment compared to subjects with normal renal function. In subjects with ESRD, SOF and GS-331007 AUC was 28-60% and 1280-2070% higher, respectively, compared to subjects with normal renal function.

Available data from the Study GS-US-334-0154 indicates that administration of SOF 400 mg with RBV 200 mg for 24 weeks in subjects with severe renal impairment was well tolerated with no specific safety signal associated with the elevated exposures of SOF or the predominant metabolite GS-331007. The exposures of SOF and GS-331007 in the GS-US-334-0154 study are consistent with the results of the Phase 1 study of SOF in subjects with severe renal impairment or ESRD. Preliminary data from the GS-US-334-0154 study suggests that the administration of LDV/SOF (90/400 mg) for 12 weeks is well tolerated and is more efficacious that administration of SOF 200 mg or 400 mg with RBV 200 mg for 24 weeks.

Based on these data, the approved dose of LDV/SOF will be evaluated in this study. Refer to the LDV/SOF IB for additional information.

1.5. Risk/Benefit Assessment for the Study

This study will provide data of the safety and efficacy of LDV/SOF in subjects with ESRD on dialysis. It is anticipated that these data will support dosing recommendations for LDV/SOF in subjects with severe renal impairment and subjects with ESRD on dialysis.

The potential benefits of LDV/SOF over the currently available treatment options are:

- LDV/SOF has broad antiviral activity against a range of HCV genotypes; it is currently approved in the US and EU for the treatment of genotypes 1, 3 (EU only), 4, 5, and 6 HCV infection. LDV/SOF may therefore provide a treatment option for a broader range of HCV infected subjects with severe renal impairment and ESRD on dialysis than the currently available treatment options which are restricted to the treatment of genotype 1 and 4 HCV infections.

- LDV/SOF will provide a highly effective and well-tolerated RBV-free treatment option for subjects on dialysis. As RBV-associated toxicities can be exacerbated in subjects with severe renal impairment, the availability of a RBV-free treatment option will enable a greater proportion of subjects with ESRD to be treated.

- The components of LDV/SOF have limited drug-drug interaction potential with medications commonly prescribed to subjects with severe renal impairment or ESRD on dialysis. This should reduce the complexity of patient management compared with the use of other antiviral treatments.

The risks associated with the evaluations of LDV/SOF in subjects with ESRD on dialysis are associated with concerns about the high exposure of the predominant SOF metabolite, GS-331007, in subjects with renal impairment and the limited data on the safety and efficacy of LDV/SOF in subjects with renal impairment. In non-clinical studies, GS-331007 exposure similar to that projected for patients with ESRD administered LDV/SOF resulted in decreased red cells counts (See Section 1.2.3).

These risks are mitigated by the following:

- Approximately 5000 subjects have been administered LDV/SOF with or without RBV to date.
- During the conduct of the study, hematologic assessments will be performed routinely and results will be reviewed by the investigator and sponsor.
- During the conduct of the study, a Data Monitoring Committee (DMC) will evaluate safety data in the study after the first n=12 subjects have completed 8 weeks of treatment, or early termination (ET), and then every 3 months until the last subject enrolled completes treatment with study drugs. Furthermore, the Sponsor and the Investigators will perform ongoing safety reviews throughout the study.

Given the medical need for a well-tolerated, highly effective, RBV-free treatment options for HCV infected subjects with ESRD on dialysis; the benefit/risk assessment of this study favors the conduct of the study.

1.6. Compliance

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

2. OBJECTIVES

The primary objectives of this study are as follows:

- To evaluate the antiviral efficacy of treatment with LDV/SOF for 8,12, or 24 weeks in subjects with chronic hepatitis C virus (HCV) infection who are on dialysis for ESRD, as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of each treatment regimen

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 each study treatment regimen (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to LDV and SOF during treatment and after cessation of treatment
- To evaluate the steady-state pharmacokinetics of LDV and SOF, and its metabolites in subjects who are on dialysis for ESRD

The exploratory objectives of this study are:

3. STUDY DESIGN

3.1. Study Design

This is a multicenter, open-label Phase 2 study that will evaluate the safety, tolerability, and antiviral efficacy of LDV/SOF in subjects on dialysis for ESRD with genotype 1, 4, 5, or 6 HCV infection.

3.2. Visit Schedule

Screening assessments will be completed within 28 days of the Day 1 visit. The screening window can be extended to 42 days for extenuating circumstances with Sponsor approval.

All subjects will complete the following study visits: Screening, Day 1, on-treatment visits at the end of Weeks 2, 4, 6, and 8. Subjects in group 2 and 3 will also complete a Week 12 visit, and subjects in group 3 only, will also complete visit at Weeks 16, 20, and 24. All subjects will complete posttreatment visits at Weeks 4 and 12, after completion of treatment. Subjects who achieve SVR12 will also complete the posttreatment Week 24 visit.

3.3. Duration of Treatment

Approximately 100 subjects will be enrolled to one of 3 groups and will receive treatment with LDV/SOF for 8, 12, or 24 weeks. The treatment group to which subjects are assigned will be determined by genotype, the absence or presence of cirrhosis and whether the subject is treatment naïve or treatment experienced.

Group 1: Treatment naïve genotype 1 subjects without cirrhosis will be treated with LDV/SOF for 8 weeks

Group 2: Treatment experienced genotype 1 subjects and treatment naïve or treatment experienced genotype 4, 5, and 6 subjects without cirrhosis will be treated with LDV/SOF for 12 weeks

Group 3: Subjects with compensated cirrhosis will be treated with LDV/SOF for 24 weeks

The total time to complete all study visits is up to a maximum of 52 weeks depending on the treatment duration (54 weeks for those requiring an extension of the screening period):

- 28 days (4 weeks) screening period (or 42 days for extenuating circumstances)
- 8, 12, or 24 week study treatment period
- 24 week posttreatment period

3.4. Stopping Rules and Discontinuation Criteria

If a subject discontinues study dosing (for example, as a result of an adverse event [AE]), every attempt should be made to keep the subject in the study, and continue to perform the required study-related follow-up procedures (Section 6.4). If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study.

There is no option for LDV/SOF dose reduction due to toxicity. If LDV/SOF is withheld due to toxicity, the subject must discontinue treatment and complete an ET visit.

For subjects who have completed an ET visit, the posttreatment Week 4 and 12 visits will be scheduled after last dose of any of the study drug. Subjects who achieve SVR12 (HCV RNA < LLOQ at posttreatment Week 12) will complete the posttreatment Week 24 visit.

When medically feasible, the medical monitor must be consulted prior to subject discontinuation.

Study drug(s) must be discontinued in the following instances:

- Unacceptable toxicity (as defined in Section 3.4.1) 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
- Virologic failure (as defined in Section 3.4.2)
- Pregnancy of female subject (refer to Appendix 4)
- Significant protocol violation that impacts subject safety
- 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
- Subject noncompliance
- Discontinuation of the study at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

3.4.1. Toxicity-Based Stopping Criteria

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

- Elevation of ALT and/or AST above the upper limit of normal and > 5x Day 1 or nadir, confirmed by immediate repeat testing
- Elevation of ALT > 3 x Day 1 *and* total bilirubin > 2 x ULN, 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 assessed as related to LDV/SOF

3.4.2. Virologic Response Base Stopping Criteria

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

- Confirmed HCV RNA ≥ LLOQ after 2 consecutive HCV RNA < LLOQ
- Confirmed > 1 $\log_{10}$ increase from on-treatment nadir
- HCV RNA ≥ LLOQ at Week 8

Confirmation should be performed as soon as possible and must occur no later than 2 weeks after an initial observation indicating virologic failure during the on-treatment phase. All subjects who terminate treatment early will complete the ET visit and posttreatment Week 4 and 12 visits.

3.5. HIV Virologic Rebound Criteria

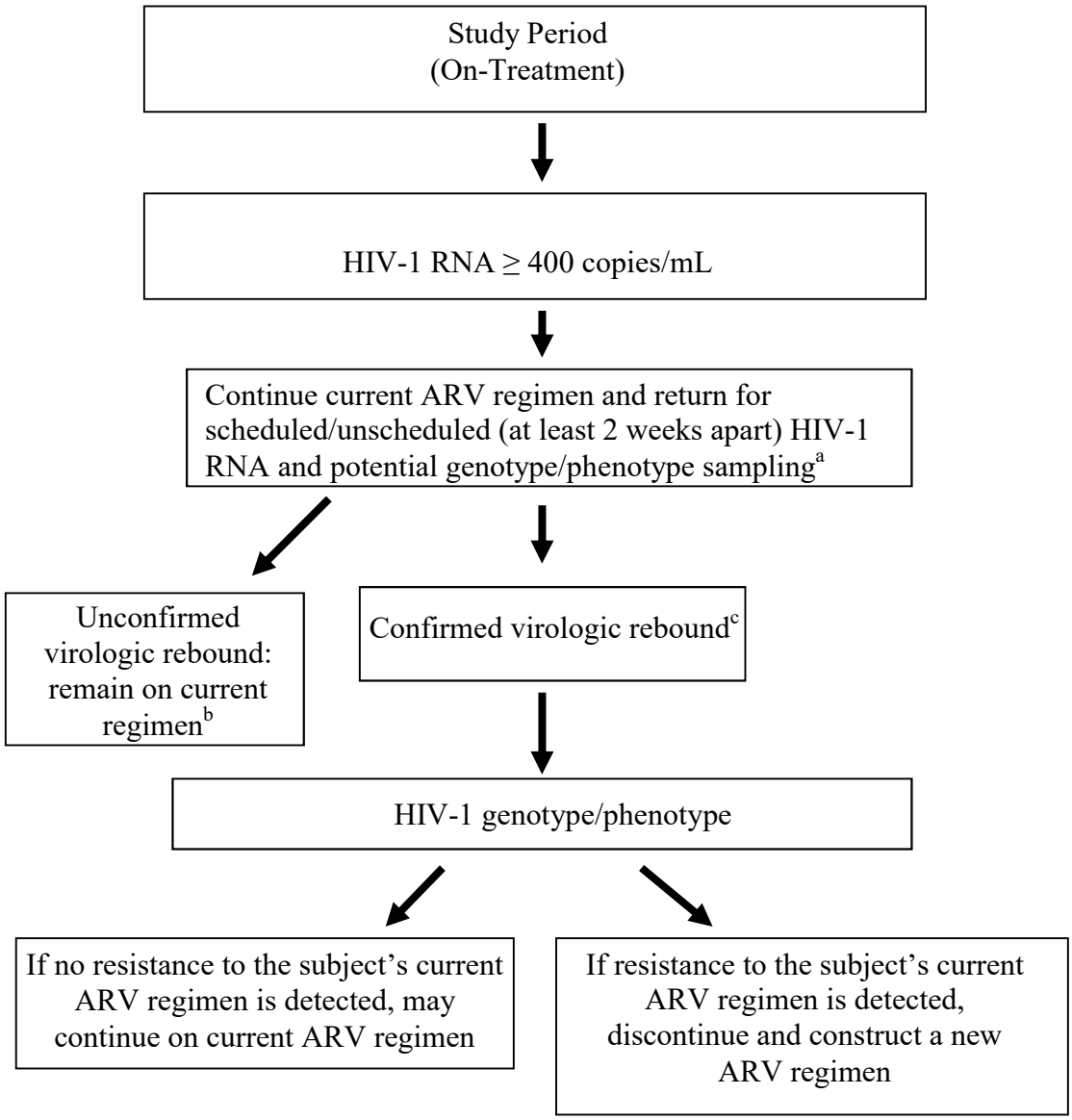
Subjects who have at least two consecutive post-baseline visit plasma HIV-1 RNA levels ≥ 400 copies/mL (at least two weeks apart) will be considered to have HIV virologic rebound.

Following an initial HIV-1 RNA result of ≥ 400 copies/mL, subjects will continue to take their current ARV regimen and be asked to return to the clinic after 2 weeks for a scheduled or unscheduled blood draw for confirmation of HIV virologic rebound. If HIV virologic rebound is confirmed at the scheduled or unscheduled visit, the blood samples from this visit will be used for HIV-1 genotype/phenotype testing. If no resistance to the subject's current ARV regimen is detected, the subject may continue on the current ARV regimen.

HCV study drug should be continued unless safety events warrant the discontinuation of the study drug, as outlined is Section 3.4 of the protocol.

Please refer to Figure 3-1 for the management of subjects who meet the criteria for HIV virologic rebound.

Figure 3-1. HIV Virologic Rebound Schema



a HCV study drug should be continued unless safety events warrant the discontinuation of these study drugs, as outlined in Section 3.4 of the protocol
b If virologic rebound is not confirmed, the subject should remain on their current ARV regimen.
c If virologic rebound is confirmed, the HIV-1 genotype and phenotype (reverse transcriptase and protease) should be analyzed. Based on the results of the genotype and phenotype assays, the subject may remain on their ARV regimen or a new ARV regimen may be configured at the discretion of the Investigator. If the genotype and/or phenotype assay fails to provide results, a new ARV regimen may be configured at the discretion of the Investigator in consultation with the Medical Monitor.

3.6. CCI

CCI

3.6.1. CCI

CCI

3.6.2. CCI

CCI

3.7. Biomarker Testing

3.7.1. Samples for Optional Future Research

CCI

3.7.2. CCI [redacted]

CCI [redacted]

4. SUBJECT POPULATION

Approximately 100 subjects will be enrolled in this study. In order to manage the total study enrollment, Gilead Sciences, Inc., at its discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

4.1. Inclusion Criteria

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

1) Willing and able to provide written informed consent
2) Male or female age ≥ 18 years
3) Chronic HCV infection (≥ 6 months) as documented by prior medical history or liver biopsy
4) HCV RNA ≥ LLOQ at screening
5) Genotype 1,4, 5, and 6 HCV as determined at Screening
6) End stage renal disease (ESRD) requiring peritoneal dialysis (PD) or hemodialysis (HD)
7) The most recent HCV treatment must have been completed at least 8 weeks prior to screening
8) Subjects must have a determination of treatment experience (treatment naïve vs. treatment experienced). Treatment naïve is defined as having never been exposed to an approved or experimental HCV-specific direct acting antiviral agents or prior treatment of HCV with interferon or ribavirin. All other subjects will be considered treatment experienced.
9) Subjects must have appropriate testing for determination of cirrhosis status.
    a) Presence of cirrhosis is defined as any one of the following:
        i) Fibroscan with a result of > 12.5 kPa
        ii) Liver biopsy showing cirrhosis (e.g., Metavir score = 4 or Ishak score ≥ 5)
        iii) In the absence of liver biopsy or availability of Fibroscan, FibroTest® score ≥ 0.75 at screening
    b) Absence of cirrhosis is defined as any one of the following:
        i) Fibroscan with a result of ≤ 12.5 kPa within ≤ 6 months of Baseline/Day 1
        ii) Liver biopsy performed within 2 years of Screening showing absence of cirrhosis
        iii) In the absence of liver biopsy or availability of Fibroscan, FibroTest® score < 0.75 at screening

10) Liver imaging within 6 months of Baseline/Day 1 is required in cirrhotic subjects only, to exclude HCC

11) Subjects with HIV-1 coinfection may be eligible, provided they satisfy these additional inclusion criteria:

    i) Completed at least 3 months of any prior HIV ARV therapy and maintained HIV RNA<50 copies/mL (or <LLOQ if the local laboratory assay's LLOQ is 50 ≥ copies/mL) and CD4 T-cell count > 100 cells/mm^3 prior to Screening. Subjects with an isolated or unconfirmed HIV RNA >50 copies/mL (or >LLOQ if the local laboratory assay's LLOQ is 50≥ copies/mL) are not excluded

    ii) On a stable ARV regimen for ≥ 8 weeks prior to Screening and is expected to continue the current ARV regimen through the end of study (See exclusion criteria 16).

12) A negative serum pregnancy test is required for female subjects (unless permanently sterile or greater than two years post-menopausal).

13) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 4.

14) Lactating females must agree to discontinue nursing before the study drug is administered.

15) Subject must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments

4.2. Exclusion Criteria

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

1) Current or prior history of any of the following:

    a) Clinically-significant illness (other than HCV, HIV and kidney disease or co-morbidities associated with ESRD except as noted below) any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol; subjects currently under evaluation for a potentially clinically significant illness (other than HCV or ESRD) are also excluded.

    b) Current or prior history of significant cardiac disease including or resulting in:

    - Hospital admission for significant cardiovascular disease (myocardial infarction, unstable angina, heart failure, hypertensive emergency) or has had a cardiovascular procedure (e.g. CABG or PTCA), within 6 months of Screening

    - Cardiomyopathy with ejection fraction <50%

c) Gastrointestinal disorder or postoperative condition that could interfere with the absorption of the study drug.

d) Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy.

e) Clinical hepatic decompensation (i.e., ascites, encephalopathy or variceal hemorrhage).

f) Solid organ transplantation other than failed kidney transplants (current use of ≤5 mg/day of prednisone, or equivalent dose of corticosteroid, allowed).

g) Significant pulmonary disease

h) Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 2 years.

i) Malignancy within the 5 years prior to screening, with the exception of specific cancers that have been cured by surgical resection (basal cell skin cancer, etc). Subjects under evaluation for possible malignancy are not eligible

2) Screening ECG with clinically significant abnormalities

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

4) Opportunistic infection (Appendix 5) within 6 months prior to Screening

5) Infection (other than HIV or HCV) requiring parenteral therapy within 30 days prior to baseline.

6) Life threatening SAE during the screening period

7) Subjects have the following laboratory parameters at screening:

a) ALT > 10 X the upper limit of normal (ULN)

b) AST > 10 X ULN

c) Direct bilirubin > 1.5 X ULN. For subjects receiving ritonavir boosted atazanavir regimen, a direct bilirubin > 1.5 x ULN will be allowed if < 25% of the total bilirubin

d) Platelets < 25,000/μL

e) HbA1c > 9%

f) Hemoglobin < 9 g/dL

g) Albumin < 2.8 g/dL

h) INR > 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR

i) Hepatitis B surface antigen positive

8) Prior exposure to any HCV NS5A inhibitor.

9) Male with pregnant female partner.

10) Females who may wish to become pregnant and/or plan to undergo egg harvesting during the course of the study and up to 30 days of the last dose of study drug

11) Males who may wish to donate sperm during the course of the study until at least 30 days after the last dose of study drug.

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

13) Use of any prohibited concomitant medications as described in Section 5.4.

14) Chronic use of systemically administered immunosuppressive agents (e.g., prednisone equivalent > 10 mg/day).

15) Known hypersensitivity to LDV, SOF, the metabolites, or formulation excipient.

16) For subjects with HIV-1 coinfection only:

- HIV-1 RNA >50 copies/mL
- CD4 T-cell count <100 cells/mm3
- HIV-2 positive test

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

This is an open-label study. An Interactive Web Response System (IWRS) will be employed to manage subject enrolment and the study drug dispensing as well as re-supply of study drug.

5.2. Description and Handling of LDV/SOF FDC

5.2.1. 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. In addition to the active ingredients, the LDV/SOF FDC tablets contain the following inactive ingredients: lactose monohydrate, copovidone, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol and FD&C yellow # 6 /sunset yellow FCF aluminum lake.

5.2.2. Packaging and Labeling

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

All LDV/SOF FDC bottles to be distributed to centers in the EU, North America and Asia Pacific shall be labelled to meet all applicable requirements of the US Food and Drug Administration (FDA), Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products and local regulations as applicable.

5.2.3. Storage and Handling

LDV/SOF FDC bottles 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 tablets to complete the entire study will be shipped to the investigator or qualified designee from Gilead Clinical Supply Management Team (or its designee).

5.3. Dosage and Administration of LDV/SOF FDC

LDV/SOF FDC tablet is to be administered once daily with or without food. CCI [redacted]

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.

Study drugs should not be cut or split. LDV/SOF tablets will be provided by Gilead Sciences for all subjects.

5.4. Prior and Concomitant Medications

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

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

- Granulocyte colony stimulating factors (GCSF) and thrombopoietin (TPO) mimetics
- Investigational agents or devices for any indication
- Chronic use of systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab.

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters, i.e., BCRP and P-gp) with study drug may result in PK interactions resulting in increases or decreases in exposure of study drug.

The use of amiodarone is prohibited from **60 days prior to Day 1** through the end of treatment; other examples of representative medications which are prohibited or are to be used with caution from **21 days prior to Day 1** through the end of treatment are listed below in Table 5-1.

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) are not listed under this Concomitant Medication section and are disallowed in the study.

Should subjects have a need to initiate treatment with any excluded concomitant medication, the Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication.

5.5. Accountability for LDV/SOF FDC

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug (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.

5.5.1. Investigational Medicinal Product Return or Disposal

Please refer to Section 9.1.7 for information pertaining to study drug return and disposal.

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. Pretreatment Assessments

6.1.1.1. Screening Visit

Subjects will be screened within 28 days of the Day 1 visit before enrollment to determine eligibility for participation in the study. The screening window can be extended up to 42 days for subjects requiring additional HCV genotyping (if initial testing is inconclusive) or for extenuating circumstances with Sponsor approval.

The following will be performed and documented at screening:

- Obtain written informed consent
  - CCI [redacted]
- Determine inclusion and exclusion eligibility
- Obtain medical history, including:
  - Determination of treatment experience (treatment naïve vs. treatment experienced).
    - Treatment naïve is defined as having never been exposed to an approved or experimental HCV-specific direct acting antiviral agents or prior treatment of HCV with interferon or ribavirin. All other subjects will be considered treatment experienced.
  - Hepatitis C history
    - Regimen(s)
    - Dates of previous treatment(s)

  - Response to previous treatment (e.g., non-responder, relapse, discontinuation including reason)
  - Renal dialysis history
    - Type: hemodialysis or peritoneal dialysis
    - Date of initiation
    - Stop date (if applicable)
  - Renal transplant history (if applicable)
    - Date of transplant
    - Date of transplant failure
    - Current immunosuppression
- Determine cirrhosis status as defined in Section 4.1.
  - Record liver biopsy or Fibroscan results (if applicable)
  - If the presence of cirrhosis is determined, then appropriate diagnostic imaging should be performed or confirmed to have been performed within 6 months of screening to exclude the presence of HCC
- Obtain details of concomitant medications
- Perform 12-lead ECG
- Complete physical examination including vital signs (resting blood pressure, pulse, respiratory rate and temperature), body weight, and height
- Pregnancy prevention counseling
- Obtain blood samples for tests as listed in Section 6.9.1:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Determination of HCV viral genotype and subtype

- HCV antibody, HIV 1/2 antibody, HBV surface antigen (HBsAg), HBV core antibody (HBcAb), and HBV surface antibody (HBsAb)
- HbA1c
- IL28B genotyping
- Serum β-hCG pregnancy test for females of childbearing potential only
- HIV-1 RNA and CD4 cell count will only be collected and analyzed for HIV co-infected subjects
- Fibrotest®
- Serum drug screen

- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

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. The screening window can be extended up to 42 days for extenuating circumstances with Sponsor approval.

Retests of Screening labs are permitted only if the initial exclusionary value was either due to a sample processing error or due to extenuating circumstances such as intercurrent illness.

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 (CRF/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 CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2. Day 1 Assessments

The following baseline tests and procedures must be completed prior to enrollment and dosing/dispensation of study drug:

- Confirm eligibility (See Sections 4.1 & 4.2)
- Perform complete physical examination, including vital signs and body weight
- Perform 12-lead ECG (prior to study drug administration)
- Assessment of AEs and concomitant medications
- Pregnancy prevention counselling

- Subject completes Health Related Quality of Life Questionnaire: SF-36, CLDQ-HCV, FACIT-F, and WPAI
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing/phenotyping
  - Serum β-hCG pregnancy test for females of childbearing potential only
  - HIV-1 RNA and CD4 cell count will only be collected and analyzed for co-infected subjects
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
  - CCI [redacted]
  - Pharmacogenomic sample (for subjects who have consented). May be collected at a subsequent visit if necessary.
- Study Drug Administration
  - Dispense study drug as directed by the IWRS
  - Instruct the subject on the packaging, storage and administration of the study drugs
  - Observe the subject taking the first dose of study drug and record the time of first dose and whether it was taken with or without food.

6.3. Treatment Assessments

6.3.1. Week 2 (± 3 days): Group 1, 2, and 3

The following procedures/assessments are to be completed at the end of Week 2:

- Obtain vital signs
- Assessment of AEs and concomitant medications

- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing/phenotyping
  - Sparse PK sample
- Assess adherence with study drug dosing regimen including pill count

6.3.2. Week 4 (± 3 days): Group 1, 2, and 3

The following procedures/assessments are to be completed at the end of Week 4:

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counselling
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing/phenotyping
  - Sparse PK sample
  - Serum β-hCG pregnancy test for females of childbearing potential only
  - HIV-1 RNA and CD4 cell count will only be collected and analyzed for HIV co-infected subjects
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
- Assess adherence with study drug dosing regimen including pill count
- Dispense study drug as directed by the IWRS

6.3.3. Week 6 (± 3 days): Group 1, 2, and 3

The following procedures/assessments are to be completed at the end of Week 6:

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing/phenotyping
  - Sparse PK sample
  - Intensive PK (for subjects who have consented)
  - Hemodialysis PK (for subjects who have consented)
- Assess adherence with study drug dosing regimen including pill count

6.3.4. Week 8 (± 3 days): Group 2 and 3 (For Group 1 Week 8, see End of Treatment Visit)

The following procedures/assessments are to be completed at the end of Week 8 for Groups 2 and 3 only:

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counselling
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing/phenotyping

- Sparse PK sample
- Serum β-hCG pregnancy test for females of childbearing potential only
- HIV-1 RNA and CD4 cell count will only be collected and analyzed for HIV co-infected subjects
- HBV DNA (only in subjects who are HBcAb+ at Screening)
- Intensive PK (for subjects who have consented)
- Hemodialysis PK (for subjects who have consented)

- Assess adherence with study drug dosing regimen including pill count
- Dispense study drug as directed by the IWRS

6.3.5. Week 12, 16, and 20 (± 3 days): Group 3 (For Group 2 Week 12, see End of Treatment Visit)

The following procedures/assessments are to be completed at the end of Week 12, 16, and 20 for Group 3 only:

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counselling
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing/phenotyping
  - HIV-1 RNA and CD4 cell count will only be collected and analyzed for HIV co-infected subjects
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
  - Sparse PK sample

- Serum β-hCG pregnancy test for females of childbearing potential only
- Week 12 only: Intensive PK (for subjects who have consented)
- Week 12 only: Hemodialysis PK (for subjects who have consented)

- Assess adherence with study drug dosing regimen including pill count
- Dispense study drug as directed by the IWRS

6.3.6. End of Treatment Visit: Group 1 Week 8 (± 3 days), Group 2 Week 12 (± 3 days), Group 3 Week 24 (± 3 days) or Early Termination (ET)

The following procedures/assessments are to be completed at the end of Week 24/ET:

- Perform complete physical examination, including vital signs and body weight
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes Health Related Quality of Life Questionnaire: SF-36, CLDQ-HCV, FACIT-F, and WPAI
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing/phenotyping
  - HIV-1 RNA and CD4 cell count will only be collected and analyzed for HIV co-infected subjects
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
  - Sparse PK sample
  - Serum β-hCG pregnancy test for females of childbearing potential only

  - — CCI [redacted]
  - — Group 1, Week 8: Intensive PK (for subjects who have consented)
  - — Group 1, Week 8: Hemodialysis PK (for subjects who have consented)
  - — Group 2, Week12: Intensive PK (for subjects who have consented)
  - — Group 2, Week 12: Hemodialysis PK (for subjects who have consented)
- Assess adherence with study drug dosing regimen including pill count
- Subjects should return all bottles of study drug

6.4. Post-treatment Assessments

6.4.1. Posttreatment Week 4 Visit (± 5 days): Group 1, Group 2, and Group 3

The following procedures/assessments are to be completed at Posttreatment Week 4:

- Perform complete physical examination, including vital signs
- Assessment of AEs and concomitant medications
- Pregnancy prevention counselling
- Subject completes Health Related Quality of Life Questionnaire: SF-36, CLDQ-HCV, FACIT-F, and WPAI
- Obtain blood samples for:
  - — Hematology
  - — Chemistry
  - — HCV RNA
  - — Viral sequencing/phenotyping
  - — HIV-1 RNA and CD4 cell count will only be collected and analyzed for HIV co-infected subjects
  - — HBV DNA (only in subjects who are HBcAb+ at Screening)
  - — Serum β-hCG pregnancy test for females of childbearing potential only

6.4.2. Posttreatment Week 12 Visit (± 5 days): Group 1, Group 2 and Group 3

The following procedures/assessments are to be completed at Posttreatment Week 12 and 24:

- Perform complete physical examination, including vital signs
- Assessment of SAEs
- Subject completes Health Related Quality of Life Questionnaire: SF-36, CLDQ-HCV, FACIT-F, and WPAI
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
  - Viral sequencing/phenotyping

6.4.3. Posttreatment Week 24 Visit (±5 Days): Only for Subjects who Achieved SVR12

The following procedures/assessments are to be completed at Posttreatment Week 24:

- Perform complete physical examination, including vital signs
- Assessment of SAEs
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
  - Viral sequencing/phenotyping

6.5. Early Termination (ET)

For subjects who have completed an ET visit, the posttreatment Week 4 and 12 follow-up visits will be scheduled after last dose of any of the study drug. Subjects who achieve SVR12 (HCV RNA < LLOQ at posttreatment Week 12) will complete the posttreatment Week 24 visit.

When medically feasible, the medical monitor must be consulted prior to subject discontinuation. If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 3.4, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.6. 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. At all unscheduled visits initiated for the purpose of confirming HCV or HIV virologic failure and a sample for HCV or HIV viral sequencing/phenotyping must be collected.

6.7. End of Study

The end of study will occur at the posttreatment Week 24 visit.

Discontinuation from study drug dosing and discontinuation from the overall study, including the Posttreatment period, will be collected as two separate events.

6.8. Post Study Care

No post study ongoing care will be provided.

6.9. Procedures and Specifications

6.9.1. 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 mean corpuscular volume (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, direct bilirubin; glucose, potassium, and sodium. Fibrotest® will be done at screening only.

Virological Tests: Serologies for HCV and HBV (HBsAg, HBsAb, and HBcAb). HBV DNA (only in subjects who are HBcAb+ at Screening). Serology testing for HIV (including reflex testing as necessary), HCV RNA will be measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 for Use with the High Pure System, HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype, INNO-LiPA 2.0 Assay. HIV-1 RNA will be measured using the AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0. If HIV-1 virologic rebound is confirmed, HIV-1 genotype/phenotype will be determined using the PhenoSense™ Integrase HIV, GeneSeq™ Integrase HIV, PhenoSense™ HIV, GenoSure MG, GeneSeq™ HIV, and PhenoSense GT™.

Gilead reserves the right to use alternate assays for HCV RNA, HIV RNA, HCV genotype, and HIV-1 genotype/phenotype should the above assays become unavailable or the results are not definitive.

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

Pregnancy Tests: Serum β-hCG

Additional Tests: Serum drug screen (for amphetamines, cocaine, methadone, opiates), HbA1c, CD4 T-lymphocyte (absolute count and %)

6.9.2. 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. Obtain HCV treatment, renal dialysis, and kidney transplant history as per Section 4.

6.9.3. Complete Physical Examination

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

6.9.4. Height & Weight Measurement

Height will be collected at Screening. Weight measurement will be collected at Screening, Day 1 and Week 8 (Group 1), Week 12 (Group 2), Week 24 (Group 3) or ET visits

6.9.5. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and temperature and will be conducted pre-dose as outlined in Appendix Table 1, Appendix Table 2 and Appendix Table 3.

Blood pressure will be measured using the following standardized process:

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

6.9.6. Body Mass Index (BMI)

BMI is calculated by the following equation:

$$\text{BMI} = \frac{\text{weight (pounds)}}{(\text{height in inches})^2} \quad \text{or} \quad \frac{\text{Weight in kilograms}}{(\text{height in meters})^2}$$

6.9.7. 12-Lead ECG

Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording.

The Investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities. End of treatment or ET results will be compared to the subject's Day 1 ECG as part of routine safety monitoring.

6.9.8. Health Related Quality of Life (HRQoL)

Health Related Quality of Life surveys (HRQoL) included in this study are the SF-36, Chronic Liver Disease Questionnaire (CLDQ-HCV), Fatigue Index (FACIT-F), and Work Productivity and Activity Impairment Questionnaire: Hepatitis C, v2.0 (WPAI: Hepatitis C) which will be completed by subjects at Day 1, and at the on-treatment Week 8 (Group 1), Week 12 (Group 2), Week 24 (Group 3) visits, ET (if applicable), and posttreatment Week 12 visit.

The Health Related Quality of Life surveys (HRQoL) will only be administered to subjects if available at Day 1. The subject should read the questionnaire by himself/herself and record the answers by himself/herself.

6.9.9. Viral Sequencing/Phenotyping (Archive)

Plasma samples will be collected at Day 1 and each subsequent visit for HCV or HIV viral sequence and phenotyping analysis. At any unscheduled visit initiated for the purpose of confirming HCV virologic breakthrough, HCV viral sequencing/phenotype plasma sample must also be collected. Unused samples may be archived.

Details regarding the collection, processing, and shipping of samples will be included in the lab manual.

6.9.10. Sparse PK Sample

Sparse PK blood samples will be collected for all subjects at each on-treatment visit and archived for PK analysis of LDV and SOF (and metabolites).

The exact time of the dose taken prior to collection of the PK sample, the exact time the PK sample is drawn, the exact time of completion of last dialysis, and the type of dialysis (peritoneal or hemodialysis) will be recorded in source documents and eCRFs.

Details regarding the collection, processing, and shipping of samples will be included in the lab manual.

6.9.11. CCI

CCI

6.9.12. CCI

CCI

CCI [redacted]

[redacted].

6.9.13. Pharmacogenomics Testing

For subjects who provide specific and separate consent to participate will allow the Sponsor to obtain and test a subject's blood sample taken on Baseline/Day 1 for pharmacogenomics discovery research. If not obtained at Baseline/Day 1, the sample may be drawn at any time during the study. CCI [redacted]

6.9.14. Archive sample

CCI [redacted]

6.9.15. Pregnancy Testing

All females of childbearing potential will have serum pregnancy testing every 4 weeks during the dosing period and 30 days after last dose of LDV/SOF, or the last visit of the study, whichever comes last.

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, lack of efficacy, 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 7.5.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

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 (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).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.

7.1.4. 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 (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

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

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

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

7.1.5. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 3). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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

7.2.1. 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 all adverse events related to protocol-mandated procedures.

7.2.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study IMP and report 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.

7.2.3. 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 CRF/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.

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 IMP, he/she should promptly document and report the event to Gilead DSPH.

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

7.2.4. Electronic Serious Adverse Event (eSAE) Reporting Process

Site personnel must record all SAE data in the eCRF database and 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 it is not possible to record and submit the SAE information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the SAE on the paper serious adverse event report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event 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 CRF/eCRF and the event description section of the SAE form.

7.3. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or

suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

7.4. Toxicity Management

7.4.1. Subject Stopping Rules

See Section 3.4 for individual subject stopping rules.

7.5. Special Situations Reports

7.5.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, occupational exposure with an AE, pregnancy reports regardless of an associated AE, and an AE in an infant following exposure from breastfeeding.

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.

7.5.2. Instructions for Reporting Special Situations

7.5.2.1. 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 using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.2 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 (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. 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
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.

Email: PPD
Fax: PPD

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

7.5.2.2. Reporting Other Special Situations

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

Special situations involving non-Gilead concomitant medications 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 7.5 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are as follows:

- To evaluate the antiviral efficacy of treatment with ledipasvir/sofosbuvir (LDV/SOF) for 8, 12 or 24 weeks in subjects as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of each treatment regimen

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 each study treatment regimen (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to LDV and SOF during treatment and after cessation of treatment
- To evaluate the steady-state pharmacokinetics of LDV and SOF and its metabolites in subjects who are on dialysis for ESRD

The exploratory objectives of this study are:

8.1.2. Primary Endpoint

The primary end point is SVR12 (HCV RNA < LLOQ 12 weeks after cessation of treatment) in the Full Analysis Set (FAS) population.

The primary safety endpoint is any AE that led to permanent discontinuation of study drug.

8.1.3. Secondary Endpoint

Secondary endpoints include the following:

- The proportion of subjects with HCV RNA < LLOQ at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- The proportion of subjects with HCV RNA < LLOQ on treatment
- HCV RNA change from Baseline/Day 1
- The proportion of subjects with virologic failure
- The proportion of subjects who develop viral resistance to LDV and SOF during treatment and after cessation of treatment
- The steady-state pharmacokinetics of LDV and SOF and its metabolites

8.1.4. Other Endpoints of Interest

Additional efficacy evaluations may include effect of treatment with LDV/SOF on HRQoL endpoints.

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 drugs in this study are 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 posttreatment time points.

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

8.2.1.2. Safety

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all subjects who took at least 1 dose of study drug.

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

8.2.1.3. Pharmacokinetics

The PK Analysis Set includes all subjects who took at least 1 dose of the study drug and have at least 1 nonmissing postdose concentration value for the corresponding analyte in plasma. The analytes of interest may include LDV and SOF (and its metabolites GS-566500 and GS-331007).

8.2.1.3.1. CCI

CCI

8.2.1.3.2. CCI

CCI

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 posttreatment HCV RNA data will have the missing data imputed. Missing on-treatment HCV RNA will have the missing data imputed up to the time of the last dose.

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 (i.e., ≥ LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (i.e., ≥ 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).

For PK plasma/blood concentrations and analysis of PK parameters natural logarithmic transformation will be used. For the intensive PK samples, plasma concentration values that are below the lower limit of quantitation (BLQ) will be presented as “BLQ” in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the lower limit of quantitation (LLOQ) at postbaseline time points, where LLOQ is corrected for the dilution factor (i.e., reported LLOQ/dilution factor) for determination of summary and order statistics.

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

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by treatment group and overall.

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

Baseline data will include a summary of body mass index, HCV RNA level (log10 IU/mL), genotype and subtype of HCV infection, IL28B genotype, and additional endpoint as necessary.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint is SVR12 in the Full Analysis Set (FAS) population.

In the primary efficacy analysis, the point estimate and the 2-sided 95% exact confidence interval of SVR12 rate will be provided for the overall FAS population and by treatment group.

8.5.2. Secondary Analyses

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

Descriptive summaries and listings will be provided for additional efficacy evaluations of the proportion of subjects who experience virologic failure, HCV RNA actual values and change from baseline.

CCI [redacted]

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 (including HIV-1 RNA and CD4 T-cell count for HCV/HIV co-infection subjects), 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 by treatment group 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 CRF. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

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

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

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, and PT) will be provided by treatment group:

- 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
- All AEs leading to temporary interruption of the study drug

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

8.6.3. Laboratory Evaluations

Graded laboratory abnormalities will be defined using the laboratory toxicity grading defined in Appendix 3. 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 postbaseline, up to the date of last dose of study drug plus 30 days will be summarized by treatment group.

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.

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

8.7. Other Safety Evaluations

Individual data for 12-lead ECG, vital signs measurements will be listed by subject and summarized by treatment group by incidence of events/abnormalities or descriptive statistical summaries (n, mean, SD, median, Q1, Q3, minimum, and maximum), as appropriate.

8.8. Pharmacokinetic Analysis

In the PK analysis set, plasma concentrations of the study drug over time will be listed. Details of the analysis will be provided in the pharmacokinetic reporting and analysis plan.

CCI [redacted]

8.9. Sample Size

With a sample size of 100 subjects, a 2-sided 95% exact confidence interval will extend at the most 20% in length.

8.10. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform an interim review of safety data once the first 12 subjects have completed 8 weeks of treatment, or early termination. After the initial meeting, safety reviews will be conducted at approximately 3 month intervals during the trial until the last enrolled subject completes study treatment. These safety reviews will alternate between the following:

- A review by the DMC chair of all SAEs and deaths
- A review of safety data by the DMC meeting as specified in the DMC charter

The DMC will provide recommendation to Gilead on whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design, conduct, and the need for additional meetings or an alternative meeting schedule. The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

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

9. 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 (IECReview 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/EC 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 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/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/IEC local requirements.The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

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/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions for further details.

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/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 (i.e., 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 casebook will be completed by an authorized study staff member whose training for this function is completed in EDC. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs 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. 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). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to any interim time points or database lock (as instructed by Gilead), 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. 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

Where possible, IMP should be destroyed at the site. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of used and unused IMP supplies.

The study monitor will provide instructions for return.

The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused IMP 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 IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead. Refer to the Pharmacy Binder for study drug disposal/return instructions.

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/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/IECs in accordance with local requirements and receive documented IRB/IECs 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 CRF/eCRF.

The monitor is responsible for routine review of the CRF/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 CRF/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.

10. REFERENCES

AbbVie Inc. VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets, for oral use. US Prescribing Information. North Chicago, IL. Revised July. 2016:

Allison RD, Tong X, Moorman AC, Ly KN, Rupp L, Xu F, et al. Increased Incidence of Cancer and Cancer-related Mortality Among Persons with Chronic Hepatitis C Infection, 2006-2010. J Hepatol 2015.

Arias A, Aguilera A, Soriano V, Benitez-Gutierrez L, Lledo G, Navarro D, et al. Rate and predictors of treatment failure to all-oral HCV regimens outside clinical trials. Antivir Ther 2016.

Bhamidimarri KR, Czul F, Peyton A, Levy C, Hernandez M, Jeffers L, et al. Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of Hepatitis C in patients with end stage renal disease. J Hepatol 2015;63 (3):763-5.

Bristol-Myers Squibb. DAKLINZA™ (daclatasvir) tablets, for oral use. US Prescribing Information. Princeton, NJ. Revised April. 2016:

Desnoyer A, Pospai D, Le MP, Gervais A, Heurgue-Berlot A, Laradi A, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C [Article in Press]. J Hepatol 2016.

Fabrizi F, Takkouche B, Lunghi G, Dixit V, Messa P, Martin P. The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies. J Viral Hepat 2007;14 (10):697-703.

Gilead Sciences Inc. HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised November 2015a:

Gilead Sciences Inc. SOVALDI® (sofosbuvir) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised August 2015b:

Gilead Sciences Inc. EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised June. 2016:

Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014.

Hundemer GL, Sise ME, Wisocky J, Ufere N, Friedman LS, Corey KE, et al. Use of sofosbuvir-based direct-acting antiviral therapy for hepatitis C viral infection in patients with severe renal insufficiency. Infectious diseases 2015;47 (12):924-9.

Ioannou GN, Beste LA, Chang MF, Green PK, Lowey E, Tsui JI, et al. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Healthcare System [Accepted Manuscript]. Gastroenterology 2016;151:457-71.

Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney international. Supplement 2008 (109):S1-99.

Merck & Co Inc. ZEPATIER™ (elbasvir and grazoprevir) tablets, for oral use. US Prescribing Information. Whitehouse Station, NJ. Revised January. 2016:

Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of Hepatitis C Virus Infection and the Development of Hepatocellular Carcinoma. Ann Intern Med 2013;158 (5 (Part I)).

Navarro-Millan I, Sattui SE, Curtis JR. Systematic review of tumor necrosis factor inhibitor discontinuation studies in rheumatoid arthritis. Clin Ther 2013;35 (11):1850-61 e1.

Nazario HE, Ndungu M, Modi AA. Sofosbuvir and simeprevir in hepatitis C genotype 1-patients with end-stage renal disease on haemodialysis or GFR <30 ml/min. Liver Int 2016;36 (6):798-801.

Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45 (4):529-38.

Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122 (5):1303-13.

van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308 (24):2584-93.

Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147 (10):677-84.

World Health Organization (WHO). Hepatitis C Fact Sheet No. 164. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/#. Accessed 20 June 2014:1-7.

11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Ledipasvir/Sofosbuvir in Subjects with Genotype 1, 4, 5 and 6 Chronic HCV Infection Who are on Dialysis for End Stage Renal Disease

GS-US-337-4063, Amendment 3.0, 02 March 2017

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

PPD

PPD
Medical Monitor

PPD

Signature

March 2, 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 Table

Appendix Table 1. Screening/Baseline/ On-Treatment and Post Treatment Study Visits for Group 1

			On-Treatment Week (±3 Days)				Post-Treatment Week (±5 Days)		
	Screen	Baseline/Day 1[a]	2	4	6	8/ET	4	12	24
Informed Consent	X								
Determine Eligibility	X	X							
Medical History	X								
Physical Examination	X	X				X	X	X	X
Height	X								
Weight	X	X				X			
Vital Signs	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X				X			
AEs/SAE[b]	X	X	X	X	X	X	X	X[b]	X[b]
Concomitant Medications	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling	X	X		X		X	X		
Health-Related Quality of Life[c]		X				X		X	
Review of Study Medication Compliance			X	X	X	X			
Study Drug Dispensing[d]		X		X					
Hematology, Chemistry	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X				X			
HCV RNA	X	X	X	X	X	X	X	X	X
Viral Sequencing/Phenotyping[e]		X	X	X	X	X	X	X	X
Sparse PK			X	X	X	X			
Intensive PK [g, h]					X[h]	X[h]			

	Screen	Baseline/Day 1[a]	On-Treatment Week (±3 Days)				Post-Treatment Week (±5 Days)		
			2	4	6	8/ET	4	12	24
Hemodialysis PK[g, i]					X[i]	X[i]			
Serum β-hCG Pregnancy Test[j]	X	X		X		X	X		
Serum Drug Screen	X								
HCV & IL28B Genotyping	X								
HCV, HIV, HBV Serology	X								
HBV DNA[k]		X		X		X	X	X	X
HbA1c	X								
Fibrotest®	X								
Archive Sample[f]		X				X			
Pharmacogenomic Sample[f]		X							
CD4 Cell Count[l]	X	X		X		X	X		
HIV-1 RNA[l]	X	X		X		X	X		

a Baseline/Day 1 assessments must be performed prior to dosing
b Only SAEs will be collected at post-treatment Weeks 12 and 24.
c Health Related Quality of Life (HRQoL) Surveys (e.g., SF-36, CLDQ-HCV, FACIT-F and WPAI) will be conducted for all subjects where the surveys are available at Day 1, Week 8, ET (if applicable), and posttreatment Week 12.
d The IWRS will provide direction on the specifics of each subject's study drug dispensing
e. Plasma samples will be collected for possible viral resistance testing and other virology studies
f Subjects may opt out of archive/pharmacogenomics sample collection.
g Only for subjects who have provided consent for this sample and testing.
h Intensive PK evaluations will be assessed at the following timepoints: 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6 ,8, 10, and 12 hours post dose once either on Week 6 or 8, per investigator discretion.
i Hemodialysis PK blood samples will be collected at one hemodialysis session between Week 6 and Week 12, inclusive (as appropriate based on treatment group), evaluations will include: 1. A single blood sample will be collected within 10 minutes before hemodialysis initiates. 2. During hemodialysis, a single sample will be collected from both the arterial and venous sides of the dialyzer within 1 hour of hemodialysis concluding. 3. Finally, a single blood sample will be collected within 10 minutes after hemodialysis concludes.
j For females of child bearing potential only
k. Only for subjects who are HBcAb+ at Screening
l For HIV/HCV co-infected subjects only.

Appendix Table 2. Screening/Baseline/ On-Treatment and Post Treatment Study Visits for Group 2

			On-Treatment Week (±3 Days)					Post-Treatment Week (±5 Days)		
	Screen	Baseline/Day1[a]	2	4	6	8	12/ET	4	12	24
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X					X	X	X	X
Height	X									
Weight	X	X					X			
Vital Signs	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X					X			
AEs/SAE[b]	X	X	X	X	X	X	X	X	X[b]	X[b]
Concomitant Medications	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling	X	X		X		X	X	X		
Health-Related Quality of Life[c]		X					X		X	
Review of Study Medication Compliance			X	X	X	X	X			
Study Drug Dispensing[d]		X		X		X				
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X					X			
HCV RNA	X	X	X	X	X	X	X	X	X	X
Viral Sequencing/Phenotyping[e]		X	X	X	X	X	X	X	X	X
Sparse PK			X	X	X	X	X			
Intensive PK [g, h]					X[h]	X[h]	X[h]			
Hemodialysis PK[g, i]					X[i]	X[i]	X[i]			

	Screen	Baseline/Day1[a]	On-Treatment Week (±3 Days)					Post-Treatment Week (±5 Days)		
			2	4	6	8	12/ET	4	12	24
Serum β-hCG Pregnancy Test[j]	X	X		X		X	X	X		
Serum Drug Screen	X									
HCV & IL28B Genotyping	X									
HCV, HIV, HBV Serology	X									
HBV DNA[k]		X		X		X	X	X	X	X
HbA1c	X									
Fibrotest®	X									
Archive Sample[f]		X					X			
Pharmacogenomic Sample[f]		X								
CD4 Cell Count[l]	X	X		X		X	X	X		
HIV-1 RNA[l]	X	X		X		X	X	X		

a Baseline/Day 1 assessments must be performed prior to dosing
b Only SAEs will be collected at post-treatment Weeks 12 and 24.
c Health Related Quality of Life (HRQoL) Surveys (e.g., SF-36, CLDQ-HCV, FACIT-F and WPAI) will be conducted for all subjects where the surveys are available at Day 1, Week 12, ET (if applicable), and posttreatment Week 12.
d The IWRS will provide direction on the specifics of each subject's study drug dispensing
e Plasma samples will be collected for possible viral resistance testing and other virology studies
f Subjects may opt out of archive/pharmacogenomics sample collection.
g Only for subjects who have provided consent for this sample and testing.
h Intensive PK evaluations will be assessed at the following timepoints: 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6 ,8, 10, and 12 hours post dose once either on Week 6, 8, or 12 per investigator discretion.
i Hemodialysis PK blood samples will be collected at one hemodialysis session between Week 6 and Week 12, inclusive (as appropriate based on treatment regimen), evaluations will include: 1. A single blood sample will be collected within 10 minutes before hemodialysis initiates. 2. During hemodialysis, a single sample will be collected from both the arterial and venous sides of the dialyzer within 1 hour of hemodialysis concluding. 3. Finally, a single blood sample will be collected within 10 minutes after hemodialysis concludes.
j For females of child bearing potential
k. Only for subjects who are HBcAb+ at Screening
l For HIV/HCV co-infected subjects only.

Appendix Table 3. Screening/Baseline/ On-Treatment and Post Treatment Study Visits for Group 3

			On-Treatment Week (±3 Days)								Post-Treatment Week (±5 Days)		
	Screen	Baseline/Day1[a]	2	4	6	8	12	16	20	24/ET	4	12	24
Informed Consent	X												
Determine Eligibility	X	X											
Medical History	X												
Physical Examination	X	X								X	X	X	X
Height	X												
Weight	X	X								X			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X								X			
AEs/SAE[b]	X	X	X	X	X	X	X	X	X	X	X	X[b]	X[b]
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling	X	X		X		X	X	X	X	X	X		
Health-Related Quality of Life[c]		X								X		X	
Review of Study Medication Compliance			X	X	X	X	X	X	X	X			
Study Drug Dispensing[d]		X		X		X	X	X	X				
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X								X			
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral Sequencing/ Phenotyping[e]		X	X	X	X	X	X	X	X	X	X	X	X
Sparse PK			X	X	X	X	X	X	X	X			
Intensive PK[g, h]					X[h]	X[h]	X[h]						
Hemodialysis PK[g, i]					X[i]	X[i]	X[i]						

			On-Treatment Week (±3 Days)								Post-Treatment Week (±5 Days)		
	Screen	**Baseline/Day1[a]**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24/ET**	**4**	**12**	**24**
Serum β-hCG Pregnancy Test[j]	X	X		X		X	X	X	X	X	X		
Serum Drug Screen	X												
HCV & IL28B Genotyping	X												
HCV, HIV, HBV Serology	X												
HBV DNA[k]		X		X		X	X	X	X	X	X	X	X
HbA1c	X												
Fibrotest®	X												
Archive Sample[f]		X								X			
Pharmacogenomic Sample[f]		X											
CD4 Cell Count[l]	X	X		X		X	X	X	X	X	X		
HIV-1 RNA[l]	X	X		X		X	X	X	X	X	X		

a Baseline/Day 1 assessments must be performed prior to dosing
b Only SAEs will be collected at post-treatment Weeks 12 and 24.
c Health Related Quality of Life (HRQoL) Surveys (e.g., SF-36, CLDQ-HCV, FACIT-F and WPAI) will be conducted for all subjects where the surveys are available at Day 1, Week 24, ET (if applicable), and posttreatment Week 12.
d The IWRS will provide direction on the specifics of each subject's study drug dispensing
e Plasma samples will be collected for possible viral resistance testing and other virology studies
f Subjects may opt out of archive/pharmacogenomics sample collection.
g Only for subjects who have provided consent for this sample and testing.
h Intensive PK evaluations will be assessed at the following timepoints: 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6 ,8, 10, and 12 hours post dose once either on Week 6 8, or 12 per investigator discretion.
i Hemodialysis PK blood samples will be collected at one hemodialysis session between Week 6 and Week 12, inclusive (as appropriate based on treatment regimen), evaluations will include: 1. A single blood sample will be collected within 10 minutes before hemodialysis initiates. 2. During hemodialysis, a single sample will be collected from both the arterial and venous sides of the dialyzer within 1 hour of hemodialysis concluding. 3. Finally a single blood sample will be collected within 10 minutes after hemodialysis concludes.
j For females of child bearing potential
k. Only for subjects who are HBcAb+ at Screening
l For HIV/HCV co-infected subjects only.

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

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months**[#]	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) Adult	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
LDL (Fasting) Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

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

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

Notes:

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

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

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

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

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

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

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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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 (e.g., 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 (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (e.g., 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 (e.g., 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 (e.g., hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (e.g., 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 (e.g., 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 weakness 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 (e.g., status epilepticus), or difficult to control (e.g., 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 (e.g., severity or focality)	Seizures of any kind that are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., 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	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	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)
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 (e.g., 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 of 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

The data of LDV/SOF on pregnant women is limited or not available. There is no suspicion of human teratogenicity based on class effects or genotoxic potential. Relevant non clinical reproductive toxicity studies for human pregnancy do not indicate a strong suspicion of human teratogenicity/fetotoxicity. Data from clinical pharmacokinetic interaction studies of LDV/SOF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception or that the effect on hormonal contraception is insignificant. Please refer to the latest version of the investigator's brochure for additional information.

b) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to enrollment. Thereafter, a pregnancy test will be performed every 4 weeks through the posttreatment Week 4 visit. Female subjects 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 an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom from the date of Screening until 30 days after the last dose of LDV/SOF.

  — Intrauterine device (IUD)

  — Intrauterine hormone-releasing system (IUS)

  — Bilateral tubal sterilization

  — Essure® micro-insert system

  — Vasectomy in the male partner

  — Barrier methods

    ■ Female barriers: Diaphragm with spermicide or cervical cap with spermicide

  — Hormonal methods

    ■ Oral contraceptives (either combined or progesterone only)

    ■ Injectable progesterone

    ■ Implants of levonorgestrel or etonorgestrel

    ■ Transdermal contraceptive patch

    ■ Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

3) Contraception Requirements for Male 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 LDV/SOF.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last dose of LDV/SOF. 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 during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.5.2.1.

Appendix 5. Opportunistic Infections

Non-inclusive list of opportunistic infections base on AIDS-Indicator Conditions from CDC Classification System for HIV Infection Clinical Category C:

- Bacterial pneumonia, recurrent (two or more episodes in 12 months)
- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month in duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month in duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1-month in duration)
- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- *Mycobacterium avium* complex (MAC) or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, pulmonary or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- *Salmonella* septicemia, recurrent (nontyphoid)
- Toxoplasmosis of brain
- Wasting syndrome caused by HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (two or more loose stools per day for ≥1 month) or chronic weakness and documented fever for ≥1 month