CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir, With or Without Ribavirin, in HCV Infected Subjects Who Have Failed Prior Treatment With Sofosbuvir-based Therapies
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
IND Number:	115268
EudraCT Number:	2015-001247-36
Clinical Trials.gov Identifier:	TBD
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-337-1746
Gilead Study Director:	Name: PPD Telephone: PPD Email: PPD
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Protocol Version/Date:	Original: 13 March 2015 Amendment 1: 12 June 2015 Amendment 2: 23 July 2015

CONFIDENTIALITY STATEMENT

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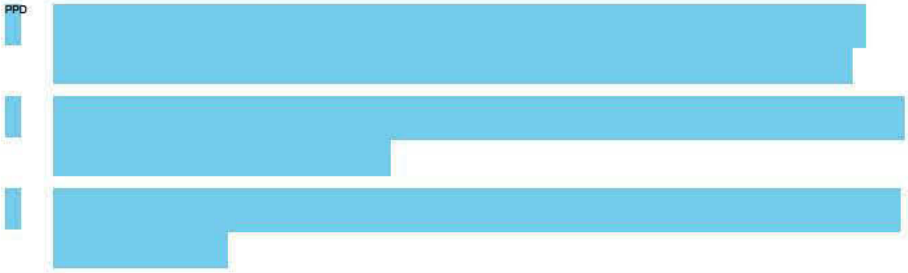
PROTOCOL SYNOPSIS

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

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir, With or Without Ribavirin, in HCV Infected Subjects Who Have Failed Prior Treatment With Sofosbuvir-based Therapies
IND Number:	115268
EudraCT Number:	2015-001247-36
Clinical Trials.gov Identifier:	TBD
Study Centers Planned:	Approximately 100 centers in North America and Europe
Objectives:	The primary objectives of this study are as follows: • To evaluate the efficacy of treatment with ledipasvir/sofosbuvir fixed-dose combination (LDV/SOF FDC) for 12 weeks with or without ribavirin (RBV) in subjects without cirrhosis, and LDV/SOF FDC for 12 weeks with RBV or LDV/SOF FDC for 24 weeks without RBV in subjects with cirrhosis, as measured by the proportion of subjects with sustained virologic response 12 weeks after discontinuation of therapy (SVR12) • To evaluate the safety and tolerability of LDV/SOF FDC for 12 weeks with or without RBV in subjects without cirrhosis, and LDV/SOF FDC for 12 weeks with RBV or LDV/SOF FDC for 24 weeks without RBV in subjects with cirrhosis, as assessed by review of the accumulated safety data The secondary objectives of this study are as follows: • To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24) • To determine the proportion of subjects with virologic failure • To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation among subjects with virologic failure

The exploratory objectives of this study are:



Study Design:

This is a Phase 3b, multicenter, open label study in adult male and female subjects with chronic genotype (GT) 1 or 4 hepatitis C virus (HCV) infection and who have failed prior sofosbuvir (SOF)-based HCV therapy, specifically, SOF in combination with simeprevir (SMV) ± RBV or with RBV ± pegylated interferon (PEG).

Approximately 50% of subjects enrolled may have had prior treatment with SOF + SMV ± RBV. Approximately 5% of subjects may be infected with GT 4 HCV.

Approximately 430 subjects will be enrolled in 2 cohorts:

- Cohort 1: subjects **without cirrhosis** (n=180) will be randomized in a 1 : 1 ratio into Groups 1 and 2:

  Group 1: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily for 12 weeks

  Group 2: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily **and** RBV at a total daily oral dose of 1000-1200 mg divided twice a day (BID) for 12 weeks

- Cohort 2: subjects **with compensated cirrhosis** (n= 250) will be randomized in a 1:1 ratio into Groups 3 and 4:

  Group 3: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily **and** RBV at a total daily oral dose of 1000-1200 mg divided BID for 12 weeks.

  Group 4: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily for 24 weeks

Randomization will be stratified by the following:

  - GT 1 or 4
  - Prior SOF therapy in combination with SMV or without SMV

Number of Subjects Planned:	Approximately 430 subjects
Target Population:	Chronic GT 1 or 4 HCV infected adults who have failed prior treatment with SOF in combination with SMV ± RBV or with RBV ± PEG
Duration of Treatment:	Subjects will be treated for 12 or 24 weeks
Diagnosis and Main Eligibility Criteria:	Chronic GT 1 or 4, HCV infected, male and non-pregnant/non-lactating female subjects, ages 18 years or older, including subjects with or without compensated cirrhosis, with prior virologic failure after treatment with SOF in combination with SMV ± RBV or with RBV ± PEG, may be eligible for the study. Prior therapy with an NS5A inhibitor will be exclusionary. Reference Section 4.2 and 4.3 for detailed Inclusion and Exclusion criteria
Study Procedures/ Frequency:	Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. The screening window can be extended to 42 days for subjects requiring additional HCV genotype testing, cirrhosis determination or for extenuating circumstances with sponsor approval. All subjects will complete the following study visits: Screening, Baseline/Day 1, on treatment visits at the end of Weeks 1, 2, 4, 8, 12 for all study groups, and at the end of Weeks 16, 20 and 24 for study group 4, and posttreatment visits at Weeks 4 and 12 after the last dose of study drug. Subjects with HCV RNA < LLOQ at the posttreatment Week 12 visit will complete a posttreatment Week 24 visit unless confirmed viral relapse occurs. After consent is obtained, screening assessments will include physical examination, medical history, historical resistance test information (if available), height, weight, vital signs, 12-lead electrocardiogram (ECG), screening procedure related adverse events (AEs), concomitant medications (CM), safety laboratory tests (including hematology, chemistry, and coagulation), HCV RNA, serology (human immunodeficiency virus [HIV], HCV, hepatitis B virus [HBV]), HCV genotyping, hemoglobin A1c (HbA1c), assessment of the presence or absence of cirrhosis, screening for hepatocellular carcinoma (HCC) for subjects with cirrhosis, serum β-hCG (females of child bearing potential only), thyroid stimulating hormone (TSH), IL28B genotyping, urinalysis and urine drug screen.

	On-treatment assessments will include AEs, CMs, study drug dosing adherence (including pill count), physical examination (Baseline/Day 1 and Week 12 [Groups 1, 2, 3] and Week 24 [Group 4]), weight (Baseline/Day 1), vital signs, safety laboratory tests, HCV RNA, urine pregnancy tests (females of child bearing potential only). Posttreatment assessments will include AEs and CMs collected through 30 days after the last dose of study drug, HCV RNA, safety laboratory tests (including hematology and chemistry), and urine pregnancy tests (females of childbearing potential only). Samples for viral RNA sequencing/phenotyping will be collected at Baseline/Day 1 and every visit thereafter. Health Related Quality of Life (HRQoL) Surveys (short form 36 [SF-36], chronic liver disease questionnaire [CLDQ-HCV], functional assessment of chronic illness therapy-fatigue [FACIT-F], and work productivity and activity impairment questionnaire [WPAI]) will be conducted at Baseline/Day 1, on-treatment Weeks 4 and 12 for all study groups and Week 24 for study Group 4, Early Termination (if applicable), and posttreatment Weeks 4 and 12.
Test Product, Dose, and Mode of Administration:	LDV/SOF is manufactured as a FDC tablet, consisting of 90 mg of LDV and 400 mg SOF, for oral administration. Subjects will take 1 tablet daily with or without food. RBV will be supplied by Gilead Sciences. Subjects in study Groups 2 and 3 will take RBV with food at a total daily oral dose of 1000 or 1200 mg (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg) divided BID.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	Adverse events will be collected through the posttreatment Week 4 Visit. Clinical laboratory tests will be performed during treatment through the posttreatment Week 4 visit. The primary safety endpoint is any AE leading to permanent discontinuation of study treatment.
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® Ampliprep / COBAS® TaqMan® HCV Quantitative Test, v2.0.

Statistical Methods:	The primary efficacy endpoint is SVR12 (HCV RNA < lower limit of quantification [LLOQ] 12 weeks posttreatment) in the Full Analysis Set. The efficacy analyses will be performed separately for cohort 1 and 2. In Cohort 1, a non-inferiority test of SVR12 rates will be performed comparing Group 1 and 2. A non-inferiority margin of 10% will be applied. Non-inferiority will be established if the lower bound of the 2-sided 95% confidence interval (CI) of the difference in SVR12 (Group 1 – Group 2) is greater than -10%. The CI will be constructed using stratum-adjusted Mantel-Haenszel (MH) proportions, stratified by the randomization stratification factors (i.e., genotype 1or 4; prior SOF therapy in combination with SMV or without SMV). In Cohort 2, a non-inferiority test of SVR12 rates will be performed comparing Group 3 and 4. A non-inferiority margin of 10% will be applied. Non-inferiority will be established if the lower bound of the 2-sided 95% confidence interval (CI) of the difference in SVR12 (Group 1 – Group 2) is greater than -10%. The CI will be constructed using stratum-adjusted Mantel-Haenszel (MH) proportions, stratified by the randomization stratification factors (i.e., genotype 1or 4; prior SOF therapy in combination with SMV or without SMV). The 2-sided 95% exact CI using binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rates in Group 3 and 4. The primary safety endpoint is the proportion of subjects who discontinued from study treatment for an AE. Secondary efficacy endpoints include the proportion of subjects with HCV RNA < LLOQ at 4 and 24 weeks posttreatment; virologic failure, and emerging resistance. Additional endpoints to be studied will include prevalence of pre-existing NS5A resistance-associated polymorphisms and NS3/4A resistance-associated variants at baseline and change in NS3/4A RAVs from available historical resistance tests to baseline, and the effect of therapy on health related quality of life. Cohort 1: for the non-inferiority comparison of SVR12 in the noncirrhotic cohort (group 1 vs. 2) with a 10% non-inferiority margin, a sample size of 90 subjects per treatment group will provide at least 90% power to establish non-inferiority at 1-sided 0.025 level, assuming the SVR12 rates are 98% for both groups.

Cohort 2: for the non-inferiority comparison of SVR12 in the compensated cirrhotic cohort (group 3 vs. 4) with a 10% non-inferiority margin, a sample size of 125 subjects per treatment group will provide at least 90% power to establish non-inferiority at 1-sided 0.025 level, assuming the SVR12 rates are 95% for both groups.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
β-hCG	β-human chorionic gonadotropin
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APRI	AST platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BID	twice a day
BMI	body mass index
BW	body weight
CI	confidence interval
CL_{cr}	creatinine clearance
CLDQ	chronic liver disease questionnaire
CM	concomitant medication
CRO	contract (or clinical) research organization
CSR	clinical study report
DAA	direct acting antiviral
dL	Deciliter
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
eCRF	electronic case report form(s)
ESA	erythropoiesis stimulating agent
eSAE	electronic serious adverse event
Emax	maximal effect
EOT	End of Treatment
ET	Early Termination
EU	European Union
FACIT-F	functional assessment of chronic illness therapy-fatigue
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed-dose combination
FEV_1	forced expiratory volume in one second

GCP	Good Clinical Practice (Guidelines)
GCSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
GT	genotype (viral)
Hb	Hemoglobin
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HLGT	high-level group term
HRQoL	health related quality of life
HLT	high-level term
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IDSA	Infectious Disease Society of America
IEC	independent ethics committee
IFN	interferon
IL28B	IL28B gene
IND	Investigational New Drug (Application)
INR	International Normalized Ratio of prothrombin time
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
IWRS	interactive web response system
kg	Kilogram
kPa	Kilopascal
L	Liter
LDH	lactate dehydrogenase
LDV	ledipasvir
LLN	lower limit of the normal range
LOD	lower limit of detection
LLOQ	lower limit of quantification
LLT	lower-level term
MCV	mean cellular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MH	Mantel-Haenszel
mL	Milliliter

Min	Minute
mmHg	millimeters mercury
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NS (3/4A/5A)	[HCV] non-structural protein
PCR	polymerase chain reaction
PEG	pegylated interferon
PI	protease inhibitor
PK	Pharmacokinetic
PT	preferred term
QD	once daily
QTcF	QT interval corrected using Fridericia' formula
RAV	resistance-associated variants
RBC	red blood cell count
RBV	Ribavirin
RDRP	RNA-dependent RNA polymerase
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	standard deviation
SF-36	short form (36)
SMV	Simeprevir
SOC	standard of care
SOF	sofosbuvir (GS-7977; formerly PSI-7977)
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	sustained virologic response
TND	target not detected
TPO	Thrombopoietin
TSH	thyroid stimulating hormone
ULN	upper limit of the normal range
US	United States
vRVR	very rapid virologic response
WBC	white blood cell count
WPAI	work productivity and activity impairment questionnaire

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) infection is a global health challenge with an estimated 150 million individuals infected worldwide {18359}. Currently there are 6 major HCV genotypes recognized {21479}. Genotypes 1, 2, and 3 are common throughout North America and Europe and when combined account for approximately 75% of the chronic HCV infections globally. Genotype 4, which is common in the Middle East and Africa, accounts for approximately 20% of the global HCV population. Genotypes 5 and 6 are the least prevalent and are generally found in South Africa and South East Asia, respectively {19851}.

In the United States (US), approximately 2.7 million people have chronic HCV infection {28338} and HCV infection causes over 15,000 deaths each year {20446}, although under-reporting of HCV infection on death certificates may contribute to as much as a 5-fold underestimation of the actual number of deaths {28339}. Of the HCV related deaths that are reported, almost three quarters occurred in the baby-boomer generation with a median age of death of 57 years, which is approximately 20 years less than the average lifespan {28472}. Successful treatment of chronic HCV infection reduces the need for liver transplant, the incidence of hepatocellular carcinoma (HCC) and overall mortality {25891}. Thus, the public health benefit of safe and effective HCV treatment regimens is high.

The development of Sovaldi® (sofosbuvir, SOF), a nucleotide analog HCV NS5B polymerase inhibitor, represents a major advance in the treatment of HCV as SOF-based regimens are shorter in duration, better tolerated and result in higher sustained virologic response (SVR) rates than prior therapies. SOF in combination with ribavirin (RBV) ± pegylated interferon (PEG) for varying durations was approved in the US and Canada in December 2013 for the treatment of genotype 1, 2, 3 and 4 HCV infection and was granted marketing authorization by the European Commission in January 2014 for the treatment of genotypes 1-6 HCV infection{27503, 27721, 27832}. The availability of these combinations has led to the treatment of HCV in thousands of patients in many countries. Furthermore, based on the results of a phase 2 study, COSMOS, which evaluated the safety and efficacy of SOF in combination with the NS3/4A protease inhibitor, simeprevir (Olysio™, Galexos™, SMV), many patients with genotype 1 or 4 HCV infection were treated with this combination with or without RBV {30255}. Similarly, the next wave of therapies for the treatment of HCV includes combinations of direct acting antivirals (DAAs), including SOF, that will obviate the need for administration of PEG and RBV. Harvoni® (ledipasvir and sofosbuvir, LDV/SOF) was recently approved for treatment of genotype 1 HCV infection in the US and Canada and for treatment of genotypes 1, 3, and 4 HCV infection in the European Union. LDV/SOF is the first interferon (IFN)-free regimen with high SVR rates following 8-24 weeks of treatment across treatment-naïve and treatment-experienced patients, including patients who failed to achieve SVR with PEG + RBV ± NS3/4A protease inhibitors, irrespective of cirrhosis {31179}.

Most current HCV drug development effort focuses on genotype 1 HCV infection as this is the most prevalent HCV genotype in developed countries. As more DAA agents are approved and available, the unmet medical need for effective treatment options for the patients who fail DAA-based HCV therapy will increase. There are limited data from Phase 2 trials that have shown high efficacy of LDV/SOF-based therapy when used for treatment of patients who did not achieve SVR with a prior SOF regimen. This is supported by the fact that in SOF Phase 3 studies, virologic failure was not associated with the emergence of the S282T SOF resistance-associated variance (RAV), and LDV would be fully active against the S282T {28585}. Emerging data from real-world cohorts, such as HCV-TARGET and Trio Health, suggest that approximately 10% to 25% of patients with HCV genotype 1 infection treated for 12 weeks with the combination of SOF + SMV have experienced treatment failure, which appears to be more common in persons infected with HCV genotype 1a and those with cirrhosis {31665, 31993}. In the Phase 2 COSMOS study, virologic failure with SMV + SOF ± RBV was associated with emergence of NS3/4A RAVs but not with the S282T {30255}. Both SOF and LDV are fully active against substitutions associated with resistance to NS3/4A protease inhibitors.

Based on early data showing high efficacy with LDV/SOF as treatment for patients who failed to achieve SVR with a SOF regimen and lack of cross-resistance of LDV/SOF with SMV, the December 19, 2014 version of the American Association for the Study of Liver Diseases (AASLD)/Infectious Disease Society of America (IDSA) HCV Treatment Guidance recommended the use of LDV/SOF ± RBV for 24 weeks for treatment of patients who need urgent treatment and in whom a previous SOF-containing regimen in combination with RBV ± PEG or SMV has failed {32887}.

Additional studies are needed to evaluate the efficacy, safety, and the optimal duration of LDV/SOF regimens for treatment of HCV in patients who failed to achieve SVR with prior SOF-based HCV therapy.

1.2. Ledipasvir/Sofosbuvir Fixed Dose Combination (LDV/SOF FDC)

Ledipasvir/sofosbuvir fixed-dose combination (LDV/SOF FDC; Harvoni®) combines two HCV specific DAA agents into a single tablet for the treatment of chronic HCV infection. Ledipasvir is a HCV NS5A inhibitor and sofosbuvir is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed HCV replication, irrespective of HCV genotype.

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

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

1.2.1. Clinical Trials of LDV/SOF Relevant to the Proposed Study

1.2.1.1. Study GS-US-337-0122 (ELECTRON-2)

Study GS-US-337-0122 is an ongoing open label Phase 2 study evaluating LDV/SOF ± RBV in a variety of patient populations. Of particular interest, 19 non-cirrhotic patients with HCV genotype (GT) 1 that relapsed after treatment with a SOF-based regimen were retreated with LDV/SOF plus RBV for 12 weeks. The mean age was 55 years (range: 39–65); 13 subjects (68%) were male; and 17 subjects (89%) were infected with HCV GT 1a. Prior SOF treatment included 12 weeks of SOF + RBV in 4 treatment-naïve subjects, 12 weeks of SOF + RBV in 6 prior null responders, 6 weeks of LDV/SOF + RBV in 8 treatment-naïve subjects, and 12 weeks of the NS5B non-nucleoside polymerase inhibitor, GS-9669, plus SOF + RBV in 1 treatment-naïve subject. All 19 subjects achieved SVR12 after treatment with 12 weeks of LDV/SOF + RBV. Adverse events (AEs) occurred in 17 of 19 (90%) subjects, but none of the subjects discontinued treatment due to an AE. The most frequent AEs, which occurred in ≥15% of subjects, were insomnia, fatigue, headache, rash, nausea, upper respiratory tract infections, cough, and hemolytic anemia. Grade 3 hemoglobin decline (<10 g/dL) occurred in 3 (16%) subjects. There were no grade 4 hemoglobin abnormalities.

1.2.1.2. Study GS-US-337-1118

GS-US-337-1118 is an ongoing Phase 2, multicenter, open-label study in a variety of patient populations. Of interest, 51 subjects who had previously participated in Gilead HCV studies and who did not achieve SVR after treatment with a SOF-based regimen were enrolled. All subjects were assigned to receive 12 weeks of LDV/SOF plus RBV. The mean age was 54 years (range: 27–68), 31 subjects (61%) were male, and 30 subjects (59%) were infected with HCV GT 1a. Cirrhosis was identified in 14 (27%) of the subjects. Prior SOF treatment included SOF + RBV + PEG in 25 (49%), SOF + RBV in 20 (39%), and SOF monotherapy in 1 (2%) of the subjects. Five subjects (10%) had received SOF placebo + RBV + PEG or GS-0938 monotherapy in their parent protocol. Overall, 50 of 51 (98%) of subjects achieved SVR12 when retreated with LDV/SOF + RBV for 12 weeks. Fifty GT 1 subjects, including 14 with cirrhosis, achieved SVR. The only subject who relapsed was incorrectly genotyped as GT 1a at baseline in the parent protocol, but viral sequencing subsequently determined that the subject was infected with GT 3a at baseline and at time of relapse. AEs occurred in 41 (80%) subjects, and 1 subject discontinued treatment due to an AE. The most frequent AEs, which occurred in ≥15% of subjects, were fatigue and headache. Grade 3 hemoglobin decline (<10 g/dL) occurred in 5 (10%) subjects. There were no grade 4 hemoglobin abnormalities.

1.2.1.3. Study CO-US-337-0117 (SYNERGY)

SYNERGY is an ongoing Phase 2a, open-label study in a variety of patients, conducted at the National Institutes of Health (NIH) in Bethesda, Maryland, and at community clinics that are part of the District of Columbia Partnership for HIV/AIDS Progress in Washington, DC. Of interest, subjects who had relapsed after 24 weeks of treatment with SOF plus RBV in the National Institute of Allergy and Infectious Disease (NIAID) SPARE study were offered retreatment in the SYNERGY study. Of the 17 eligible subjects, 3 did not participate in the study. Fourteen

subjects enrolled and were treated with LDV/SOF, administered daily as a single tablet regimen, for 12 weeks. Most study subjects were black men with IL28B non-CC genotype and had a median age of 59 years (range: 48-70). Eight (57%) of the subjects had HCV GT 1a infection, and 7 (50%) had advanced liver disease (Knodell Histology Activity Index score of 3 or 4). All 14 subjects treated with LDV/SOF for 12 weeks achieved SVR, including 7 with advanced liver disease and 1 with a detectable NS5B S282T mutation after previous SOF + RBV therapy. AEs occurred infrequently, and none of the subjects discontinued treatment due to AEs. No significant hemoglobin abnormalities were observed during LDV/SOF therapy.

Another cohort of interest in the SYNERGY study is 21 HCV GT 4 infected treatment-naïve and experienced subjects, with or without cirrhosis. Subjects in this cohort were administered 12 weeks of LDV/SOF as a single tablet regimen. The mean age was 55 years; 8 (38%) subjects were treatment-experienced; 2 (10%) subjects had F3 stage of fibrosis; and 7 (33%) subjects had cirrhosis at baseline. One subject had not reached the 12 Week posttreatment time point at the time of the interim analysis. Nineteen of 20 subjects (95%) achieved SVR12, and one subject relapsed after treatment with 12 weeks of LDV/SOF. The most frequent AEs, which occurred in ≥10% of subjects, were fatigue, nausea, diarrhea, and upper respiratory tract infection. There were no treatment discontinuations due to AEs, no serious AEs, and no hemoglobin abnormalities during treatment with LDV/SOF.

1.2.1.4. Study GS-US-337-0121 (SIRIUS)

SIRIUS is a Phase 2, randomized, double-blind, placebo controlled study evaluated LDV/SOF + RBV for 12 weeks and LDV/SOF for 24 weeks in HCV GT 1 subjects with compensated cirrhosis who previously failed sequential treatments of PegIFN + RBV and HCV PI + PegIFN + RBV regimens. Among 155 subjects enrolled, the mean age was 56 years (23-77), 74% were male, 97% were White, mean BMI was 27 kg/m^2, 26% had varices, 63% had GT 1a. Overall, SVR12 was achieved in 96% (74/77) of subjects with LDV/SOF + RBV and 97% (75/77) of subjects with 24 weeks LDV/SOF. Of the 155 patients enrolled and treated, five (3%) had virologic failure. The effect of pre-treatment NS5A resistance associated polymorphisms (RAPs) on SVR12 in patients who have not been previously exposed to an NS5A inhibitor was also evaluated (GS-US-337-0121; Final Clinical Study Report, Dated 04 March 2015). Fifteen subjects in the 24 week LDV/SOF arm and 15 subjects in the 12 week LDV/SOF + RBV arm had pre-treatment NS5A RAPs. In the 24 week arm, 13/15 subjects with pre-treatment NS5A RAPs achieved SVR12; whereas in the 12 week LDV/SOF + RBV arm, 15/15 achieved SVR12. One LDV/SOF + RBV subject discontinued treatment due to AE. The most frequent AEs, which occurred in ≥10% of subjects, were asthenia, headache, pruritus, and fatigue. Hemoglobin decline (< 10 g/dL) occurred in 5 (3%) subjects. Hemoglobin decline (< 8.5 g/dL) was reported in 4 (3%) subjects.

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}. RBV monotherapy has little or no effect on the replication of HCV in vivo but can result in normalization of serum alanine aminotransferase (ALT) activity

and improvement in liver histology. When combined with IFN or PEG therapy, RBV decreases substantially the relapse rate seen after cessation of IFN therapy {12557}, {12558}.

Ribavirin is a known teratogen (Food and Drug Administration [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 (7 months for males).

A comprehensive review of RBV is contained in the package insert/SmPC.

1.4. Rationale for This Study

There are limited data from small Phase 2 trials that have evaluated the efficacy and safety of retreating GT 1 HCV infected subjects who did not achieve SVR after treatment with SOF in combination with other antivirals. ELECTRON-2 is a Phase 2, open-label study, in which 19 non-cirrhotic subjects with HCV GT 1 that relapsed after treatment with a SOF-based regimen were retreated with LDV/SOF plus RBV for 12 weeks. All 19 subjects achieved SVR, including 8 who had been previously treated with 6 weeks of LDV/SOF + RBV and 1 who had been previously treated with 12 weeks of the NS5B non-nucleoside polymerase inhibitor, GS-9669 + SOF + RBV {29292}. GS-US-337-1118 is another Phase 2, multicenter, open-label study that evaluated the safety and efficacy of LDV/SOF plus RBV for 12 weeks as treatment for 51 subjects who had previously participated in Gilead HCV studies and who did not achieve SVR after treatment with a SOF-based regimen. Fifty GT 1 subjects, including 14 with cirrhosis, achieved SVR when retreated with LDV/SOF + RBV for 12 weeks. The only subject who relapsed was incorrectly genotyped as GT 1a at baseline in the parent protocol, but viral sequencing subsequently determined that the subject was infected with GT 3a at baseline and at time of relapse {34995}. Finally, SYNERGY was a Phase 2a, open-label study, in which 14 subjects with HCV GT 1 that relapsed after treatment with SOF plus RBV for 24 weeks were re-treated with LDV/SOF, administered as a single tablet regimen for 12 weeks. All 14 subjects treated with LDV/SOF alone for 12 weeks achieved SVR, including 7 with advanced liver disease (Knodell Histology Activity Index score of 3 or 4) and 1 with a detectable NS5B S282T mutation after previous SOF plus RBV therapy {31601}. The results of these studies indicate that GT 1 patients who fail to achieve SVR with SOF-based HCV therapy may be successfully cured with 12 weeks of treatment with LDV/SOF ± RBV. There have been no studies to evaluate the efficacy and safety of treatment with LDV/SOF ± RBV in the setting of SOF + SMV failure.

In order to confirm the efficacy data observed in the above mentioned studies and to evaluate the duration of therapy, this Phase 3b multicenter, open-label study has been designed to evaluate the efficacy and safety and the optimal duration of treatment with LDV/SOF with or without RBV for 12 or 24 weeks in GT 1 or 4 HCV infected subjects with or without compensated cirrhosis, who have not achieved SVR after treatment with SOF + SMV or SOF + RBV ± PEG. Approximately 50% of subjects enrolled may have had prior treatment with SOF + SMV ± RBV, and approximately 5% of subjects may be infected with GT 4 HCV. Patients previously treated with a NS5A inhibitor will be excluded given that there is very limited data on the efficacy of LDV/SOF utilized for treatment of HCV in this population.

1.4.1. Rationale for Length and Composition of Treatment Regimens in Study Design

In the Phase 3 ION-2 study, which evaluated the safety and efficacy of LDV/SOF ± RBV for 12 and 24 weeks in subjects who had failed treatment with PEG + RBV ± a NS3/4A protease inhibitor, the addition of RBV did not improve SVR and led to higher rates of AEs {28585}. Overall, 94% (102/109) of subjects who were treated with 12 weeks of LDV/SOF and 99% (108/109) of subjects who were treated with 24 weeks of LDV/SOF achieved SVR. Subjects with cirrhosis in the ION-2 study achieved a 100% (22/22) SVR rate with 24 weeks of LDV/SOF treatment as compared with 86% (19/22) after 12 weeks of treatment; however, the study was not powered to detect a statistically significant difference in this population. In a retrospective pooled analysis of GT 1 HCV-infected treatment-experienced subjects with cirrhosis enrolled in LDV/SOF Phase 2 and 3 studies, LONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, and SIRIUS, SVR rates of 90% (64/71), 96% (153/159), and 98% (98/100) were observed with 12 weeks of LDV/SOF alone, 12 weeks of LDV/SOF + RBV and 24 weeks of LDV/SOF alone, respectively {34557}. Based on 95% confidence intervals, no statistical differences were observed in this analysis although numerically higher SVR rates were seen with 12 weeks of LDV/SOF + RBV and 24 weeks of LDV/SOF. In particular, in the double-blind, placebo controlled SIRIUS study, SVR12 was achieved in 96% (74/77) after 12 weeks of treatment with LDV/SOF + RBV vs. 97% (75/77) after 24 weeks of treatment with LDV/SOF in subjects with HCV genotype 1 and cirrhosis, who were non-responsive to previous therapy with PEG + RBV and protease inhibitors (PI) + PEG + RBV {34411}. The effect of pre-treatment NS5A resistance associated polymorphisms (RAPs) on SVR12 in patients who have not been previously exposed to an NS5A inhibitor was also evaluated in the Phase 2 SIRIUS study (GS-US-337-0121; Final Clinical Study Report, Dated 04 March 2015). Fifteen subjects in the 24 week LDV/SOF arm and 15 subjects in the 12 week LDV/SOF + RBV arm had pre-treatment NS5A RAPs. In the 24 week arm, 13/15 subjects with pre-treatment NS5A RAPs achieved SVR12; whereas in the 12 week LDV/SOF + RBV arm, 15/15 achieved SVR12. This data suggest that 12 weeks of LDV/SOF + RBV is at least as effective in patients with pre-treatment NS5A RAPs as 24 weeks of LDV/SOF.

Most recently, 335 HCV GT 1 and GT 4 treatment-naïve and treatment-experienced subjects, co-infected with HIV-1 and with or without cirrhosis, were enrolled in the Phase 3, multicenter, open-label ION-4 study {34324}. All subjects were treated with 12 weeks of LDV/SOF. Overall, 96% (321/335) of subjects achieved SVR. SVR rates were similar across subgroups of subjects and without regard to prior treatment regimen or response nor presence or absence of cirrhosis. Forty-six of 47 treatment-experienced subjects with cirrhosis (98%) achieved SVR after receiving 12 weeks of LDV/SOF therapy. Furthermore, all 13 subjects who failed a prior SOF-containing regimen achieved SVR. In another Phase 3 study conducted in Japan, 28 of 28 (100%) of GT 1 treatment-experienced subjects with cirrhosis also achieved SVR after treatment with just 12 weeks of LDV/SOF {34608}. Thus, data from these two phase 3 trials, contrary to the ION-2 trial, suggest that 12 weeks of therapy, even without RBV, may be equally efficacious to 24 weeks of therapy in treatment experienced patients, including those with cirrhosis.

In summary, high efficacy was observed in Phase 2 studies that evaluated 12 weeks of LDV/SOF ± RBV for treatment of HCV GT 1 infected subjects who did not achieve SVR after treatment with SOF-based therapy, including those with cirrhosis. However given the lack of statistical power for subgroup analyses in these and other Phase 3 trials, there remains a need to further evaluate the optimal duration of treatment and the need for RBV. Duration of therapy and the need for RBV are important factors for patients and healthcare providers in terms of adherence, adverse events, and cost of healthcare. Therefore, this study is designed as a prospective, randomized, multicenter study for treatment of GT 1 and GT 4 HCV in subjects who failed to achieve SVR after treatment with SOF in combination with RBV ± PEG or with SMV ± RBV, with Cohort 1 being statistically powered to evaluate the need for RBV as part of a 12 week LDV/SOF regimen in non-cirrhotic subjects and Cohort 2 being statistically powered to evaluate the efficacy of LDV/SOF + RBV for 12 weeks compared to LDV/SOF for 24 weeks among subjects with cirrhosis.

1.5. Compliance

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

2. OBJECTIVES

The primary objectives of this study are as follows:

- To evaluate the efficacy of treatment with LDV/SOF FDC for 12 weeks with or without RBV in subjects without cirrhosis, and LDV/SOF FDC for 12 weeks with RBV or LDV/SOF FDC for 24 weeks without RBV in subjects with cirrhosis, as measured by the proportion of subjects with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)

- To evaluate the safety and tolerability of LDV/SOF FDC for 12 weeks with or without RBV in subjects without cirrhosis, and LDV/SOF FDC for 12 weeks with RBV or LDV/SOF FDC for 24 weeks without RBV in subjects with cirrhosis, as assessed by review of the accumulated safety data

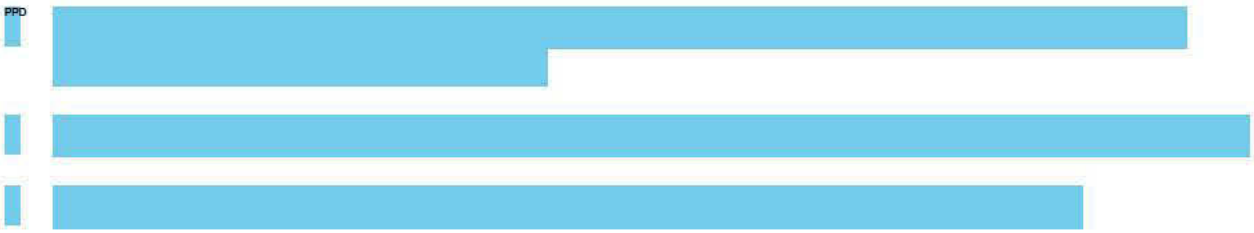
The secondary objectives of this study are as follows:

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

- To determine the proportion of subjects with virologic failure

- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation among subjects with virologic failure

The exploratory objectives of this study are:



3. STUDY DESIGN

3.1. Treatment Plan and Regimen

This is a Phase 3b, multicenter, open label study in adult male and female subjects with chronic GT 1 or 4 HCV infection and who have failed prior SOF-based HCV therapy, specifically, SOF in combination with SMV ± RBV or with RBV ± PEG.

Approximately 50% of subjects enrolled may have had prior treatment with SOF + SMV ± RBV. Approximately 5% of subjects may be infected with GT 4 HCV.

Approximately 430 subjects will be enrolled in 2 cohorts:

- Cohort 1: subjects **without cirrhosis** (n=180) will be randomized in a 1:1 ratio into Groups 1 and 2:

  Group 1: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily for 12 weeks

  Group 2: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily **and** RBV at a total daily oral dose of 1000-1200 mg divided twice a day (BID) for 12 weeks

- Cohort 2: subjects **with compensated cirrhosis** (n=250) will be randomized in a 1:1 ratio into Groups 3 and 4:

  Group 3: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily **and** RBV at a total daily oral dose of 1000-1200 mg divided BID for 12 weeks.

  Group 4: LDV/SOF FDC tablet (LDV 90 mg/SOF 400 mg) once daily for 24 weeks

Randomization will be stratified by the following:

  - GT 1 or 4
  - Prior SOF therapy in combination with SMV or without SMV

3.2. HCV Virologic Response-Based Treatment Stopping Criteria

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

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

Confirmation should be performed as soon as possible and must occur no later than 2 weeks after an initial observation indicating virologic failure.

All subjects who terminate treatment early will complete the Early Termination visit and the posttreatment Week 4 and 12 visits. Subjects with HCV RNA < LLOQ at the posttreatment Week 12 visit will complete a posttreatment Week 24 visit unless confirmed viral relapse occurs.

3.3. Treatment Discontinuation Criteria

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

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

- Unacceptable toxicity, as defined in Section 7 of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Pregnancy of female subject, or female partner of male subject
- Efficacy failure as defined in Section 3.2
- Significant protocol violation that impacts subject safety
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy or other reason
- Discontinuation of the study at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

If a subject meets discontinuation criteria during treatment, an Early Termination visit will be required. Early Termination visits should be scheduled as soon as possible following discontinuation of treatment. All subjects should subsequently complete the posttreatment Week 4 and 12 visits. Subjects with HCV RNA < LLOQ at the posttreatment Week 12 visit will complete a post treatment Week 24 visit unless confirmed viral relapse occurs.

3.4. Biomarker Testing

3.4.1. Biomarker Samples for Optional Future Research

PPD

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A total of approximately 430 subjects will be enrolled in 2 Cohorts. Approximately 180 subjects without cirrhosis will be enrolled in Cohort 1 per the assignments described in Section 3.1, and approximately 250 subjects with compensated cirrhosis will be enrolled in Cohort 2 per the assignments described in Section 3.1.

Approximately 50% of subjects enrolled may have had prior treatment with SOF + SMV ± RBV. Approximately 5% of subjects may be infected with GT 4 HCV.

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. HCV RNA > 15 IU/mL at Screening
4. HCV genotype 1 or 4 at Screening by the Central Laboratory
5. Chronic HCV infection (≥ 6 months) documented by prior medical history
6. Prior virologic failure after treatment with SOF in combination with SMV ± RBV or with RBV ± PEG.
    a. Virologic failure is defined as having relapse in HCV RNA after the cessation of treatment, having achieved unquantifiable levels while on treatment; patients who experienced virologic breakthrough are excluded.
    b. Subject must not have discontinued the prior SOF regimen due to an AE, unless the AE was considered to be directly related to PEG.
    c. Subjects must not have failed the prior SOF regimen due to treatment non-adherence.
    d. The most recent treatment must be completed at least 8 weeks prior to Screening.
    e. The subject's medical records must include sufficient detail to confirm eligibility.
7. Cirrhosis Determination
    a. Presence of cirrhosis is defined as any one of the following:
        i. FibroTest® score ≥ 0.75 and AST:platelet ratio index (APRI) ≥ 2 during Screening
        ii. Liver biopsy showing cirrhosis (eg, Metavir score = 4 or Ishak score ≥5)

iii. Transient elastography (FibroScan®) with a result of >12.5 kPa

b. Absence of cirrhosis is defined as any one of the following:

i. FibroTest® score ≤ 0.48 and APRI ≤ 1.0 performed during Screening

ii. Liver biopsy within 2 years of Screening showing absence of cirrhosis

iii. Transient elastography (FibroScan®) with a result of ≤ 12.5 kPa within 6 months of Baseline/Day 1

In the absence of a definitive diagnosis of presence or absence of cirrhosis by Fibrotest® and APRI using the above criteria, a liver biopsy or Fibroscan® is required. Presence of cirrhosis, defined by any of the above criteria, will supersede absence of cirrhosis determined via the other methods.

8. Liver imaging within 6 months prior to Baseline/Day 1 is required in cirrhotic subjects to exclude hepatocellular carcinoma (HCC). [Note: Study sites in Germany will not use CT and will only use ultrasound imaging to determine absence of HCC]
9. Females of childbearing potential (as defined in Appendix 4) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Baseline/Day 1 prior to randomization
10. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 4
11. Lactating females must agree to discontinue nursing before the study drug(s) are administered
12. Subject must be of generally good health, with the exception of chronic HCV infection, as determined by the Investigator
13. Subject must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments

4.3. Exclusion Criteria

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

1. Prior exposure to approved or experimental NS5A inhibitors
2. Prior exposure to nucleos(t)ide polymerase inhibitors, other than SOF
3. Current or prior history of any of the following:
   a. Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol; subjects currently under evaluation for a potentially clinically significant illness (other than HCV) are also excluded
   b. Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug

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

d. Clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage). The presence of varices is acceptable.

e. Solid organ transplantation

f. Significant pulmonary disease, significant cardiac disease

g. Psychiatric hospitalization and/or suicide attempt within the last 2 years

h. Malignancy within 5 years prior to Screening, with the exception of basal cell skin cancer or squamous cell cancer/carcinoma in situ cured by surgical resection. Subjects under evaluation for possible malignancy are not eligible

i. Significant drug allergy (eg, hepatotoxicity)

4. Pregnant or nursing female or male with pregnant female partner
5. Females who may wish to become pregnant and/or plan to undergo egg harvesting during the course of the study and up to 30 days of the last dose of study drug if not using RBV or up to 6 months if using RBV
6. Screening ECG with clinically significant abnormalities
7. Subjects has the following laboratory parameters at Screening:
   a. ALT > 10 x the upper limit of normal (ULN)
   b. AST > 10 x ULN
   c. Direct bilirubin > 1.5 x ULN
   d. Platelets < 50,000/μL
   e. HbA1c > 10%
   f. Creatinine clearance (CLcr) < 60 mL/min as calculated by the Cockcroft-Gault equation
   g. Hemoglobin < 11 g/dL for female subjects; < 12 g/dL for male subjects
   h. Albumin < 3.0 g/dL
   i. INR > 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR
8. Chronic liver disease of a non-HCV etiology (eg, hemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency, cholangitis)
9. Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV)
10. Clinically-relevant alcohol or drug abuse within 12 months of screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator
11. Contraindications to RBV therapy, including significant history of clinically significant hemoglobinopathy (e.g., sickle cell disease, thalassemia)

12. Use of any prohibited concomitant medications as described in Section 5.4
13. Chronic use of systemically administered immunosuppressive agents (e.g., prednisone equivalent > 10 mg/day)
14. Known hypersensitivity to ribavirin, ledipasvir, sofosbuvir, metabolites or formulation excipients

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization and Blinding

An Interactive Web Response System (IWRS) will be employed to manage subject randomization and treatment assignment. The study is open-label therefore blinding is not required.

Randomization will be stratified by the following:

- GT 1 or 4
- Prior SOF therapy in combination with SMV or without SMV

5.2. Description and Handling of LDV/SOF FDC

5.2.1. Formulation of LDV/SOF FDC

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

5.2.2. Packaging and Labeling of LDV/SOF FDC

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

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

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

5.2.3. Storage and Handling of LDV/SOF FDC

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

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

5.2.4. Dosage and Administration of LDV/SOF FDC

LDV/SOF FDC tablet is to be administered once daily with or without food. Each subject must be given instructions to maintain approximately the same daily dosing interval between study drug doses.

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

5.3. Description and Handling of RBV – Applicable to Study Groups 2 & 3

5.3.1. Formulation of RBV

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.

5.3.2. Packaging and Labeling of RBV

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.

All RBV bottles to be distributed to centers shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA), Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (Feb 2010) and local regulations as applicable.

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

5.3.3. Storage and Handling of RBV

RBV tablets should be stored at 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F).

All study 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 study 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.

5.3.4. Dosage and Administration of RBV

RBV will be administered as 1000-1200 mg by mouth daily (1000 mg for subjects weighing <75 kg and 1200 mg for subjects weighing ≥ 75 kg) given in a divided daily dose. Subjects who are to receive total daily doses of 1000 mg, should be instructed to take 3 tablets in the morning and 2 tablets in the evening (or 2 tablets in the morning and 3 in the evening). For those who are to receive 1200 mg of RBV, subjects should take 3 tablets twice daily. RBV should be dosed with food.

5.4. Prior and Concomitant Medications

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

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

- Hematologic stimulating agents (e.g., erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)

- Investigational agents or devices for any indication

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e., P-gp) with study drug(s) may result in pharmacokinetic (PK) interactions resulting in increases or decreases in exposure of study drug(s) or these medications. The use of the following agents is **prohibited from 21 days prior to Baseline/Day 1 through the end of treatment.** 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 or are to be used with caution 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
Anticonvulsants[c]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials[c]	Rifabutin, Rifapentine, Rifampin	
Cardiac Medications	Amiodarone[e]	Digoxin[b], Dabigatran etexilate[f]
Herbal/Natural Supplements[c]	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[d]	Rosuvastatin	Atorvastatin, Simvastatin, Pravastatin, Pitavastatin, Fluvastatin, Lovastatin

a It is recommended to separate antacid and LDV/SOF FDC administration by 4 hours. H2-receptor antagonists may be administered simultaneously with or staggered from LDV/SOF FDC at a dose that does not exceed doses comparable to famotidine 40 mg twice daily. Proton-pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with LDV/SOF FDC. Proton-pump inhibitors should not be taken before LDV/SOF FDC.

b Co-administration of LDV/SOF FDC with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when co-administered with LDV/SOF FDC.

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

d Use with study drug may result in an increase in the concentration of the HMG-CoA Reductase Inhibitors. When co-administered with LDV/SOF, a reduced dose of statin should be considered. 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

f Co-administration of LDV/SOF FDC with dabigatran etexilate may increase dabigatran exposure. Clinical monitoring, looking for signs of bleeding and anaemia, is recommended when dabigatran etexilate is co-administered with LDV/SOF. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.

5.5. Accountability of Study Drug(s)

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

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

- Record the date received and quantity of study drug(s) bottles
- Record the date, subject number, subject initials, the study drug(s) bottle number dispensed
- Record the date, quantity of used and unused study drug(s) returned, along with the initials of the person recording the information.

5.5.1. Return or Disposal of Study Drug(s)

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

6. STUDY PROCEDURES

All subjects will complete the following study visits: Screening, Baseline/Day 1, on treatment visits at the end of Weeks 1, 2, 4, 8 and 12 for all study groups, and at the end of Weeks 16, 20 and 24 for study Group 4. All subjects will complete the posttreatment visits at Weeks 4 and 12 after the last dose of study drug. Subjects with HCV RNA < LLOQ at the posttreatment Week 12 visit will complete a posttreatment Week 24 visit unless confirmed viral relapse occurs.

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

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

6.1. Screening Visit

Subjects will be screened within 28 days of the Baseline/Day 1 randomization visit to determine eligibility for participation in the study. The screening window can be extended to 42 days for subjects requiring additional HCV genotype testing, cirrhosis determination or for extenuating circumstances with sponsor approval.

The following will be performed and documented:

- Obtain written informed consent
- Determine eligibility (Reference Sections 4.2 & 4.3)
- Obtain medical history, including information on prior HCV treatment history and available historical resistance tests
- Complete physical examination including body weight, and height
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Perform 12-lead ECG
- Obtain blood samples (Reference Study Procedures Table, Appendix 2)
- Obtain urine sample (Reference Study Procedures Table, Appendix 2)
- Obtain blood sample for pregnancy test (for females of child bearing potential only)
- Obtain details of concomitant medications
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form

- Determine cirrhosis status (Reference Section 4.2). If the presence of cirrhosis is determined, then the appropriate diagnostic imaging must be performed within 6 months prior to Baseline/Day 1 to exclude the presence of HCC.

A single retest of screening labs is permitted only if there is reason to believe the retest value will be within accepted parameters, if the initial value was either due to a sample processing error or due to an extenuating circumstance.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the Baseline/Day 1 visit for enrollment into the study.

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

6.2. Baseline/Day 1 Visit

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

The following will be performed and documented:

- Confirm eligibility (Reference Sections 4.2 & 4.3)
- Perform physical examination including body weight
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications
- Obtain blood samples (Reference Study Procedures Table, Appendix 2)
- PPD
- Obtain urine sample for pregnancy test (for females of child bearing potential only)
- Conduct pregnancy prevention counseling
- Subject completes Health Related Quality of Life Surveys

- Randomization and study drug(s) administration
  - Enter subject information in the IWRS to receive study group assignment
  - Dispense study drug(s) as directed by the IWRS
  - Instruct the subject on the packaging, storage and administration of the study drug(s)
  - Administer the first dose of study drug(s)

6.3. Week 1 & 2 Visits (± 3 days)

The following will be performed and documented:

- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications
- Obtain blood samples (Reference Study Procedures Table, Appendix 2)
- Conduct pregnancy prevention counseling
- Assess adherence with study drug(s) dosing regimen including pill count

6.4. Week 4, 8, (16 and 20 for Study Group 4 only) Visits (± 3 days)

The following will be performed and documented:

- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications
- Obtain blood samples (Reference Study Procedures Table, Appendix 2)
- Obtain urine sample for pregnancy test (for females of child bearing potential only)
- Conduct pregnancy prevention counseling
- Subject completes Health Related Quality of Life Surveys (Week 4 only)
- Assess adherence with study drug(s) dosing regimen including pill count
- Dispense study drug(s) as directed by the IWRS

6.5. Week 12 (and 24 for Study Group 4 only) or Early Termination Visit (± 3 days)

The following will be performed and documented:

- Perform physical examination (Week 12 [study groups 1, 2, 3] or Week 24 [study group 4])
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications
- Obtain blood samples (Reference Study Procedures Table, Appendix 2)
- PPD
- Obtain urine sample for pregnancy test (for females of child bearing potential only)
- Conduct pregnancy prevention counseling
- Subject completes Health Related Quality of Life Surveys
- Assess adherence with study drug(s) dosing regimen including pill count
- Dispense study drug as directed by the IWRS (Week 12 for study group 4 only)

6.6. Posttreatment Week 4, 12 & 24 Visits (± 5 days)

The posttreatment Week 4, 12 and 24 visits should be timed from the date of last administration of study drug. All subjects must complete the posttreatment Week 4 and 12 visits. Subjects with HCV RNA < LLOQ at the post treatment Week 12 visit will complete the posttreatment Week 24 visit unless viral relapse is determined. The end of study will occur at the posttreatment Week 24 visit.

The following will be performed and documented:

- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications (posttreatment Week 4 only)
- Obtain blood samples (Reference Study Procedures Table, Appendix 2)
- Obtain urine sample for pregnancy test for females of child bearing potential only (only posttreatment Week 4 visit for study Groups 1 and 4; or all posttreatment visits for study Groups 2 or 3)

- Subject completes Health Related Quality of Life Surveys
- Conduct pregnancy prevention counseling
- Female subjects of childbearing potential in study Groups 2 and 3, who received RBV, should be provided with urine pregnancy test-kits, instructed on their use and requested to continue to self-monitor for pregnancy every 4 weeks, for 6 months after their last dose of RBV. If required by regulations, additional pregnancy tests beyond 6 months may be added. The subject will be contacted every 4 weeks and asked to report results of the urine pregnancy tests. If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

6.7. Unscheduled Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments are at the investigator's discretion as clinically indicated, but the investigator should at a minimum collect AE and concomitant medication information. At all unscheduled visits initiated for the purpose of confirming virologic failure a viral RNA sequencing / phenotyping sample must be collected.

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

6.8. End of Study

Subjects are considered to have completed the study after the posttreatment Week 24 visit, regardless of treatment duration or early termination from study drug.

6.9. Procedures and Specifications

6.9.1. Clinical Laboratory Analytes

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

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

Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatinine, Creatine Kinase, Total Bilirubin (reflex to Direct Bilirubin if Total Bilirubin is abnormal), Glucose, Lipase, Potassium, and Sodium; Direct Bilirubin, APRI & Fibrotest® [a] at Screening only; Gamma-glutamyl transferase (GGT) at Baseline/Day 1 only.

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

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

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

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

Additional Tests: Urine Drug screen (for Amphetamines, Cocaine, Methadone, Opiates); Hemoglobin A1c (HbA1c), and TSH (reflex free T4).

6.9.2. Medical History

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

Obtain HCV treatment history in order to categorize the subject as per inclusion criteria. The data required will include all prior HCV treatments, including the SOF-containing regimen(s), the duration(s) of the prior treatment(s), and the virologic outcome(s). In addition, obtain and record any available historical resistance tests data.

6.9.3. Complete Physical Examination

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

6.9.4. Vital Signs

Vital sign collection will include measurement of resting blood pressure, pulse, respiratory rate, and temperature.

Blood pressure will be measured using the following standardized process:

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

- Measure and record the blood pressure to the nearest 2 mm Hg mark on the manometer or to the nearest whole number on an automatic device.

6.9.5. 12-Lead ECGs

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

The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities.

6.9.6. Viral RNA Sequencing / Phenotyping Sample

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

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

6.9.7. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period and 1 month following last dose of study drug without RBV or for a minimum of 6 months following the last dose of RBV. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drugs immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

Female subjects of childbearing potential, in study Groups 2 and 3 who received RBV, will be dispensed urine pregnancy test kits at the posttreatment Week 4 Visit to self-monitor for pregnancy, every 4 weeks, for 6 months after their last dose of RBV. If required by regulations, additional pregnancy tests beyond 6 months may be added. The subject will be contacted every 4 weeks and asked to report results of the urine pregnancy tests. If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

6.9.8. Health Related Quality of Life Surveys

Health Related Quality of Life surveys (HRQoL) included in this study are SF-36, Chronic Liver Disease Questionnaire (CLDQ-HCV), Fatigue Index (FACIT-F), Work Productivity and Activity Impairment Questionnaire: Hepatitis C, v2.0 (WPAI: Hepatitis C) which will be completed by subjects at Baseline/Day 1, on-treatment Weeks 4 and 12 for all study groups and Week 24 for study group 4, Early Termination (if applicable), and posttreatment Weeks 4 and 12.

The subject should read the questionnaire by himself/herself and record the answers by himself/herself.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

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 study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug(s) using clinical judgment and the following considerations:

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

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

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

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

7.2.2. Assessment of Severity

Severity should be recorded and graded according to the GSI Grading Scale for Severity of AEs 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 eCRF: all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events:

Following initiation of study drug(s) until 30 days after the last administration of study drug(s), all AEs, regardless of cause or relationship, must be collected and reported to the 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 occurs 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 posttreatment follow-up period, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period, however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug(s), he/she should promptly document and report the event to Gilead DSPH.

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

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
  Fax (Europe): +44 (0) 208587 2386
  Email: 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 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 European Union (EU) Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the

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

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

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

7.5. Toxicity Management

7.5.1. Ribavirin Dose Adjustments – Applicable to Study Groups 2 & 3

In the event a female partner of a male subject becomes pregnant, the male subject must permanently discontinue RBV.

Dose reduction or discontinuation of RBV due to hemoglobin toxicity or related symptoms is allowed at the discretion of the Investigator; otherwise, the Medical Monitor must be consulted prior to any dose reduction or discontinuation of RBV, unless the Investigator believes that immediate action is warranted to ensure the continued safety of the subject.

All dose reductions for RBV should be performed according to the product label. Information is provided in Table 7-1.

RBV may be permanently discontinued due to laboratory abnormality or clinical manifestation without stopping LDV/SOF FDC.

Table 7-1. RBV Dose Reduction Guidelines

Laboratory Values	Reduce RBV Dose to 600 mg/day[a] if:	Discontinue RBV if:
Hemoglobin in subjects with no cardiac disease	< 10 g/dL	< 8.5 g/dL
Hemoglobin in subjects with history of stable cardiac disease	≥ 2 g/dL decrease in hemoglobin during any 4 week period treatment	< 12 g/dL despite 4 weeks at reduced dose

a Recommended: 1 tablet in AM, 2 tablets in PM.

Once RBV has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart RBV at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that RBV be increased to the original assigned dose.

7.5.2. Subject Stopping Rules

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

Due to a clinical or laboratory event, administration of all study drug(s) may be discontinued. There is no option for LDV/SOF FDC dose reduction. If LDV/SOF FDC is stopped due to toxicity, it must not be restarted; if LDV/SOF FDC is discontinued, RBV must also be discontinued and the subject must complete an Early Termination visit. The posttreatment Week 4 and Week 12 visits must also be completed. Subjects with HCV RNA < LLOQ at the posttreatment Week 12 visit will complete the posttreatment Week 24 visit unless viral relapse is determined.

Subjects receiving RBV (study Groups 2 & 3) that require discontinuation of only RBV should continue with LDV/SOF FDC for the remainder of the treatment period and complete all scheduled study visits as planned.

Subjects who meet any of the following laboratory criteria must stop all study drug(s):

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

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

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

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

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study drug(s) and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 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 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: 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 study Group 2 or 3 pregnancies to the Ribavirin Pregnancy Registry at 1-800-593-2214, in accordance with local requirements (see also http://www.ribavirinpregnancyregistry.com).

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

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the 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 drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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

Refer to Section 7.3 and the 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 efficacy of treatment with LDV/SOF FDC for 12 weeks with or without RBV in subjects without cirrhosis, and LDV/SOF FDC for 12 weeks with RBV or LDV/SOF FDC for 24 weeks without RBV in subjects with cirrhosis, as measured by the proportion of subjects with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)

- To evaluate the safety and tolerability of LDV/SOF FDC weeks with or without RBV in subjects without cirrhosis, and LDV/SOF FDC for 12 weeks with RBV or LDV/SOF FDC for 24 weeks without RBV in subjects with cirrhosis, as assessed by review of the accumulated safety data

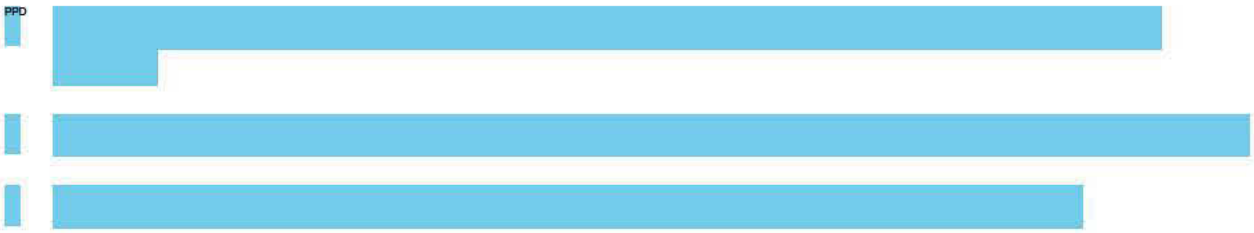
The secondary objectives of this study are as follows:

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

- To determine the proportion of subjects with virologic failure

- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation among subjects with virologic failure

The exploratory objectives of this study are:



8.1.2. Primary Endpoint

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

The primary safety endpoint is the proportion of subjects who discontinued from study treatment for an AE.

8.1.3. Secondary Endpoint

Secondary efficacy endpoints include the proportion of subjects with HCV RNA < LLOQ at 4 and 24 weeks posttreatment; viral breakthrough, relapse, and emerging resistance.

8.1.4. Other Endpoints of Interest

Additional endpoints to be studied will include prevalence of pre-existing NS5A and NS3/4A resistance-associated variants at baseline and change in NS3/4A RAVs from available historical resistance tests to baseline, and the effect of therapy on health related quality of life.

8.2. Analysis Conventions

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

The study drugs in this study are LDV/SOF FDC and RBV. Last dose of study drug refers to the last dose of LDV/SOF FDC or RBV, and will be used in the definition of treatment emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various posttreatment time points.

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis is defined as the Full Analysis Set (FAS) which includes all randomized/enrolled subjects who took at least 1 dose of study drug.

8.2.1.2. Safety

The primary analysis set for safety analyses includes all subjects who took at least 1 dose of study drug.

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

8.3. Data Handling Conventions

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

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

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

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

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

Values for missing vital signs data will not be imputed; however, a missing Baseline/Day 1 result will be replaced with a screening result, if available.

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

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

8.4. Demographic Data and Baseline Characteristics

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

Demographic summaries will include sex, race/ethnicity, randomization stratification group, and age.

Baseline characteristic data will include body mass index, HCV RNA level (log_{10} IU/mL), genotype HCV infection, IL28B genotype, and additional endpoints as necessary.

8.5. Efficacy Analysis

The efficacy analyses will be performed separately for cohort 1 and 2.

8.5.1. Primary Analysis

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

In Cohort 1, a non-inferiority test of SVR12 rates will be performed comparing Group 1 and 2. A non-inferiority margin of 10% will be applied. Non-inferiority will be established if the lower bound of the 2-sided 95% confidence interval (CI) of the difference in SVR12 (Group 1 – Group 2) is greater than -10%. The CI will be constructed using stratum-adjusted Mantel-Haenszel (MH) proportions, stratified by the randomization stratification factors (i.e., genotype 1or 4; prior SOF therapy in combination with SMV or without SMV).

A similar non-inferiority tests of SVR12 rates will be performed comparing Group 3 and 4 in Cohort 2.

The NI margin of 10% is chosen primarily based on clinical judgment. The statistical justification of a NI margin is based on a two-step process in which: 1) we estimate the treatment benefit of the control regimens (LDV/SOF + RBV for 12 weeks for cohort 1; LDV/SOF for 24 weeks for cohort 2) and the historical control (M1), and 2) we define a margin which preserve some fraction of the treatment benefit characterized in Step 1 above (M2).

The M1 and M2 in the current study design as follows:

- M1 = the smallest treatment benefit of the control regimens over the historical control
- M2 = 50% of M1

Based on the Phase 2 ELECTRON-2, GS-US-337-1118, and SYNERGY data, the SVR12 rates for LDV/SOF + RBV for 12 weeks are summarized below:

Table 8-1. Summary of SVR12 Rates in Phase 2 Studies

Study	SVR12 Rates			
	LDV/SOF 12 Weeks		LDV/SOF + RBV 12 Weeks	
Electron-2			n/a	Without cirrhosis: 100% (19/19)
GS-US-337-1118			With cirrhosis: 100% (14/14)	Without cirrhosis: 100% (36/36)
SYNERGY	Advanced liver disease (Knodell score 3, 4) 100% (7/7)	Other (Knodell score 0, 1) 100% (7/7)		
Overall	100% (7/7) 95% CI: (59%, 100%)	100% (7/7) 95% CI: (59%, 100%)	100% (14/14) 95% CI: (77%, 100%)	100% (55/55) 95% CI: (94%, 100%)

The smallest treatment benefit of LDV/SOF 12 weeks and LDV/SOF + RBV 12 weeks are 59% and 77%, respectively (the smaller lower bound of the two 95% CIs).

Note: SVR12 rate of LDV/SOF for 24 weeks is assumed to be at least as high as that of LDV/SOF for 12 weeks.

Since there is no approved standard of care in this patient population, a spontaneous SVR12 rate of at most 5% is assumed as the historical control rate.

Using the smallest treatment benefit for the control regimens (ie, the smaller of 59% and 77%) and the highest spontaneous SVR12 rate of the historical control, M1=59%-5%=54%. Based on these conservative estimates, a 10% NI margin would retain at least ensure at least 81.5% of the treatment benefit of LDV/SOF + RBV for 12 weeks or LDV/SOF for 24 weeks over the historical control.

8.5.2. Secondary Analyses

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

Descriptive summaries and listings will be provided for additional efficacy evaluations of the proportion of subjects who experience virologic failure, HCV RNA actual values and change from baseline, other endpoints of interest including health related quality of life endpoints.

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

8.6. Safety Analysis

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

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

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

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

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug; or any AEs leading to premature discontinuation of study drug.

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

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- All treatment-related SAEs
- All AEs leading to premature discontinuation of any study drug
- All AEs leading to premature discontinuation of LDV/SOF

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

8.6.3. Laboratory Evaluations

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

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

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

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

8.6.4. Other Safety Evaluations

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

8.7. Sample Size

Cohort 1: for the non-inferiority comparison of SVR12 in the noncirrhotic cohort (group 1 vs. 2) with a 10% non-inferiority margin, a sample size of 90 subjects per treatment group will provide at least 90% power to establish non-inferiority at 1-sided 0.025 level, assuming the SVR12 rates are 98% for both groups.

Cohort 2: for the non-inferiority comparison of SVR12 in the compensated cirrhotic cohort (group 3 vs. 4) with a 10% non-inferiority margin, a sample size of 125 subjects per treatment group will provide at least 90% power to establish non-inferiority at 1-sided 0.025 level, assuming the SVR12 rates are 95% for both groups.

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, and 21 CFR, part 56.

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

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

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The

investigator must use the most current IRB/IEC approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/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, eCRF, the study drug, 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, eCRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled

- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug(s), 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. The 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. Investigational Medicinal Product Accountability and Return

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

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

The study monitor will review study drug 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/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. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

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

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT
A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir, With or Without Ribavirin, in HCV Infected Subjects Who Have Failed Prior Treatment With Sofosbuvir-based Therapies

GS-US-337-1746, Amendment 2, 23 July 2015

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

PPD

William Guyer on behalf of:
Lorenzo Rossaro (Printed)
Medical Monitor

23 July 2015
Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed) _____ Signature _____

Date _____ Site Number _____

Appendix 2. Study Procedures Table

			On-Treatment Study Week (±3 Days)									Posttreatment Study Week (±5 Days)		
	Screen	**Baseline/ Day 1[a]**	**1**	**2**	**4**	**8**	**12**	**16[b]**	**20[b]**	**24[b]**	**ET**	**4[c]**	**12[c]**	**24**
Clinical Assessments														
Informed Consent	X													
Determine Eligibility	X	X												
Medical History	X													
Historical Resistance Test Data[d]	X													
Physical Examination	X	X					X[e]			X[e]	X			
Height	X													
Weight	X	X												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X													
Imaging for HCC[f]	X													
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X
Health Related Quality of Life Surveys		X			X		X			X	X	X	X	
Study Drug Dispensing		X[g]			X	X	X[h]	X[h]	X[h]					
Review of Study Medication Adherence (Pill Count)			X	X	X	X	X	X	X	X	X			

			On-Treatment Study Week (±3 Days)									Posttreatment Study Week (±5 Days)		
	Screen	**Baseline/ Day 1[a]**	**1**	**2**	**4**	**8**	**12**	**16[b]**	**20[b]**	**24[b]**	**ET**	**4[c]**	**12[c]**	**24**
Laboratory Assessments														
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation Tests	X	X					X			X	X			
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral Sequencing/phenotyping[i]		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing[j]	X	X			X	X	X	X	X	X	X	X[k]	X[k]	X[k]
Urinalysis & Urine Drug Screen	X													
HCV Genotyping, IL28B	X													
HCV, HIV, HBV Serology	X													
TSH, HbA1c, Fibrotest®/APRI	X													
Future Research Blood Sample[l]		X					X			X	X			

a Baseline/Day 1 assessments must be performed prior to dosing
b On-Treatment Visits at Weeks 16, 20 and 24 are only applicable to subjects in study group 4
c All subjects will complete the posttreatment Week 4 and Week 12 visits ; subjects with HCV RNA < LLOQ at the posttreatment (PT) Week 12 visit will complete the PT Week 24 visit
d Collect and record information regarding historical resistance test data if available
e A physical exam will be performed at the end of treatment visit (Week 12 for study groups 1,2,3; and Week 24 for study group 4)
f Liver imaging within 6 months prior to Baseline/Day 1 is required in subjects with cirrhosis to exclude HCC
g The IWRS will provide randomization to study Group
h Study drug dispensing at Week 12, 16 and 20 is only applicable to study group 4
i Plasma samples will be collected and stored for potential HCV sequencing/phenotyping and other virology studies.
j For females of childbearing potential only: serum β-hCG at Screening, urine test thereafter. If urine is positive, confirm immediately with serum β-hCG

k Females of childbearing potential in study Groups 2 & 3 will have additional urine pregnancy testing every 4 weeks for a minimum of 6 months following last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. In the event of a positive urine pregnancy result, subjects will be instructed to return to the clinic as soon as possible for a serum pregnancy test. Pregnancy test kits will be dispensed to female subjects of childbearing potential at the 4 and 12 Week posttreatment visits to self-monitor for pregnancy. The subject will be contacted by telephone monthly to confirm that urine pregnancy testing has been performed posttreatment and to record the outcome. Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine pregnancy tests.

l Sample for optional future research will be collected at the Baseline/Day 1 visit and at the end of treatment (Week 12 for study groups 1,2,3; and Week 24 for study group 4) for subjects who have not opted out

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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 to <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
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/L to <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
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

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

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

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

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

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

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

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

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

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

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

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

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

1. Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

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

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.

2. Definition of Female of Childbearing Potential

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

Women who are < 54 years of age (including those with amenorrhea of any duration) who have not had a hysterectomy, 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 Baseline/Day 1 visit prior to randomization. They must also agree to one of the following from 3 weeks prior to Baseline/Day 1 until 30 days after last dose of LDV/SOF in the absence of RBV or 6 months after last dose of RBV (if applicable):

1) 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

2) Consistent and correct use of 1 of the following methods of birth control listed below in addition to a male partner who correctly uses a condom from the date of Screening until 30 days after last dose of LDV/SOF in the absence of RBV or 6 months after the last dose of RBV(if applicable):
   a) intrauterine device (IUD) with a failure rate of < 1% per year
   b) female barrier method: cervical cap or diaphragm with spermicidal agent (if locally available)

c) tubal sterilization

d) vasectomy in male partner

e) hormone-containing contraceptive:

i) implants of levonorgestrel

ii) injectable progesterone

iii) oral contraceptives (either combined or progesterone only)

iv) contraceptive vaginal ring

v) 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, while their female partner agrees to use 1 of the methods of birth control listed above, from the date of Screening until 90 days after administration of the last dose of LDV/SOF in the absence of RBV or 7 months after the last dose of RBV (if applicable):

Male subjects must agree to refrain from sperm donation for at least 90 days after the last dose of LDV/SOF in the absence of RBV or 7 months after the last dose of RBV (if applicable).

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 30 days (90 days for partners of male subjects) of last LDV/SOF FDC dose or 6 months (7 months for partners of male subjects) of last RBV dose (if applicable). 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 7.6.2.1.