CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24 Weeks in Genotype 1 or 3 and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablet for 12 weeks in Genotype 1 or 4 HCV-Infected Subjects with Renal Insufficiency
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
IND No.:	106739
EudraCT No:	2013-002897-30
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-334-0154
Gilead Sciences Study Director	Name: PPD Telephone: PPD Fax: PPD E-mail: PPD
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PROTOCOL SYNOPSIS

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IND Number:	106739
Eudra CT Number:	2013-002897-30
Study Centers Planned:	Multiple sites in New Zealand, Europe, North America and South America
Number of Subjects Planned:	Approximately 35 subjects
Target Population:	Adults with chronic renal insufficiency and HCV infection
Treatment Duration:	12 weeks or 24 weeks
Objectives:	The primary objectives of this study are: • To evaluate the safety of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks and LDV/SOF for 12 weeks as assessed by review of the accumulated safety data in each treatment arm • To evaluate the efficacy of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks and LDV/SOF for 12 weeks measured by the proportion of subjects with renal insufficiency who have achieved a sustained viral response 12 weeks after treatment discontinuation (SVR12) in each treatment arm • To evaluate the steady state pharmacokinetics of SOF and its metabolites and LDV upon dosing SOF 200 mg or 400 mg or LDV/SOF in subjects with renal insufficiency

The secondary objectives of this study are:

- To evaluate the proportion of subjects with renal insufficiency who attain SVR at 4 and 24 weeks after discontinuation of treatment (SVR4 and SVR24)
- To evaluate the kinetics of plasma HCV RNA during and after treatment discontinuation
- To evaluate the emergence of viral resistance to SOF and LDV during and after treatment discontinuation

The exploratory objective of this study is:

PPD [redacted]

Study Design:

This study will enroll approximately 35 subjects with severe renal insufficiency.

- Cohort 1: 10 subjects will receive SOF 200 mg QD + RBV 200 mg QD for 24 weeks.
- Cohort 2: Following review of safety, efficacy and PK data through post-treatment Week 4 of Cohort 1, 10 additional subjects will receive SOF 400 mg QD + RBV 200 mg QD for 24 weeks.
- Cohort 3: Following review of safety and available PK data through Week 12 of Cohort 2, 15 additional subjects will receive LDV/SOF QD for 12 weeks.

Diagnosis and Main Eligibility Criteria:

Adults (≥ 18 years) with chronic genotype 1 or genotype 3 (for Cohorts 1 and 2) or genotype 1 or 4 (for Cohort 3) HCV infection. Reference Sections 4.2 and 4.3 for detailed Inclusion and Exclusion criteria.

Study Procedures/ Frequency:

Screening assessments will be completed within 42 days of the Day 1 visit.

Study visits will occur at Screening, Day 1, and at the end of Weeks 1, 2, 4, 6, 8, 10, 12 (all cohorts), and Weeks 16, 20 and 24 (Cohorts 1 and 2 only) and at Post-Treatment Weeks 4, 12, and 24 (all cohorts). Screening assessments will include physical examination, height, weight, vital signs, 12-lead ECG, echocardiogram, concomitant medications, safety laboratory tests,

HCV RNA, serology (HIV, HCV, HBV), hemoglobin A1c (HbA1c), serum β-hCG (females of child bearing potential only), IL28B genotyping.

On-treatment assessments will include adverse events (AEs), concomitant medications, study medication pill count, physical examination, vital signs, 12-lead ECGs, echocardiogram, safety laboratory tests, HCV RNA, pharmacokinetic samples, and serum pregnancy tests (females of child bearing potential only).

Post-treatment assessments will include AEs, concomitant medications, vital signs, safety laboratory tests, HCV RNA, and serum pregnancy tests (females of child bearing potential only).

Samples for viral RNA sequencing will be collected at Day 1 and every visit thereafter. Samples will be collected during treatment visits for PK analysis of study drug(s).

PK assessments

Intensive PK Assessments

Cohorts 1 and 2:

Serial blood samples will be collected on week 2 and 12 at the following timepoints:

- 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose.

Cohort 3:

Serial blood samples will be collected once either on week 2 or 4 (per investigator discretion) at the following timepoints:

- 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose.

Plasma concentrations of SOF and its metabolites and LDV will be determined and PK parameters will be estimated as appropriate. Plasma concentrations of RBV may be determined, if necessary.

Trough PK Assessments:

Trough PK plasma samples for analyses of SOF, its metabolites, RBV (as applicable) and LDV concentrations will be collected at all other on treatment visits beginning at the Week 1 visit.

PK Parameters for SOF, its metabolites, LDV and RBV will be estimated as appropriate.

	Optional Genetic Sample Collection PPD **Archived Plasma Sample** Archive plasma samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing and other possible predictors of response as determined by Gilead.
Test Product, Dose, and Mode of Administration:	Sofosbuvir is manufactured as 100 mg and 400 mg tablets for oral administration. Subjects enrolled to take the 200 mg dose will take 2 × 100 mg tablets for a total dose of 200 mg orally QD in the morning with RBV and with food. Subjects enrolled to take the 400 mg dose will take 1 × 400 mg tablet for a total dose of 400 mg orally QD in the morning with RBV and with food. RBV will be supplied as a 200 mg tablet for oral administration by Gilead Sciences. Subjects will take 1 × 200 mg tablet in the morning with SOF and with food. LDV/SOF is manufactured as a fixed-dose combination tablet, consisting of 90 mg LDV and 400 mg SOF, for oral administration. All subjects will take 1 tablet daily with or without food.
Reference Therapy:	None
Criteria for Evaluation:	
Safety:	AEs, SAEs, and safety labs will be collected throughout the study. Safety will be evaluated by assessment of clinical laboratory tests, ECG, echocardiogram, periodic physical examinations including vital signs at various time points during the study, and by the documentation of adverse events.
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® AmpliPrep/COBAS® TaqMan® HCV Test.

PK:	Plasma PK parameters will be calculated for sofosbuvir and its metabolites GS-566500 and GS-331007, LDV and RBV, as applicable. Examples are AUC_{last}, AUC_{tau}, C_{max}, C_{last}, C_{tau}, and $t_{1/2}$.
Statistical Methods:	Safety data will be listed by subject and summarized by treatment cohort using frequency of event/abnormality or descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, % coefficient of variation [CV], standard deviation [SD], minimum, Q1, median, Q3, and maximum). The steady state PK plasma concentrations and parameters will be listed by subject and summarized by treatment cohort using descriptive statistics for each analyte (SOF, GS-566500, GS-331007, RBV and LDV, as appropriate). In the efficacy analysis, no statistical hypothesis testing will be performed and no formal inferences will be made on the primary efficacy endpoint SVR12. A point-estimate with two-sided 95% exact confidence interval (CI) using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate by treatment cohort. Similar analysis will be also performed for secondary endpoints SVR4 and SVR24. To evaluate the kinetics of circulating HCV RNA during and after treatment discontinuation, viral load data will be listed by subject and summarized by treatment cohort and visit using descriptive statistics. Due to the exploratory nature of this study, no formal power or sample size calculations were performed to determine treatment group size. The total sample size of 35 is largely based on feasibility.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
β-hCG	β-human chorionic gonadotropin
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BID	twice a day
BLQ	below the lower limit of quantification
BMI	body mass index
BW	body weight
CL_{cr}	Creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CRF	case report form(s)
CRO	Contract (or clinical) research organization
DAA	direct-acting antiviral
dL	Deciliter
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
ESAs	Erythropoiesis stimulating agents
ESRD	End Stage Renal Disease
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FEV_1	forced expiratory volume in one second
GCP	Good Clinical Practice (Guidelines)
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
GT	Genotype (viral)
Hb	Hemoglobin
HbA_{1c}	Hemoglobin A_{1c}

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	high-density polyethylene
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
IBW	Ideal Body Weight
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL28B	IL28B gene
IND	Investigational New Drug (Application)
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
kg	Kilogram
L	Liter
LDH	Lactase dehydrogenase
LDV	Ledipasvir
LLN	lower limit of the normal range
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MH	Mantel-Haenszel
mL	Milliliter
Min	Minute
mmHg	millimeters mercury
NS (3/4A/5A/5B)	Non-structural Protein
PBMC	peripheral blood mononuclear cell(s)
PEG	Pegylated interferon
P-gp	P-glycoprotein
PI	Protease inhibitor
PK	Pharmacokinetic
po	Per os (by mouth)
QD	once daily (use only in tables)
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell count

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

RBV	Ribavirin
RNA	ribonucleic acid
RVR	rapid virologic response
SADR	Serious adverse drug reaction
SAE	serious adverse event
SD	Standard deviation
SOC	Standard of Care
SOF	Sofosbuvir
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
t_{max}	The time (observed time point) of C_{max}
TND	Target not detected
TSH	Thyroid stimulating hormone
$t_{½}$	An estimate of the terinal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate contstant (λ_z)
ULN	upper limit of the normal range
US	United States
WBC	white blood cell count

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) is responsible for a large proportion of chronic liver disease worldwide and accounts for 70% of cases of chronic hepatitis in industrialized countries. The global prevalence of chronic hepatitis C is estimated to average 3% {23338}. The most common genotype worldwide is genotype 1 followed by genotypes 2 and 3 {23338}. Although there is evidence that the incidence of viral infection may be decreasing, the prevalence of liver disease caused by HCV is on the rise, primarily due to the lag between the onset of infection and the clinical manifestation of liver disease {23338}. The prevalence of chronic HCV is significantly higher among patients with chronic renal failure, and HCV itself is associated with impaired renal function. Treatment of these individuals is therefore recommended but is often complicated by the substantial increase in hematologic toxicities associated with the use of ribavirin in the setting of low creatinine clearance {23275}.

1.2. Sofosbuvir (formerly GS-7977)

Sovaldi® (sofosbuvir) is a potent nucleotide analogue that inhibits HCV RNA replication in vitro and has demonstrated high rates of sustained viral response (SVR) when administered with RBV, with or without pegylated interferon, to subjects with chronic genotype 1-6 HCV infection {34475}, {23275}, {24713}, {24715}, {27832}. Sovaldi® has been approved in the United States (GT1-4) and in the European Union (GT1-6) for the treatment of chronic HCV infection including treatment naïve and experienced patients and HIV/HCV co-infected patients.

For further information on the clinical pharmacology, virology, safety and efficacy of sofosbuvir (SOF), please refer to the current version of the Investigator's Brochure and US and EU prescribing information.

1.3. Ribavirin (RBV)

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

Ribavirin is a known teratogen (FDA category X). Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment. A comprehensive review of RBV is contained in the package insert/SmPC.

1.4. Ledipasvir/Sofosbuvir Fixed-Dose Combination

Harvoni® (ledipasvir/sofosbuvir fixed-dose combination (LDV/SOF) combines two HCV specific-direct acting antivirus (DAA) agents into a single tablet for the treatment of chronic HCV infection. Sofosbuvir is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed HCV replication, irrespective of HCV genotype. Ledipasvir is a novel HCV NS5A inhibitor that has demonstrated potent anti-HCV activity against genotypes 1 and 4 HCV infection. Harvoni® has been approved in the United States and Europe for the treatment of chronic HCV infection including treatment naïve and experienced patients with genotype 1.

For further information on the clinical pharmacology, virology, safety and efficacy of LDV/SOF, please refer to the current version of the Investigator's Brochure and US prescribing information.

1.5. Preliminary Results of Study GS-US-334-0154, Cohort 1

Preliminary results are available and presented below for Cohort 1: 10 subjects with estimated glomerular filtration rate (eGFR by Cockcroft-Gault) less than 30 mL/min within six months of screening, not on dialysis, treated with SOF 200 mg + RBV 200 mg daily for 24 Weeks. A review of the integrated safety, PK and efficacy from this first cohort demonstrate that SOF 200 mg + RBV 200 mg daily for 24 weeks is safe and relatively well tolerated.

1.5.1. Pharmacokinetics

Preliminary pharmacokinetic data are available for subjects in Cohort 1 who received 200 mg SOF + 200 mg RBV for 24 weeks. Exposure (from intensive PK sampling) of SOF and its predominant circulating renally eliminated metabolite (GS-331007) were similar at Week 2 and Week 12; as such further PK analyses are conducted with the Week 12 data (Table 1-1).

As expected, in the Cohort 1 HCV-infected subjects, severe renal impairment increases GS-331007 and SOF exposures. In general, when normalized to subjects with normal renal function, the results are comparable to that observed in the non HCV-infected renal impairment study (P7977-0915, %GMR in Table 1-1). The only exception was the increase in GS-331007 C_{max} seen in severe renal impaired HCV-infected subjects as opposed to the non-infected subjects (%GMR HCV-infected vs. non-infected: 589% vs. 134%). This difference in GS-331007 C_{max} is likely a result of expected accumulation of GS-331007 upon steady state dosing in the Study GS-US-334-0154 as compared to single dose administration in the P7977-0915 study.

Table 1-1. Preliminary Comparison of the Effect of Severe Renal Impairment on GS-331007 and SOF Exposure in HCV-infected and Non-HCV-Infected Subjects

Mean (%CV) PK Parameter	GS-331007		SOF	
	$AUC_{inf\ or\ tau}$ (ng•hr/ml)	C_{max} (ng/ml)	$AUC_{inf\ or\ tau}$ (ng•hr/ml)	C_{max} (ng/ml)
HCV-Infected Subjects				
GS-US-334-0154 SOF 200 mg cohort Week 12 (n = 10)	31,100 (53.9)	1730 (44.9)	1280 (50.3)[a]	904 (66.2)
Phase 2/3 Population Dose normalized to SOF 200 mg (SOF n = 838, GS-331007 n = 1695)	3561 (30.7)	291 (36.3)	513 (36.5)	256 (32.5)
%GMR (90% CI)	817 (694, 963)	589 (481, 721)	233 (193, 282)	321 (261, 395)
Non HCV-Infected Subjects (P7977-0915)				
%GMR (90% CI) (Severe Impairment/Normal Function)	551 (313, 968)	134 (98.6, 183)	271 (183, 402)	177 (96.6, 324)

Note: PK parameters are presented as mean (%CV) to three significant digits.
a n = 9
Source: Ad Hoc Table 6822.2, P7977-0915 Table 11.13

1.5.2. Safety

Sofosbuvir was generally well-tolerated and safe when administered with RBV in Cohort 1. Most adverse events (AEs) were mild to moderate in severity. There were two serious AEs (SAEs) of unstable angina and hyperglycaemic hyperosmolar nonketotic syndrome which were assessed by the investigators as not related to the study drugs. Neither event led to change in study drug administration. The most frequently reported AEs were anemia, headache, pruritus, and rash. Renal function and cardiac function were stable during treatment as assessed by eGFR, safety ECG and echocardiograms, respectively.

1.5.3. Efficacy

All subjects experienced rapid on-treatment virologic decline similar to those with normal renal function and full-dose SOF+RBV. There were no subjects with virologic breakthrough. One subject withdrew consent and stopped treatment at Week 12; he did not return for post-treatment visits. One subject prematurely discontinued treatment at Week 21. Overall, 4 of the 10 (40%) subjects achieved SVR4.

1.6. Rationale for the Current Study

This study will evaluate the safety, efficacy and pharmacokinetics of treatment with SOF+RBV for 24 weeks (for genotype 1 or 3) and of treatment with LDV/SOF for 12 weeks (for genotype 1 or 4) in subjects with chronic HCV infection and severe renal impairment.

Interferon monotherapy, however, is associated with poor tolerability, a 48 week treatment duration, and efficacy of approximately 40%. Furthermore, once patients have failed this course of treatment, they have no further treatment options and are at risk for progression of liver disease, cirrhosis, and hepatocellular carcinoma.

1.6.1. Cohorts 1 and 2

To date, SOF+RBV has demonstrated safety and efficacy in a broad range of subjects with chronic HCV infection in Phase 2 and Phase 3 clinical trials. However, subjects with Cr clearance <60 mL/min have been excluded from these studies due to the recommendation that RBV not be administered to patients with Cr clearance <50 mL/min. In addition, study P7977-0915 has shown the major circulating metabolite of SOF, GS-331007, is renally cleared and a single dose study conducted in subjects with severe renal impairment or end-stage renal disease on hemodialysis demonstrated exposures approximately 1.6-fold and 14 to 22-fold higher, respectively, than those observed in matched controls with normal renal function. Whilst dose reduction of SOF would reduce these exposures, viral efficacy is dependent on SOF exposures such that lower SOF doses or intermittent administration could be associated with reduced efficacy. Thus, this exploratory study of safety and efficacy of standard (400 mg) and reduced (200 mg) doses of SOF in combination with low-dose RBV in a small number of subjects will provide important data regarding dosing recommendations for use of SOF in this patient population with a high unmet medical need.

Phase 3 studies of SOF+RBV for 12 or 16 weeks in treatment-naïve and treatment-experienced genotype 3 HCV-infected subjects demonstrated SVR12 rates of 56% and 62%, respectively. Increasing treatment duration to 24 weeks may further improve response rates. In Phase 2 studies of SOF+RBV for 12 or 24 weeks in treatment-naïve genotype 1 HCV-infected subjects, SVR rates have varied from 47% to 84% depending on the study and patient population. In both genotypes 1 and 3, lower doses of RBV have been associated with reduced efficacy of the regimen. Given the safety need for a reduced RBV dose in the current study (Section 1.8), treatment with SOF+RBV will be administered for 24 weeks to maximize efficacy. Subjects with genotypes 1 or 3 HCV infection have been selected for this study since they represent the largest group of HCV-infected individuals in the regions where this study will be conducted and because the 24 week treatment regimen is appropriate. In contrast, genotype 2 HCV-infected subjects have been shown to have high response rates following 12 weeks of SOF+RBV therapy. If SOF+RBV is well tolerated for 24 weeks in patients with severe renal insufficiency, safety for 12 weeks in this smaller HCV population may be inferred.

1.6.2. Cohort 3

To date in subjects with a CLcr > 60 mL/min, LDV/SOF without RBV has an excellent safety profile, with efficacy > 93% in all patient populations {34474}. Cohort 3, in which LDV/SOF for 12 weeks will be the treatment regimen, will generate clinical data in a patient population with a regimen which is the Standard of Care (SOC) for genotype 1.

Phase 3 trials with LDV/SOF demonstrated the addition of RBV to LDV/SOF for the treatment of HCV in genotype 1 subjects did not increase efficacy. As such, Cohort 3 will not include RBV which is of particular benefit for this patient population in which chronic anemia is common; the preliminary data from Cohort 1 with SOF 200mg + RBV indicate that anemia was the most frequent AE and led to increased epoetin use.

In Cohort 3, the safety, efficacy and pharmacokinetics of LDV/SOF 90/400 mg will be evaluated in subjects with severe renal impairment. Data from GS-US-344-0108 demonstrated that severe renal impairment had no effect on LDV exposure. As described above for Cohorts 1 and 2, impaired renal function significantly increases GS-331007 exposure. As such, progression of GS-331007 exposure across cohorts was a major consideration in determining the appropriate design for this study (see Section 1.9).

Because over 70% of HCV-infected individuals in the US and Europe have genotype 1, they represent the greatest unmet medical need, and therefore will be the priority for generating data in renal impairment across cohorts of this study. For Cohort 3, both preclinical and clinical data support the inclusion of genotype 4 HCV-infected subjects. Activity of LDV was evaluated in a subgenomic genotype 4d HCV replicon. In the replicon system, the EC_{50} value of LDV against genotype 4d HCV was 0.60 nM and 0.39 nM for genotype 4a HCV (compared with EC_{50} values of LDV against genotype 1a and genotype 1b of 0.031 nM and 0.004 nM, respectively).

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

In Study GS-US-337-1119, a European study investigating the efficacy and safety of LDV/SOF in treatment-naive and treatment-experienced subjects with chronic genotype 4 or genotype 5 HCV infection, a total of 44 subjects with genotype 4 HCV infection, of whom 10 (23%) have cirrhosis and 22 (50%) are treatment experienced, have been enrolled to receive LDV/SOF for 12 weeks. SVR4 data are available from Study GS-US-337-1119 in 25 subjects with genotype 4 and18 subjects with genotype 5 HCV infection.

Table 1-2. SVR4 Rates in Genotype 4 Subjects from Study GS-US-337-1119

	Genotype 4
Overall	96% (24/25)
Treatment Naive	100% (12/12)
Treatment Experienced	92% (12/13)
Cirrhosis	100% (7/7)
No Cirrhosis	94% (17/18)

In addition, preliminary data are available from Group E of the NIAID/NIH collaborative Study CO-US-337-0117. In this group, 21 subjects with genotype 4 HCV infection, of whom 13 are treatment naive and 8 are treatment experienced, are receiving 12 weeks of LDV/SOF treatment. In total, 6 subjects have cirrhosis. Post-treatment week 12 data is available for 20 subjects, 19 of 20 subjects have achieved SVR12.

Study GS-US-337-0115 (ION-4) is investigating the efficacy and safety of LDV/SOF in genotype 1 and genotype 4 HCV-infected subjects coinfected with HIV. A total of 8 subjects with genotype 4 HCV infection have been enrolled. All 8 subjects have achieved SVR4.

1.7. Rationale for SOF Dose Selection

Sofosbuvir 400 mg, once daily, when dosed in combination with RBV with or without PEG has demonstrated broad genotypic efficacy and a favorable safety profile in over 3300 HCV-infected subjects across multiple patient populations in Phase 2 and 3 trials. This dose (400 mg) is the proposed to be marketed dose of sofosbuvir for the treatment of HCV-infection.

In study P7977-0915, a single dose PK study in subjects with varying degrees of renal impairment, exposure (AUC_{inf}) of sofosbuvir and the renally eliminated metabolite, GS-331007, were 2.7- and 5.5-fold higher respectively in subjects with severe renal impairment compared to matched controls with normal renal function. A significant dose reduction (eg, 2- to 4-fold) of sofosbuvir would be necessary to provide comparable GS-331007 exposures in subjects with severe renal impairment and those with normal renal function. Data from dose-finding and Phase 2 studies demonstrated that sofosbuvir, dosed once daily, was necessary to provide the active anabolite at the site of action (circulating GS-331007 cannot be phosphorylated to the active anabolite); therefore, dose interval modifications may not be appropriate. The efficacy of a substantially reduced dose of sofosbuvir in subjects with severe renal impairment has not been established.

Cohorts 1 and 2 of this study will evaluate the safety, efficacy and pharmacokinetics of 2 doses of sofosbuvir (200 and 400 mg) in subjects with severe renal impairment. The reduced dose of 200 mg sofosbuvir provided comparable systemic exposures of sofosbuvir, and approximately 4-fold higher GS-331007 exposure compared to HCV-infected in subjects with normal renal function at the 400 mg dose. As such, GS-331007 and SOF exposures in Cohort 2 (400 mg SOF) are expected to increase 2-fold over that observed in Cohort 1. Review of safety, efficacy and pharmacokinetic data from Cohort 2 through 12 weeks of treatment will inform the initiation of Cohort 3 (90/400 mg LDV/SOF in subjects with severe renal impairment).

1.8. Rationale for RBV Dose Selection

Ribavirin increases treatment response rates when administered with interferon or PEG. In addition, reducing the RBV dose from 1000-1200 mg/day to 600 or 800 mg/day when given in combination with SOF reduced SVR rates, as did SOF monotherapy. It is therefore desirable to keep RBV as part of the SOF treatment regimen. Since RBV is cleared renally and its main toxicity is hemolytic anemia which is poorly tolerated in patients with advanced renal insufficiency who are usually anemic at baseline and have little bone marrow reserve, the

starting dose of RBV must be substantially lower than 1000-1200 mg/day. For this study, a dose of 200 mg/day has been selected based on investigator input in light of the high frequency of hemotoxicity of RBV and the general desire to optimize the efficacy of the treatment regimen {24149}.

To date there has been no safety signal identified that is attributable to SOF when administered as part of a combination regimen. Furthermore, SOF does not exacerbate the toxicities associated with RBV, most notably hemolytic anemia. Clinical data with SOF in severe renal insufficiency and in subjects requiring hemodialysis is limited to a single dose study in non-HCV infected subjects. No specific safety signals were identified. The current study is designed to assess the safety and efficacy of therapeutic treatment with SOF+RBV in a small number of subjects with severe renal insufficiency.

The potential benefit of successful treatment of HCV in these subjects is substantial. Few patients with severe renal insufficiency can tolerate combination therapy with PEG+RBV due to profound anemia. SVR rates to interferon monotherapy administered for 48 weeks are less than 50%. Interferon-free treatment for 24 weeks could provide substantial improvements in safety, tolerability and efficacy for individuals with chronic HCV infection.

1.9. Rationale for Ledipasvir/Sofosbuvir Fixed Dose Combination (FDC) Dose Selection

A fixed-dose combination tablet (FDC) of ledipasvir/sofosbuvir 90/400 mg with or without RBV has demonstrated favorable safety and efficacy profiles in over 3000 HCV-infected subjects across different patient populations in Phase 2 and 3 trials. This FDC represent the marketed doses of ledipasvir and sofosbuvir (Harvoni®, LDV/SOF) approved in the US and Europe for the treatment of chronic HCV infection including treatment naïve and experienced patients with GT1.

In support of dosing LDV/SOF to HCV-infected subjects with severe renal impairment, available pharmacokinetic data has been evaluated to project mean exposures of GS-331007 and SOF that may be achieved in these subjects (Table 1-3). Overall, increased GS-331007 exposures are expected in the context of LDV/SOF as compared to SOF administered as single agent (SOF USPI and LDV/SOF NDA, Module 2.7.2). Minimal safety data is available at these high exposures, irrespective of SOF being administered with LDV or as a single agent. The study design allows for consistent progression (~2-3 fold increase) of GS-331007 exposure across cohorts enabling assessment of exposure vs. safety relationships while potentially providing greater efficacy with the two-drug combination.

Table 1-3. Observed and Predicted GS-331007 and SOF Exposure in Subjects with Renal Impairment

Mean (%CV, if applicable) PK Parameter		GS-331007		SOF	
		AUC_{tau} (ng•hr/ml)	C_{max} (ng/ml)	AUC_{tau} (ng•hr/ml)	C_{max} (ng/ml)
Observed Data	GS-US-334-0154 Cohort 1 SOF 200 mg Week 12 (n = 10)	31,100 (53.9)	1730 (44.9)	1280 (50.3)	904 (66.2)
Predicted Data	Cohort 3: LDV/SOF 90/400 mg in Severe RI[a]	111,000	4400	3430	2330

Pharmacokinetic parameters are shown to 3 significant digits

a Predicted as the LDV/SOF Phase 2/3 population multiplied times the ratio of predicted SOF 400 mg in severe RI to SOF Phase 2/3 population.

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the safety of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks and LDV/SOF for 12 weeks as assessed by review of the accumulated safety data in each treatment arm
- To evaluate the efficacy of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks and LDV/SOF for 12 weeks measured by the proportion of subjects with renal insufficiency who have achieved a sustained viral response 12 weeks after treatment discontinuation (SVR12) in each treatment arm
- To evaluate the steady state pharmacokinetics of SOF and its metabolites and LDV upon dosing SOF 200 mg or 400 mg or LDV/SOF in subjects with renal insufficiency

The secondary objectives of this study are:

- To evaluate the proportion of subjects with renal insufficiency who attain SVR at 4 and 24 weeks after discontinuation of treatment (SVR4 and SVR24)
- To evaluate the kinetics of plasma HCV RNA during and after treatment discontinuation
- To evaluate the emergence of viral resistance to SOF and LDV during and after treatment discontinuation

The exploratory objective of this study is:

PPD

3. STUDY DESIGN

This is a multicenter, open label study that will evaluate the safety, tolerability and antiviral efficacy of SOF with RBV or LDV/ SOF in chronic renal insufficiency and HCV infection subjects with genotype 1, 3 or genotype 4 HCV infection, including those with compensated cirrhosis.

This study will have 3 cohorts.

Approximately 35 subjects with severe renal insufficiency will be enrolled.

- Cohort 1: 10 subjects will receive SOF 200 mg QD + RBV 200 mg QD for 24 weeks.
- Cohort 2: Following review of safety, efficacy and PK data through post-treatment Week 4 of Cohort 1, 10 additional subjects will receive SOF 400 mg QD + RBV 200 mg QD for 24 weeks.
- Cohort 3: Following review of safety and available PK data through Week 12 of Cohort 2, 15 additional subjects will receive LDV/SOF QD for 12 weeks.

3.1. Treatment Plan and Regimen

Following screening procedures and Day 1 assessments, eligible subjects will receive one of the following treatments:

Cohort 1: SOF 200 mg QD + RBV 200 mg QD for 24 weeks

Cohort 2: SOF 400 mg QD + RBV 200 mg QD for 24 weeks

Cohort 3: LDV/SOF QD for 12 weeks

Additional information about study drug administration can be found in Section 5.

3.2. Visit Schedule

All subjects will complete screening, on-treatment and post-treatment assessments. Screening assessments will be completed within 42 days of the Day 1 visit. All subjects will complete the Week 4 Post-Treatment visit. Weeks 12 and 24 Post-Treatment visits will be dependent on subject viral load.

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

3.3. Virologic Response-Based Stopping Criteria

The following stopping criteria will be used for subjects on treatment:

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

Confirmation should be performed as soon as possible but within 2 weeks after determination of initial observation.

Cardiac Function-Based Stopping Criterion

The following stopping criterion will be used for subjects on treatment:

- Left ventricular ejection fraction ≤ 40%

3.4. Treatment Discontinuation Criteria

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

- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Pregnancy of female subject, or female partner of male subject.
- Efficacy failure as defined in Section 3.3.
- Declining cardiac function, defined as left ventricular ejection fraction ≤ 40%.
- Significant protocol violation including non-compliance with study assessments.
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy or other reason.
- Discontinuation of the study at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Subjects who discontinue treatment earlier than the assigned 12 or 24-week treatment duration will complete an Early Termination Visit (Section 6.7).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 35 subjects will be treated in this study.

In order to manage the total study enrollment, Gilead Sciences, Inc., at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

4.2. 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 documented by either:

   a) a positive anti-HCV antibody test or positive HCV RNA or positive HCV genotyping test at least 6 months prior to the Day 1 visit, or

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

4) Infection with HCV GT 1, 3 or 4 as determined at Screening, as applicable to cohort

5) Subjects must have the following laboratory parameters at Screening:

   a) HCV RNA ≥ 10^4 IU/mL

   b) ALT ≤ 10 × the upper limit of normal (ULN)

   c) AST ≤ 10 × ULN

   d) Hemoglobin ≥ 9 g/dL

   e) Albumin ≥ 3.0 g/dL

   f) Direct bilirubin ≤ 1.5 × ULN

   g) HbA1c ≤ 10%

h) Creatinine clearance (CL_{cr}) ≤ 30 mL/min, as calculated by the Cockcroft-Gault equation {2202} using ideal body weight (IBW).

Male: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times IBW\ (kg)}{72 \times S_{cr}}$$

Female: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times IBW(kg) \times 0.85}{72 \times S_{cr}}$$

S_{cr} = serum creatinine (mg/dL)

Ideal body weight (IBW) is estimated by the following equations:

Males: IBW (kg) = 50 kg + 2.3 kg for each inch over 5 feet

Females: IBW (kg) = 45.5 kg + 2.3 kg for each inch over 5 feet

a. Subjects with CL_{cr} 30-40 mL/min are eligible if they have a prior CL_{cr} ≤ 30 mL/min within 6 months of Screening

6) INR ≤ 1.5 × ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR.

7) A negative serum pregnancy test for female subjects of childbearing potential (see Appendix 2 for definition).

8) Male subjects and female subjects of childbearing potential (see Appendix 2 for definition) must agree to use protocol specified method(s) of contraception as described in Appendix 2.

9) Lactating females must agree to discontinue nursing before administration of study drug.

10) Subject must be of generally good health as determined by the Investigator.

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

12) Cirrhosis Determination (For all cohorts)

- Cirrhosis is defined as any one of the following:

  — Liver biopsy showing cirrhosis

  — Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa

  — FibroTest® score of > 0.75 AND an AST: platelet (APRI) ratio of > 2 during Screening

- Absence of cirrhosis is defined as any one of the following:
  - — Liver biopsy within 2 years of Screening showing absence of cirrhosis
  - — Fibroscan (in countries where locally approved) with a result of ≤ 12.5 kPa within ≤ 6 months of Day 1
  - — FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 during Screening

In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy is required.

4.3. Exclusion Criteria

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

1) BMI < 18
2) Prior exposure to an direct-acting antiviral targeting HCV NS5B (all cohorts) or HCV NS5A (Cohort 3 only)
3) Prior null response to PEG+RBV therapy (Cohorts 1 and 2) or for patients with cirrhosis, prior treatment failure with IFN-based therapy not resulting from treatment intolerance (Cohort 3)
4) Male with pregnant female partner (Cohorts 1 and 2 only)
5) Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cholangitis)
6) Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV)
7) Unstable psychiatric condition
8) Significant cardiac disease including or resulting in:
   a) Cardiomyopathy
   b) Left ventricular ejection fraction ≤ 50%
   c) Hospital admission for myocardial infarction, heart failure within 1 year of Screening
   d) Pulmonary hypertension within 1 year of Screening
9) Clinically significant abnormality on ECG at Screening, including a QTcF > 500 msec, or > 450 msec in patients who concomitantly use methadone.

10) History of clinically significant hemoglobinopathy (Cohorts 1 and 2 only)

11) History of porphyria (Cohorts 1 and 2 only)

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

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

14) Clinically-relevant drug or alcohol abuse within 12 months of Screening

15) Current or prior history of clinical hepatic decompensation (e.g., ascites, jaundice, encephalopathy or variceal hemorrhage)

16) History of clinically-significant illness or any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol

17) History of a primary gastrointestinal disorder (or post operative condition) that could interfere with the absorption of the study drug

18) Excessive alcohol ingestion, defined as > 3 glasses/day (1 glass is equivalent to: beer [284 mL], wine [125 mL], or distilled spirits [25 mL]) for females and > 4 glasses/day for males)

19) Inability to collect blood for safety, PK, and efficacy throughout the study

20) Donation or loss of more than 400 mL blood within 2 months prior to Day 1

21) Use of any prohibited concomitant medications as described in Section 5.8 within 21 days of the Day 1 visit

22) Known hypersensitivity to RBV (Cohorts 1 and 2 only), the study investigational medicinal product, the metabolites, or formulation excipients

23) Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 4 weeks prior to study drug administration

24) Subjects with hepatocellular carcinoma (HCC) are excluded from the study. In cirrhotic patients, liver imaging (e.g., ultrasound) within 6 months of Day 1 is required to exclude hepatocellular carcinoma (HCC)

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Sofosbuvir (SOF)

5.1.1. Formulation

SOF tablets, 100 mg, are yellow, round, film-coated, plain-faced tablets.

SOF tablets, 400 mg, are yellow, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "7977" on the other side.

In addition to the active ingredient, SOF tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, and yellow iron oxide.

5.1.2. Packaging and Labeling

SOF tablets, 100 mg, are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

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

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

5.1.3. Storage and Handling

SOF bottles should be stored at a 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 SOF.

Sufficient quantities of SOF tablets to complete the entire study will be shipped to the investigator or qualified designee from Gilead Sciences Clinical Supply Management (or its designee).

5.1.4. Sofosbuvir (SOF) Dosage and Administration

SOF will be administered as 200 mg or 400 mg po daily. SOF (100 mg or 400 mg) tablets will be supplied by Gilead Sciences for all subjects.

5.2. Ribavirin (RBV)

5.2.1. Formulation

RBV tablets, 200 mg, are blue, capsule-shaped, film-coated tablets debossed with "3RP" on one side and "200" on the other side. In addition to the active ingredient, RBV tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, FD&C blue #2.

5.2.2. Packaging and Labeling

The RBV tablets are packaged in white, HDPE bottles. Each bottle contains 168 tablets and rayon coil packing material and is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

RBV bottles to be distributed to centers in the US and other countries shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (February 2013) and/or other local regulations as applicable.

5.2.3. Storage and Handling

RBV tablets should be stored at 25 °C (77 °F); excursions are permitted between 15 and 30 °C (59 and 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 RBV.

5.2.4. RBV Dosage and Administration

RBV will be administered as 200 mg po daily. RBV should be dosed with food and with SOF to maximize adherence. RBV dose may be managed at the discretion of the Investigator in communication with the Medical Monitor.

RBV tablets (200 mg) will be supplied by Gilead Sciences for all subjects.

5.3. Co-administration of Sofosbuvir (SOF) and Ribavirin (RBV)

Each subject will be given instructions to maintain approximately the same daily dosing interval between study drug doses.

If a subject forgets to take the medication at the correct time, it may be taken later in the day; however, no more than 400 mg dose of SOF should be taken on any calendar day. The subject should resume the standing dosing schedule on the next day. Study medications should not be cut or split. No food restrictions apply to SOF; however, SOF should be taken with RBV and with food for optimal adherence.

On the day of clinic visits, subjects will be instructed to take their study medication on the day prior to clinic visits, 20-28 hours before the administration of the study medication at the clinic. Subjects should bring their medication with them to the clinic and take their study medication after all pre-dose assessments are completed.

5.4. Ledipasvir/ Sofosbuvir (LDV/SOF)

5.4.1. Formulation

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

5.4.2. Packaging and Labeling

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

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

5.4.3. Storage and Handling

LDV/SOF 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 tablets.

Sufficient quantities of LDV/SOF tablets to complete the entire study will be shipped to the investigator or qualified designee from Gilead Sciences Clinical Supply Management (or its designee).

5.4.4. LDV/SOF Dosage and Administration

LDV/SOF will be administered as one 90 mg/400 mg tablet po daily with or without food for 12 weeks. LDV/SOF tablets will be supplied by Gilead Sciences for all subjects.

5.5. Study Drug Compliance

On Day 1, subjects will be administered study drugs and the assigned bottles will be dispensed to them along with a dosing diary to be used to document at home dosing. Subjects will be instructed to return dosing diaries and any unused study drug in the original container at each visit following Day 1 for study drug compliance assessment.

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

5.6. Dispensing and Accountability of Study Drugs

The Investigator (or designee, e.g., study center pharmacist) will acknowledge receipt of the study drugs (after reviewing the shipment's content and condition) from Gilead Sciences (or designee). The Investigator will maintain an accurate inventory of all study drugs. Each dose of the study drug(s) administered at the study center will be administered by qualified study center personnel. All doses of study drug(s) administered to subjects in the clinic under the supervision of staff will be accurately recorded on the Investigational Product Inventory Logs provided by Gilead Sciences (or on equivalent documentation maintained by the study center), which indicates the date and quantity of all doses of study drug(s) dispensed to individual subjects. The requirements of all applicable Federal and State drug dispensing laws will apply to all doses of study drugs dispensed by the Investigator (or designee). At the end of the study, all unused study drugs (both bulk and individual subject returns) will be returned to a location designated by Gilead Sciences.

5.7. Study Drug Return or Disposal

At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for return or destruction of unused study drug supplies. If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drug supplies performed in accordance with the site's (hospital/pharmacy) SOP. 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 unused study drug supplies. Where possible, study drug will be destroyed at the site. If drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. All study drug records must be maintained at the site and copies must be submitted to Gilead Sciences at the end of the study.

5.8. Concomitant Medications

Concomitant medications taken within 30 days of Screening, up to and including the date of the visit four weeks after discontinuation of study treatment, need to be recorded in the source documents and eCRFs.

5.8.1. Cohorts 1 and 2

The following medications are prohibited from 21 days prior to the Day 1 visit through the end of treatment:

- Drugs disallowed per prescribing information of RBV (COPEGUS®)
- Concomitant use of certain medications or herbal/natural supplements (inducers of drug transporters i.e. P-gp) with study drug(s) may result in pharmacokinetic interactions resulting in decreases in exposure of study drug(s). Representative medications which are excluded from 21 days prior to Day 1 through the end of treatment are listed below:

Drug	Agents Disallowed	Concomitant use with study drug may potentially result in changes of study drug concentration as listed below
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	Decrease in concentration of study drug
Antimycobacterials	Rifampin, rifabutin, rifapentine	Decrease in concentration of study drug
Herbal/Natural Supplements	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	Decrease in concentration of study drug
Other	Modafinil	Decrease in concentration of study drug

5.8.2. Cohort 3

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

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
Antiarrhythmics[b]		Quinidine
Anticonvulsants[c]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials[c]	Rifabutin, Rifapentine, Rifampin	
Cardiac Medications[b]	Amiodarone[e]	Digoxin
Herbal/Natural Supplements[c]	St. John's Wort, Echinaccea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[d]	Rosuvastatin	Pravastatin, Pitavastatin

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 an increase in the concentration of study drugs and/or concomitant medications. Coadministration of LDV/SOF with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when coadministered with LDV/SOF.

c May result in a decrease in the concentrations of study drugs.

d Use with study drugs may result in an increase in the concentration of the HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

e May result in symptomatic bradycardia. Mechanism is not currently known. The use of amiodarone is prohibited from **60 days prior to Baseline/Day 1** through the end of treatment.

5.8.3. All Cohorts

Medications for disease conditions excluded from the protocol (e.g., HIV-1 infection, active cancer, transplantation are not listed under this Concomitant Medication section and are prohibited in the study.

Should it become medically necessary for patients to start treatment with any excluded concomitant medication, the sponsor must be consulted prior to initiation of the new medication and the subject's continued participation must be discussed with the Gilead Medical Monitor.

5.8.3.1. Medications Associated with QT Prolongation

Medications that are known to cause or are associated with QT prolongation and/or a risk of causing torsades de pointes should be avoided in patients with risk factors for developing long QT intervals or those receiving other QT-prolonging medications. These medications include, but may not be limited to those listed below (see table below) and must be approved by the Gilead Medical Monitor prior to study enrollment or coadministration during the study.

Representative List of Medications Known or Associated with QT Prolongation

QT Prolonging Medication Class	Known or Strongly Suspected to cause QT Prolongation	Weaker Association with QT Prolongation
Antibiotics/Anti-infectives:		
Macrolide Antibiotics	azithromycin, clarithromycin, erythromycin, roxithromycin, telithromycin	
Quinolone Antibiotics	gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin	ciprofloxacin
Certain antimalarials/pneumocystis prophylaxis; others	artenimool+piperaquine, bedaquiline, chloroquine, halofantrine, pentamidine	trimethoprim-sulfa, quinine sulfate
Antipsychotics:		
Phenothyazine Antipsychotics	chlorpromazine, mesoridazine, thioridazine	
Other Antipsychotics	clozapine, haloperidol, iloperidone, olanzepine, paliperidone, pimozide, quetiapine, risperidone, sertindole, ziprasidone	amisulpride,
Anit-mania Bipolar Disorders:	lithium	
Anti-depressants:		
Serotonin re-uptake inhibitors	citalopram, escitalopram, venlafaxine	fluoxetine, paroxetine, sertraline
Tricyclic anti-depressants		amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline trimipramine,
Tetracyclic anti-depressants	mirtazepine	trazodone

QT Prolonging Medication Class	Known or Strongly Suspected to cause QT Prolongation	Weaker Association with QT Prolongation
Cardiology Medications:		
Class I (Na^+) and III (K^+) anti-arrhythmics	disopyramide, dofetilide, dronedarone, flecainide, ibutilide, mexiletine, procainamide, quinidine	
Class II (β blockers) and IV (Ca^{2+}) anti-arrythmics	isradipine, sotalol (Class II/III)	
Certain anti-anginals/ calcium blocker	bepridil, nicardipine, ranolazine	
Anesthetics, Pain Medications and Additional Treatment:	levomethadyl, methadone	general anesthetics (e.g., enflurane, halothane, isoflurane, sevoflurane)
Anti-nausea:	domperidone, droperidol, dolasetron, granisetron, ondansentron, promethazine	
Azole anti-fungals (systemic use only)	ketoconazole, voriconazole	fluconazole, itraconazole
Others:	alfuzosin, amantadine, astemizole, cisapride, famotidine, felbamate, fosphenytoin, galantamine, indapamide, moexipril/HCTZ, octreotide, oxytocin, pasireotide, perflutren lipid microspheres, probucol, sibutramine, terfenadine, tizanidine, tolterodine, vardenafil	chloral hydrate, diphenhydramine, solifenacin

Should it become medically necessary for patients to start treatment with any excluded concomitant medication, the sponsor must be consulted prior to initiation of the new medication and the subject's continued participation must be discussed with the Gilead Medical Monitor.

5.8.3.2. Hematopoietic Growth Factors

Erythropoiesis stimulating agents (ESAs) should not be used during Screening solely to elevate hematology laboratory parameters to facilitate entry into the study. Patients taking ESAs for anemia related to chronic kidney disease may enter the study. Granulocyte colony-stimulating agents and thrombopoietic growth factors should not be used while the subject is receiving study treatment.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in Table 6-1 and Table 6-2 and described in the following text.

Any deviation from protocol procedures should be noted in the subject's clinical chart and appropriate eCRFs. In addition, the Sponsor should be promptly notified of any protocol deviations.

The study center will not be released to initiate dosing until:

- The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) reviewed and approved the study and the informed consent document;
- All requested regulatory documents have been submitted to and approved by Gilead Sciences;
- A Master Services Agreement and/or Study Agreement is executed;
- The study initiation meeting has been conducted by the Gilead Sciences clinical monitor (or designee).

The initiation meeting will include a review of the protocol, the Investigator's Brochure, and Investigator responsibilities.

Documentation of the personally signed and dated informed consent of each subject, using the study-specific informed consent form (ICF), is required before initiating the screening process. Generic screening consent forms should not be used in lieu of the study-specific ICF.

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study.

Once consent has been obtained, all screening tests and procedures have been assessed, and study eligibility has been confirmed, subjects will be enrolled and assigned a unique subject identification number.

Subjects will receive the study treatment as described in Section 5.

Table 6-1. Schedule of Assessments for Cohorts 1 and 2

Study Procedure	Screen[a]	Day 1[b]	Treatment Visits[i]										Post-Treatment Visits[j]			ET[c]
			Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 4	Week 12	Week 24	
Written Informed Consent	X															
Medical History	X															
HCV RNA Genotype	X															
IL28B Genotyping	X															
HbA1c	X															
HCV, HBV, HIV Serology	X															
TSH	X															
Physical Exam, including Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X			X		X		X	X	X	X	X	X	X	X
Echocardiogram	X								X			X				
Height	X															
Weight	X															
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Screen[a]	Day 1[b]	Treatment Visits[i]										Post-Treatment Visits[j]			ET[c]
			Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 4	Week 12	Week 24	
Coagulation (PT, PTT, and INR)	X	X							X				X			X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV RNA Viral Load	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV RNA Sequencing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[e]	X	X			X		X		X	X	X	X	X	X	X	X
Creatinine Clearance	X															
Optional Pharmacogenetic Sample[k]		X														
Intensive PK				X[f]					X[f]							
Trough PK Sample[g]			X		X	X	X	X		X	X	X				X
Archive Plasma Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration		X	Weeks 1-24													

Study Procedure	Screen[a]	Day 1[b]	Treatment Visits[i]										Post-Treatment Visits[j]			ET[c]
			Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 4	Week 12	Week 24	
Review Dosing Diary/Perform Accountability[h]			X	X	X	X	X	X	X	X	X	X				
AEs/ Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X			X

a Screening evaluations must be completed within 42 days prior to Day 1.

b Day 1 tests and procedures must be completed prior to administration of the first dose of study drugs

c Within 72 hours of permanently discontinuing study drug.

d Full PE at Day 1 and ET visits only; symptom-directed PE at all other timepoints. Vital signs include blood pressure, pulse, respiration rate, and temperature

e Females of childbearing potential only. To confirm eligibility at Day 1, a urine pregnancy test may be collected for subjects able to pass urine. For subjects unable to pass urine, a serum pregnancy test at Day 1 must be performed at a local lab prior to dosing to confirm eligibility along with sample collected and send to central lab. During post-treatment of the study, serum or urine pregnancy testing will occur every month during non-clinic post treatment visits. The subject will be contacted by telephone to confirm that pregnancy testing has been performed post-treatment during non-clinic visits.

f Intensive plasma PK evaluations will be assessed at the following timepoints: 0 (predose -5 minutes), 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose.

g Trough plasma PK samples will be drawn prior to dosing.

h Dosing Diaries will be completed for all non-observed doses and will be reviewed at every visit. Unused study drug will be returned to perform study drug accountability in the original container at each visit following Day 1 for study drug compliance assessment.

i A window of ± 2 days is allowed for the treatment visits on weeks 1, 2, and 12. A window of ± 4 days is allowed for the treatment visits weeks, 4-10, and 16-24. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

j A window of ± 7 days is allowed for the post treatment visits.

k The sample should be collected on Day 1 prior to dosing, but may be collected at any time during the study or at a separate post-study visit, if necessary.

Table 6-2. Schedule of Assessments for Cohort 3

Study Procedure	Screen[a]	Day 1[b]	Treatment Visits[i]							Post-Treatment Visits[j]			ET[c]
			Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 4	Week 12	Week 24	
Written Informed Consent	X												
Medical History	X												
HCV RNA Genotype	X												
IL28B Genotyping	X												
HbA1c	X												
HCV, HBV, HIV Serology	X												
TSH	X												
Physical Exam, including Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X			X		X		X	X	X	X	X
Echocardiogram	X								X				
Height	X												
Weight	X												
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation (PT, PTT, and INR)	X	X				X				X			X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV RNA Viral Load	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV RNA Sequencing		X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[e]	X	X			X		X		X	X	X	X	X
Creatinine Clearance	X												

Study Procedure	Screen[a]	Day 1[b]	Treatment Visits[i]							Post-Treatment Visits[j]			ET[c]
			Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 4	Week 12	Week 24	
Optional Pharmacogenetic Sample[k]		X											
Intensive PK				X[f]	X[f]								
Trough PK Sample[g]			X			X	X	X	X				X
Archive Plasma Sample		X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration		X	Weeks 1-12										
Review Dosing Diary/ Perform Accountability[h]			X	X	X	X	X	X	X				
AEs/Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X

a Screening evaluations must be completed within 42 days prior to Day 1.

b Day 1 tests and procedures must be completed prior to administration of the first dose of study drugs

c Within 72 hours of permanently discontinuing study drug.

d Full PE at Day 1 and ET visits only; symptom-directed PE at all other timepoints. Vital signs include blood pressure, pulse, respiration rate, and temperature

e Females of childbearing potential only. To confirm eligibility at Day 1, a urine pregnancy test may be collected for subjects able to pass urine. For subjects unable to pass urine, a serum pregnancy test at Day 1 must be performed at a local lab prior to dosing to confirm eligibility along with sample collected and send to central lab. During post-treatment of the study, serum or urine pregnancy testing will occur every month during non-clinic post treatment visits. The subject will be contacted by telephone to confirm that pregnancy testing has been performed post-treatment during non-clinic visits.

f Intensive plasma PK evaluations will be assessed at the following timepoints: 0 (predose -5 minutes), 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose once either on Week 2 **OR** 4, per investigator discretion.

g Trough plasma PK samples will be drawn prior to dosing.

h Dosing Diaries will be completed for all non-observed doses and will be reviewed at every visit. Unused study drug will be returned to perform study drug accountability in the original container at each visit following Day 1 for study drug compliance assessment.

i A window of ± 2 days is allowed for the treatment visits on weeks 1, 2, and 12. A window of ± 4 days is allowed for the treatment visits weeks, and 4-10. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

j A window of ± 7 days is allowed for the post treatment visits.

k The sample should be collected on Day 1 prior to dosing, but may be collected at any time during the study or at a separate post-study visit, if necessary.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Prospective subjects should be screened within 42 days prior to first dose on Day 1. If the subject does not begin the treatment phase within this 42-day window, all screening evaluation procedures must be repeated. No more than one repeat screen visit is allowed for each subject, unless prior written approval has been provided by the Sponsor.

Written informed consent must be obtained from each subject before initiation of any screening procedure. After a subject has provided informed consent, the investigator and other study personnel will determine if the subject is eligible for participation in the study. This assessment will include a review of the inclusion/exclusion criteria and completion of all screening procedures as outlined in Table 6-1 and Table 6-2.

Once eligibility is confirmed, the study site will complete an eligibility worksheet for each screened subject and submit for Sponsor review. The sponsor will assign a unique subject number for each eligible subject and provide the subject number information to the site prior to Day 1 visit.

6.2.2. 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. Information related to HCV infection will be collected. In addition, a cirrhosis determination will be made as follows:

Cirrhosis determination

- Cirrhosis is defined as any one of the following:
  - Liver biopsy showing cirrhosis
  - Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa within 6 months of Day 1
  - FibroTest® score of > 0.75 AND an AST:platelet (APRI) ratio of > 2 during Screening
- Absence of cirrhosis is defined as any one of the following:
  - Liver biopsy within 2 years of Screening showing absence of cirrhosis
  - Fibroscan (in countries where locally approved) with a result of ≤ 12.5 kPa within ≤ 6 months of Day 1
  - FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 during Screening

In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy is required.

In addition, a determination of cardiac function will be made as follows:

- Echocardiogram demonstrating left ventricular ejection fraction > 50% performed prior to Day 1 visit. Enrollment allowed based on local read of study if central read is not available.

6.3. Day 1 Assessments

Subjects meeting all eligibility criteria following the screening evaluation will return to the study site within 42 days for Day 1 assessments as outlined in Table 6-1 and Table 6-2.

6.3.1. Dosing Diary

Subjects will be provided with self-administration instructions and study drug diaries to record the exact date, time and number of tablets of study drug administration. The site staff will record the information from the study drug dosing diary into the eCRF. In the event that the dosing diary is not available, the site may obtain dosing information via subject interview and record this information in the source notes

6.4. Treatment Assessments

6.4.1. Cohorts 1 and 2

Study visits will occur at the end of Weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24.

Study procedures and assessments are outlined in Table 6-1.

6.4.2. Cohort 3

Study visits will occur at the end of Weeks 1, 2, 4, 6, 8, 10, and 12

Study procedures and assessments are outlined in Table 6-2.

6.5. Safety Assessments

Safety will be evaluated throughout the study. Refer to Table 6-1 and Table 6-2 for a schedule of assessments.

6.5.1. Safety ECGs

Subjects should rest quietly in the supine position for a minimum of 10 minutes prior to each scheduled ECG acquisition and should remain in that position until the recording is complete. There must be no environmental distractions (television, radio, conversation, etc.) while the subjects are resting prior to and during the recordings.

ECGs will be recorded at a sampling frequency of 500+ Hz, at a speed of 25 mm/sec and at a standard duration of 10 seconds. All ECGs will be obtained using instruments that analyze data using the same algorithms and produce the same data for interpretation. When ECGs are performed on an ECG machine, site standard operating procedures (SOPs) will be used.

ECG measurements will be collected pre-dose at time-points as per Table 6-1 and Table 6-2.

The Investigator or other qualified individuals at the study center will review ECGs to assess for changes in ECG intervals and morphology as compared to pre-dose ECGs. Collection of additional ECGs for routine safety monitoring at additional time-points or days is at the discretion of the Investigator based on GCP.

6.5.2. Safety Echocardiograms

Safety echocardiograms will be performed as outlined in Table 6-1 and Table 6-2. A window of ± 10 days is allowed for the on-treatment visits. These safety echocardiograms will be performed locally and sent to a central location for standardized reading.

6.5.3. Physical Examination

Complete physical examinations or a symptom directed physical examination will be conducted pre-dose as outlined in Table 6-1 and Table 6-2. 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.

6.5.4. 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 Table 6-1 and Table 6-2.

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.

6.5.5. BMI

Height and weight will be collected at the times shown in the schedule of assessments Table 6-1 and Table 6-2.

BMI is calculated by the following equation.

$$\text{BMI} = \frac{\text{weight (pounds)} \times 703}{(\text{height in inches})^2} \quad \text{or} \quad \frac{\text{weight in kilograms}}{(\text{height in meters})^2}$$

6.5.6. Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation {2202} using ideal body weight (IBW).

Male: $$CL_{cr}\ (\text{mL/min}) = \frac{[140 - \text{age (years)}] \times \text{IBW (kg)}}{72 \times S_{cr}}$$

Female: $$CL_{cr}\ (\text{mL/min}) = \frac{[140 - \text{age (years)}] \times \text{IBW (kg)} \times 0.85}{72 \times \text{Scr}}$$

S_{cr} = serum creatinine (mg/dL)

Ideal body weight (IBW) is estimated by the following equations:

Males: IBW (kg) = 50 kg + 2.3 kg for each inch over 5 feet

Females: IBW (kg) = 45.5 kg + 2.3 kg for each inch over 5 feet

6.5.7. Clinical Laboratory Tests/Assessments

In addition to the PK blood samples that will be collected, blood samples will be collected pre-dose as outlined in the schedule of assessments, Table 6-1 and Table 6-2 for the following laboratory analyses:

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, MCV, and Coagulation Panel (PT, PTT, and INR).

Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatinine, Total Bilirubin (reflex to Direct Bilirubin), Glucose, Total Protein, Bicarbonate, BUN, Calcium, Chloride, Phosphorus, Magnesium, Potassium, Sodium, and FibroTest®.

Thyroid-stimulating hormone (TSH)

Haemoglobin A1C (HbA1c)

Virological Tests: Serologies for HCV, HBV and HIV. HCV RNA will be measured using COBAS® AmpliPrep/COBAS® TaqMan® HCV Test. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV genotype should the above assays become unavailable or are not definitive.

Viral RNA Sequencing/Phenotyping plasma samples will be collected to confirm virologic breakthrough. Untested samples may be archived.

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 an alternate assay for IL28B determination should the above assay become unavailable.

Pregnancy Tests: All females of childbearing potential will have serum or urine pregnancy testing every 4 weeks during the dosing period and for a minimum of 6 months following the last dose of RBV. If required by local regulations, additional pregnancy tests may be collected. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drugs immediately and return to the clinic as soon as possible for a serum pregnancy test.

Pregnancy tests must be completed for all females of childbearing potential (see Appendix 2 for definition) as specified in Table 6-1 and Table 6-2. When feasible for subjects, a urine pregnancy test may also be taken. During post treatment of the study, subject will be contacted by telephone monthly to confirm that the serum or urine pregnancy testing has been performed post-treatment during non-clinic visits. Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine or serum pregnancy tests post treatment.

6.5.8. Adverse Events/Concomitant Medications/Protocol Restrictions

Evaluation for adverse events, review of concomitant medications, and review of protocol restrictions will occur at the times shown in the schedule of assessments Table 6-1 and Table 6-2. See Section 7 for more information regarding adverse events and Section 5 for more information about concomitant medications.

6.6. Pharmacokinetic (PK) Assessments

Subjects will be instructed to take their SOF or LDV/SOF dose on the day prior to clinic visits, 20-28 hours before the clinic visit. On the day of clinic visits, subjects should bring their medication with them to the clinic and take their dose after the trough PK sample is collected, or after the predose intensive PK sample is taken.

The exact time of the dose taken prior to collection of the PK sample and the exact time the PK sample is drawn will be recorded on the appropriate eCRF.

Intensive PK Assessments:

Cohorts 1 and 2:

Serial plasma PK samples will be collected on week 2 and 12 at the following timepoints:

- 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose.

Cohort 3:

Serial blood samples will be collected once either on week 2 OR 4 (per investigator discretion) at the following timepoints:

- 0 (pre-dose -5 minutes), 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose.

Plasma concentrations of SOF and its metabolites and LDV will be determined and PK parameters will be estimated as appropriate. Plasma concentrations of RBV may be determined, as applicable.

Trough PK Assessments:

Trough PK plasma samples for analyses of SOF, its metabolites, RBV and LDV concentrations will be collected at all other on treatment visits beginning at the Week 1 visit as applicable.

PK Parameters for SOF, its metabolites, LDV and RBV will be estimated as appropriate.

6.7. Early Termination (ET)/Unscheduled Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments at the unscheduled visits are at the investigator's discretion. At all unscheduled visits initiated for the purpose of confirming virologic failure a Viral RNA Sequencing/Phenotyping Sample must be collected.

The Sponsor (e.g. Medical Monitor and Clinical Program Manager)/CRO must be informed, as soon as possible, when a subject prematurely discontinues treatment. The primary reason for premature treatment discontinuation must be provided to the Sponsor/CRO.

If a subject discontinues treatment early for any reason then the following assessments for the Early Termination (ET) Visit must be performed:

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Assessment of AEs and concomitant medications

- Pregnancy prevention counseling
- Obtain blood samples for:
  - Hematology & Chemistry
  - Coagulation (PT, PTT, and INR)
  - HCV RNA
  - Viral Sequencing / Phenotyping Sample
  - Trough PK
  - Serum pregnancy test (females of childbearing potential only)
- Review study drug adherence with subject including recording the date and time of the subject's last dose of study drug prior to the PK draw (subject should return all study drugs at this visit)

All subjects will attend the 4-Week Post-Treatment Visit.

6.8. Post-Treatment Assessments

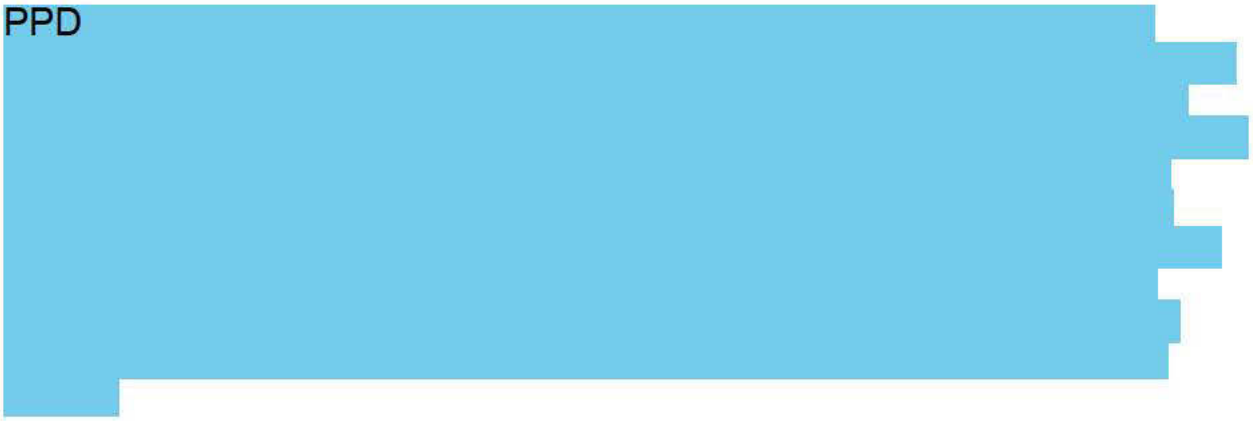
Subjects with HCV RNA < LLOQ at the 4-Week Post-Treatment Visit will attend the 12-Week Post-Treatment Visit.

Subjects with HCV RNA ≥ LLOQ do not need to return for additional visits and they will be terminated early from the study.

Subjects with HCV RNA < LLOQ at the Post-Treatment Week 12 Visit will return at the post-treatment Week 24 Visit.

6.9. Optional Samples for Pharmacogenetic Testing

PPD



6.10. Archived Plasma Sample

Archive plasma samples will be collected at the study visits, indicated in Table 6-1 and Table 6-2. Archive plasma samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing and other possible predictors of response as determined by Gilead.

In the event of a subject's death or loss of competence, the subject's specimens and data will continue to be used as part of the future biomarker research.

If a subject wishes to withdraw the testing of his or her specimens for future research, the investigator must inform the Gilead Sciences Medical Monitor in writing of the subject's wishes.

6.11. Blood Storage

Archived plasma samples will be collected for future testing. These samples will be frozen and stored. The stored plasma samples may be used by the Sponsor or its research partner for future clinical laboratory testing to provide additional clinical data. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences, Inc. at its research partner facility for a period up to 10 years.

7. ADVERSE EVENTS 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 pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol 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 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

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

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

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

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

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

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

7.2.2. Assessment of Severity

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.

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

Requirements for collection prior to study drug initiation:

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

Adverse Events

Following initiation of study medication until 30 days after last administration of study IMP, all AEs, regardless of cause or relationship, must be reported to the CRF/eCRF database as instructed.

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

Serious Adverse Events

All SAEs, regardless of 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.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30-days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the 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 CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead DSPH:	Fax:	+1-650-522-5477
	E-mail:	safety_fc@gilead.com

- 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.

7.4. Gilead Reporting Requirements

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

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

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

7.5. Toxicity Management

7.5.1. Stopping Rules for Toxicity

Subjects who meet any of the following criteria should be instructed to immediately stop all study drugs and return for an Early Termination Visit:

- Confirmed elevation of ALT and/or AST > 5× Day 1 or nadir, confirmed by immediate repeat testing
- Confirmed elevation of ALT > 3× Day 1 and total bilirubin > 2 × ULN
- Confirmed elevation of ALT >15 x ULN
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 event assessed as related to treatment
- Echocardiogram demonstrating left ventricular ejection fraction ≤ 40%

7.5.2. Sofosbuvir (SOF) or LDV/SOF

Administration of SOF or LDV/SOF may be discontinued due to a clinical or laboratory event. There is no option for sofosbuvir or LDV/SOF dose reduction. In the event that SOF is stopped, RBV should also be discontinued.

7.5.3. Ribavirin (RBV)

Dose reduction or interruption of RBV due to toxicity should be performed based on the clinical experience of the Investigator. RBV may be temporarily discontinued due to toxicity without stopping SOF. However, if RBV is permanently discontinued due to toxicity, SOF should also be discontinued.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

A pregnancy report is used to report any pregnancy following maternal or paternal exposure to the medicinal product.

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

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

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

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report all pregnancies that are identified after the subject first consents to participate in the study (ie, signs the informed consent) and throughout the study, including the post study drug follow-up period, to the Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.3 and 7.4. 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: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

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

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

Refer to Appendix 2 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

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

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

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

Refer to Section 7.3 and the 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 safety of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks and LDV/SOF for 12 weeks as assessed by review of the accumulated safety data in each treatment arm
- To evaluate the efficacy of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks and LDV/SOF for 12 weeks measured by the proportion of subjects with renal insufficiency who have achieved a sustained viral response 12 weeks after treatment discontinuation (SVR12) in each treatment arm
- To evaluate the steady state pharmacokinetics of SOF and its metabolites and LDV upon dosing SOF 200 mg or 400 mg or LDV/SOF in subjects with renal insufficiency

The secondary objectives of this study are as follows:

- To evaluate the proportion of subjects with renal insufficiency who attain SVR at 4 and 24 weeks after discontinuation of treatment (SVR4 and SVR24)
- To evaluate the kinetics of plasma HCV RNA during and after treatment discontinuation
- To evaluate the emergence of viral resistance to SOF and LDV during and after treatment discontinuation

The exploratory objective of this study is:

PPD

8.1.2. Primary Endpoint

The primary safety endpoints include incidences of AEs, laboratory, 12-lead ECG, and vital sign abnormalities.

The primary PK endpoints are parameters AUC_{tau}, C_{max}, and C_{tau} for analytes SOF, its metabolites, LDV and RBV as applicable.

The primary efficacy endpoint is SVR12 (HCV RNA < LLOQ 12 weeks after discontinuation of therapy).

8.1.3. Secondary Endpoint

Secondary PK endpoints are parameters AUC_{last}, C_{last}, T_{max}, T_{last}, λ_z, and $t_{1/2}$ for analytes SOF, its metabolites, LDV and RBV as applicable.

Secondary efficacy endpoints include the proportion of subjects with SVR4 and SVR24, the proportion of subjects with virologic failure including viral breakthrough and relapse.

8.1.4. Other Endpoints of Interest

Additional efficacy evaluations may include HCV RNA change from baseline; ALT normalization, andviral kinetic parameters.

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 include SOF, RBV and LDV/SOF. Last dose of study drug refers to the last dose of any of the study drugs in a treatment group and will be used in the definition of treatment-emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various post-treatment time points.

All analyses will be presented by treatment cohort. Subjects who receive study drug other than that to which they were assigned will be analyzed according to the study drug received.

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

8.2.1.2. Safety

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

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

8.2.1.3. Pharmacokinetics

The PK analysis set will include all subjects who are enrolled and have received at least one dose of study drug and for whom PK concentration data of interested analytes (SOF, its metabolites, LDV or RBV) are available. The PK analysis set will be used for analyses of general PK.

8.2.2. Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed.

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

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

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

- If a subject received study medication, the subject will be included in a summary of adverse events according to the treatment received; otherwise, if the subject is not dosed then they will be excluded from the summary.

- If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a predose value, then the subject will be excluded from the calculation of 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 result will be replaced with a screening result, if available. If no pretreatment laboratory value is available, the baseline value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities.

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

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

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

PK concentration values below the lower limit of quantitation (BLQ) will be treated as zero for determination of summary and order statistics. Individual values that are BLQ will be presented as “BLQ” in the concentration data listing. For the presentation of summary and order statistics, if at least 1 subject has a concentration value BLQ for the time point, then the minimum value will be displayed as “BLQ.” If more than 50% of the subjects have a concentration data value

BLQ for the time point, then the minimum and median values will be displayed as "BLQ." If more than 75% of the subjects have a concentration data value of BLQ for a given time point, then the minimum. 1st quartile [q1], median, and 3rd quartile [Q3] values will be displayed as "BLQ." If all subjects have concentration data values BLQ for the time point, then all order statistics (minimum, first quartile [Q1], median, third quartile [Q3], maximum) will be displayed as "BLQ".

Exposure parameters that are selected for statistical analysis will be natural log-transformed. Concentration values that are BLQ will be excluded for any ratio or natural log-transformed statistical analysis.

8.2.3. Interim Analysis

Interim analyses will be performed to support external multidisciplinary data monitoring committee meetings (Section 8.9).

8.3. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods by treatment cohort.

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

Baseline characteristic data will include body weight/body mass index, HCV RNA level (log_{10} IU/mL), IL28B genotype, baseline ALT level, creatinine clearance estimated by Cockcroft-Gault, and additional endpoints as necessary.

8.4. Efficacy Analysis

8.4.1. Primary Analysis

The primary efficacy endpoint is SVR12 in the FAS population. The primary analysis will be performed after all enrolled subjects have been followed through 12 weeks post-treatment or discontinued from study.

A point estimate with a 2-sided 95% exact confidence interval (CI) using the exact binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate by treatment cohort.

No statistical hypothesis testing will be performed.

8.4.2. Secondary Analysis

The proportion of subjects with HCV RNA below the LLOQ over time (including SVR12) will be presented by treatment cohort in tabular and graphical form.

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

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

8.5. Safety Analysis

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

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug will be summarized according to the study drug received. Safety endpoints will be summarized as the number (proportion) of subjects with events or abnormalities for categorical data or as an 8-number summary (n, mean, standard deviation, minimum, Q1, median, Q3, maximum) for continuous data.

8.5.1. Extent of Exposure

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

8.5.2. Adverse Events

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

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

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

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

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

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

8.5.3. Laboratory Evaluations

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

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

Values for missing safety laboratory data will not be imputed; however, a missing baseline result will be replaced with a screening result, if available. If no pretreatment laboratory value is available, the baseline value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities. Thus, any post-baseline graded abnormality (i.e., at least Grade 1) will be considered treatment emergent.

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

8.6. Pharmacokinetic Analysis

Plasma concentrations of the study drug over time will be listed and summarized using descriptive statistics. PK parameters (e.g., AUC_{tau}, C_{max}, and C_{tau}) will be listed and summarized for study drug (i.e., SOF and its metabolites, LDV and RBV) using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, % coefficient of variation [%CV], SD, minimum, Q1, median, Q3, maximum).

8.7. Stopping Rules for Individual Groups

There are no predetermined futility criteria which would require enrollment to be halted or treatment discontinued.

8.8. Sample Size

Due to the exploratory nature of this study, no formal power or sample size calculations were performed to determine treatment group size. The total sample size of 35 is largely based on feasibility.

8.9. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety, efficacy, and PK data for each cohort of the study before proceeding to the next. Specifically, all of the data through post-treatment week 4 from the SOF 200 mg group (Cohort 1) will be reviewed before screening, enrollment and dosing for the SOF 400 mg group (Cohort 2). A similar review and initiation process will occur between SOF 400 mg (Cohort 2) and LDV/SOF dose group (Cohort 3), with review of safety and PK data through Week 12 from Cohort 2 prior to initiating Cohort 3. The DMC will provide recommendations to Gilead 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 the need for additional meetings or an alternative 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 (IEC) 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 or IEC. The investigator will not begin any study subject activities until approval from the IRB or 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 or IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB or 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- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or 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 or 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. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

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

9.1.5. Study Files and Retention of Records

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

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

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the

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

9.1.7. Drug Accountability

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP 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. Documentation of GSI review and approval 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.

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 IRBs or IECs 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 Sciences. All protocol modifications must be submitted to the Competent Authorities, IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

9.2.2. Study Report and Publications

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

9.3.2. Access to Information for Auditing or Inspections

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

9.3.3. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24 Weeks in Genotype 1 or 3 and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablet for 12 weeks in Genotype 1 or 4 HCV-Infected Subjects with Renal Insufficiency

GS-US-334-0154, Amendment 4, 23 April 2015

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

Theo Brandt-Sarif MD

Theo Sarif, MD (Printed)
Medical Monitor

PPD

27 April 2015

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed) _____ Signature _____

Date _____ Site Number _____

Appendix 2. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Background

For Cohorts 1 and 2

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

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

For Cohort 3

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

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

Women ≥54 years of age with cessation for ≥ 12 months of previously occurring menses, or women of any age who have had a hysterectomy, or have had both ovaries removed, or have had medically documented ovarian failure will be considered to be of non-childbearing potential.

Women < 54 years of age (including those with amenorrhea of any duration) who have not had a hysterectomy, and have not had both ovaries removed, and have not had medically documented ovarian failure will be considered to be of childbearing potential.

Women of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Day 1 visit prior to enrollment. They must also agree to one of the following from 3 weeks prior to Day 1 until 6 months after last dose of RBV (Cohorts 1 and 2) or until 30 days after the last dose of study drug in the absence of RBV (Cohort 3):

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

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom, from the date of Screening until 6 months after the last dose of RBV (Cohorts 1 and 2) or 30 days after last dose of study drug in the absence of RBV (Cohort 3):

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

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

  — tubal sterilization

  — vasectomy in male partner

  — implants of levonorgestrel

  — injectable progesterone

  — oral contraceptives (either combined or progesterone only)

  — contraceptive vaginal ring

  — transdermal contraceptive patch

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

All male study participants must agree to consistently and correctly use a condom from Baseline until 7 months after the last dose of RBV (Cohorts 1 and 2) or until 90 days after administration of the last dose of study drug in the absence of RBV (Cohort 3). If their female partner is of childbearing potential (as defined above), their female partner must use 1 of the methods of birth control listed above from the date of Screening until 7 months after last dose of RBV (Cohorts 1 and 2) or until 90 days after administration of the last dose of study drug in the absence of RBV (Cohort 3).

Male subjects must agree to refrain from sperm donation for at least 7 months after the last dose of RBV (Cohorts 1 and 2) or for at least 90 days after the last dose of study drug in the absence of RBV (Cohort 3).

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 6 months (7 months for partners of male subjects) of last RBV dose or within 30 days (90 days for partners of male subjects) of last LDV/SOF dose. Subjects who become pregnant or who suspect that they are pregnant must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.

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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

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

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

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

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

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

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

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

Notes:

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

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

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

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

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

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

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

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 (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

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

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

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

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

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

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

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

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

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

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.