CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 2 HCV Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
IND Number:	This is a non-IND study
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	Not Available
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-337-1903
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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Study Title:	A Phase 3b, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 2 HCV Infection
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	This is a non-IND study Not Applicable Not Available
Study Centers Planned:	Approximately 40 centers in Japan.
Objectives:	The primary objectives of this study are follows: • To evaluate the antiviral efficacy of therapy with ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) as measured by sustained virologic response 12 weeks after cessation of treatment (SVR12) • To evaluate the safety and tolerability of each regimen 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 cessation of treatment (SVR4 and SVR24) • To evaluate the proportion of subjects with virologic failure • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of each treatment regimen • To evaluate the emergence of viral resistance to SOF and LDV during treatment and after cessation of treatment Exploratory objectives of this study are: PPD [redacted]

Study Design:	This is a multicenter, randomized, open-label study in treatment-naïve and treatment-experienced adults with chronic genotype 2 HCV infection. Cohort 1: Approximately 200 subjects will be randomized in a 1:1 ratio to one of the following two treatment groups: • LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks • SOF tablet (400 mg) once daily and RBV (600-1000 mg daily as a divided dose) for 12 weeks Approximately 10% of subjects may have Child-Pugh-A compensated cirrhosis. Approximately 50% of subjects will be treatment-naïve and 50% will be treatment-experienced. Randomization will be stratified by cirrhosis status (presence/absence) and prior treatment experience (treatment-naïve/treatment-experienced). Cohort 2: Up to 25 subjects who are ineligible or intolerant for RBV therapy will receive LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks. Approximately 10% of subjects may have Child-Pugh-A compensated cirrhosis.
Number of Subjects Planned:	Approximately 225 subjects
Target Population:	Treatment naïve and treatment experienced, chronic genotype 2 HCV infected adults
Duration of Treatment:	Subjects will be treated for 12 weeks.
Diagnosis and Main Eligibility Criteria:	Chronic genotype 2 HCV-infected male and non-pregnant/non-lactating female subjects, aged 20 years or older, treatment naïve or treatment-experienced. Approximately 10% in each cohort may have Child-Pugh-A compensated cirrhosis. In Cohort 2 subjects must be ineligible or intolerant of RBV.

Study Procedures/ Frequency:	Screening assessments will be completed within 28 days prior to the Day 1 visit. The screening window can be extended up to 42 days in extenuating circumstances, including the need for a liver biopsy or additional HCV genotyping (if initial testing is inconclusive). Study visits will occur at Screening, Day 1, and on-treatment at the end of Weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12. Following the last dose of study medication, all subjects will complete 4-Week, 12-Week and 24-Week Posttreatment Visits. Screening assessments will include medical history, physical examination, height, weight, vital signs, 12-lead electrocardiogram (ECG), adverse events (AEs) related to screening procedures, concomitant medications, liver imaging to exclude hepatocellular carcinoma (HCC) within 6 months for non-cirrhotics and within 4 months for cirrhotics, safety laboratory tests (including hematology, chemistry, coagulation, urinalysis), HCV RNA, serum β-hCG (females of child bearing potential only), HCV genotype, host IL28B genotype, serology (HIV, HCV, HBV), hemoglobin A1c (HbA1c). On-treatment assessments include physical examination, weight, vital signs, 12-lead ECG, AEs, concomitant medications, pregnancy prevention counseling, review of study drug adherence and drug accountability, study medication dispensing, safety laboratory tests (including hematology, chemistry, coagulation, urinalysis), HCV RNA, viral RNA sequencing/phenotyping sample, urine pregnancy tests (females of child bearing potential only). Posttreatment assessments include physical examination, weight, vital signs, AEs and concomitant medications, pregnancy prevention counseling, safety laboratory tests (including hematology and chemistry), HCV RNA, viral RNA sequencing/phenotyping, and urine pregnancy tests (females of childbearing potential only). For subjects who provide their additional and specific consent, a single blood sample will be collected at the Day 1 visit for human genomic testing (this sample may be drawn after Day 1, if necessary). Health Related Quality of Life (HRQoL) Survey will be conducted at Day 1, On-treatment Weeks 4, 8, and 12, Early Termination (if applicable), and Posttreatment Week 4, 12, and 24. Archive plasma samples will be collected at each on-treatment and posttreatment study visit for potential future testing.

Test Product, Dose, and Mode of Administration:	1. Ledipasvir/sofosbuvir (HARVONI®, LDV/SOF) is manufactured as a FDC tablet, consisting of 90 mg LDV and 400 mg SOF, for oral administration. Subjects will take 1 tablet daily for 12 weeks. 2. Sofosbuvir (SOVALDI®, SOF) is manufactured as a 400mg tablet for oral administration. Subjects will take 1 tablet daily for 12 weeks. 3. Ribavirin (REBETOL®, RBV) is manufactured as a 200mg capsule. Subjects will take weight-based RBV every day (600-1000 mg/day in a divided daily dose) in accordance with RBV product labeling. The morning dose of RBV will be taken with the SOF tablet and with food. The evening dose of RBV will be taken alone with food. Ribavirin dose reductions and modifications will be performed according to the approved RBV labeling.
Reference Therapy, Dose, and Mode of Administration:	None

Criteria for Evaluation:

Safety:	AEs and safety laboratory tests will be collected throughout the study.
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using Ampliprep® TaqMan® HCV Test, v2.0.

Statistical Methods:

The primary efficacy endpoint is SVR12 in all randomized/enrolled and treated subjects.

Cohort 1: The primary analyses will consist of a non-inferiority test of treatment LDV/SOF FDC for 12 weeks versus SOF+RBV for 12 weeks at the 0.05 significance level.

Non-inferiority will be assessed using the conventional confidence interval approach, and a clinically meaningful non-inferiority margin of 10% will be applied. The two-sided 95% confidence intervals will be constructed using stratum-adjusted Mantel-Haenszel (MH) proportions, stratified by the randomization stratification factors (ie, cirrhosis status and prior treatment experience).

A sample size of 100 per treatment group will provide over 90% power to establish non-inferiority in the SVR12 rates between the two groups. It is based on the assumptions that the clinically meaningful non-inferiority margin is 10%, both groups have a SVR12 rate of 96%, and the significance level is 0.025 one-sided.

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

	The secondary efficacy endpoints include SVR measured at 4 and 24 weeks after discontinuation of study drug (SVR4 and SVR24); proportion of subjects who have HCV RNA < LLOQ by visit while on study treatment; absolute and change from baseline in HCV RNA through end of treatment; and virologic failure.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

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

FACIT-F	Fatigue Index
FAS	full analysis set
FCF	yellow # 6 / sunset yellow FCF aluminum lake
FD&C	Federal Food, Drug and Cosmetic
FDA	(United States) Food and Drug Administration
FDC	Fixed-dose combination
FEV1	forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
g	grams
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	giga
GS-7977	formerly PSI-7977
GSI	Gilead Sciences, Inc.
GT	genotype
GT-2	genotype 2
h	hour
H2	Histamine
Hb	Hemoglobin
HbA_{1c}	Hemoglobin A_{1c}
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HLGT	High-Level Group Term
HLT	High-Level Term
HMG-CoA	3-hydroxy-3-methyl-glutaryl coenzyme A
HPF	high power field
HRQoL	Health Related Quality of Life
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IFN	Interferon
IL28B	Interleukin-28B gene
IMB	Intermenstrual Bleeding
IMP	Investigational Medical Product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio of prothrombin time

IRB	institutional review board
IU	International Units
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IWRS	interactive web response system
JSH	Japanese Society of Hepatology
J-GCP	Ministerial Ordinance on Good Clinical Practice for Drugs
kg	Kilogram
kPA	kilopascal
L	liter
LAM	Lactational amenorrhea method
LAR	legally-authorized representative
LDL	low-density lipoprotein
LDV	ledipasvir
LLN	lower limit of the normal range
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
m^2	square meter
MCV	mean corpuscular volume or mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalents
mg	milligram
MGB	minor groove binder
MH	Mantel-Haenszel
MHLW	Japan's Ministry of Health, Labour and Welfare
mL	Milliliter
mm^3	cubic millimeter
mmHg	millimeters mercury
mmol	millimole
n	number
NS (3/4A/5A/5B)	Non-structural Protein
PCR	Polymerase Chain Reaction
Peg-IFN	pegylated interferon
P-gp	P-glycoprotein
PK	Pharmacokinetic
PMDA	Pharmeceuticals and Medical Devices Agency
PPIs	Proton-pump inhibitor
PR	P and R waves (in electrocardiography)
PT	preferred term or prothrombin time
Q1	Quartile 1

Q3	Quartile 3
QA	Quality assurance
QTc	corrected QT
RAV	Resistance-associated variants
RBC	Red blood cell count
RBV	ribavirin
RNA	ribonucleic acid
SADR	Serious adverse drug reaction
SAE	serious adverse event
S_{cr}	serum creatinine (mg/dL)
SD	Standard deviation
sec	seconds
SF-36	36-Item Short Form Health Survey
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SNP	Single nucleotide polymorphism
SOC	System Organ Class
SOF	sofosbuvir, formerly GS-7977
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
SVR12	Sustained Virologic Response 12 weeks after cessation of treatment
SVR24	Sustained Virologic Response 24 weeks after cessation of treatment
SVR4	Sustained Virologic Response 4 weeks after cessation of treatment
TEN	toxic epidermal necrolysis
TND	Target not detected
ULN	Upper limit of normal
US	United States
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment
β-hCG	β-human chorionic gonadotropin
µg	microgram
µL	microliter
µmol	micromole

1. INTRODUCTION

1.1. Background

Hepatitis C Virus (HCV) infection is a global health challenge with an estimated 180 million individuals infected worldwide {Ghany et al 2009}. Up to 85% of individuals infected with HCV fail to clear the virus and progress to chronic infection {Lauer et al 2001}. Consequences of chronic infection include cirrhosis and hepatocellular carcinoma {Thein et al 2008}. The annual rate of progression to cirrhosis in chronic HCV infected patients with advanced fibrosis is ~10 % {Dienstag et al 2011}. Approximately 1 to 4% of patients per year with established cirrhosis will progress to hepatocellular carcinoma (HCC) {Degos et al 2000}, {Dienstag et al 2011}, {Nishiguchi et al 1995}, {Serfaty et al 1998}. Given the asymptomatic nature of early infection, the slow progression to chronic liver disease, and the lack of adequate screening in at-risk individuals, it is expected that the prevalence of subjects diagnosed with HCV-related complications will peak over the next 2 decades {Hoofnagle et al 2006}, {World Health Organization (WHO) 2015}, {El-Serag 2004}, {Davis et al 2003}.

1.1.1. HCV Infection in Japan

With published HCV prevalence estimates from blood-donor and subgroup-based studies on the order of 1-1.9% in Japan {Sievert et al 2011}, it is estimated that there are approximately1.3-2.4 million people chronically infected with HCV. In Japan, it is estimated that approximately 20-30% of the 1.3-2.4 million people infected with chronic hepatitis C virus have genotype 2 {Sievert et al 2011}, {Chung et al 2010}. The highest prevalence rates of HCV antibodies in first-time blood donor studies have been reported in the 50-59 year (1.8%) and 60-69 year (3.4%) age groups {Tanaka et al 2004}. Consequently, the majority of Japanese patients with chronic hepatitis C are elderly (average age ~ 70 years) and are more likely to be treatment-experienced and have progressive liver disease. Comorbid conditions (e.g., diabetes and cardiovascular disease) are common in this population and pose challenges to the use of RBV therapy. It is estimated that approximately 15-30% of patients with chronic hepatitis C will go on to develop complications, including liver cirrhosis, HCC, and end stage liver disease (ESLD); {Thein et al 2008}.

In Japan, the current standard of care for chronic genotype 2 HCV infection is the combination of sofosbuvir (SOF) 400 mg taken once daily and ribavirin (RBV; 600-1000 mg based on weight, split over two daily doses) {The Japan Society of Hepatology 2015}; this regimen is only indicated for patients without cirrhosis or for those with compensated cirrhosis. For treatment naïve patients with genotype 2 HCV infection, the combination of pegylated interferon (PEG-IFN) plus RBV can also be considered; or PEG-IFN monotherapy for treatment naïve patients with low viral load. For treatment experienced patients with genotype 2 infection, the protease inhibitor telaprevir, in combination with PEG-IFN and RBV, can also be considered.

The fixed-dose combination of ledipasvir (LDV) 90 mg/SOF 400 mg taken once daily for 12 weeks is approved in Japan for the treatment of genotype 1 HCV infection in patients with or without compensated cirrhosis.

1.2. Sofosbuvir and Ledipasvir/Sofosbuvir FDC

Sofosbuvir (SOF; Sovaldi®) is a nucleotide analog that is a potent and selective inhibitor of non-structural protein (NS) 5B-directed HCV replication.

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

1.2.1. General Information

Please refer to the current Investigator's Brochures (IBs) for additional information on SOF and 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

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

1.2.2.1. GS-US-334-0111 Pharmacokinetic Bridging Study in Japanese Subjects

This study evaluated SOF (and its metabolites) and LDV PK parameters following single dose administration of the SOF or LDV/SOF combination to healthy Japanese and Caucasian subjects. SOF and LDV/SOF FDC were well tolerated in this study. PK results support the use of the 400 mg SOF dose and the LDV (90 mg)/SOF (400 mg) FDC in both Japanese and non-Japanese subjects.

1.2.2.2. GS-US-334-0118 SOF+RBV in Treatment Naïve and Treatment Experienced Japanese subjects with Chronic Genotype 2 HCV Infection

This Phase 3b study included 140 subjects with genotype 2 HCV who were treated with SOF+RBV for 12 weeks. All subjects completed the full 12 weeks of treatment with SOF+RBV. Rates of SVR12 in the overall population were 96% (135/140). For treatment-naïve, non-cirrhotic subjects, SVR12 was achieved in 97% (73/75) which was superior to the adjusted historical control rate of 69% ($p<0.001$). All 5 virologic failures had HCV RNA <LLOQ for the PCR assay at the end of treatment and relapsed following discontinuation of treatment.

SOF+RBV was safe and well-tolerated in this study. Most adverse events were mild to moderate in severity and were generally not considered related to study drug. The exception being RBV-related anemia. The results from this study formed the basis for registration of sofosbuvir (Sovaldi) in Japan for the treatment of chronic genotype 2 HCV infection {Omata et al 2014}.

1.2.2.3. GS-US-337-0113: LDV/SOF±RBV in Japanese Subjects with Genotype 1 HCV With or Without Compensated Cirrhosis

This Phase 3b study included 318 Japanese subjects with genotype 1 HCV treated with LDV/SOF±RBV for 12 weeks. In the group receiving LDV/SOF, all subjects (100%; 157/157) completed the full 12 weeks of treatment and achieved SVR12, regardless of previous treatment history, IL28B genotype, or presence of NS5A RAVs at baseline. In the group receiving LDV/SOF+RBV, the SVR12 rate was 98% (158/161), with one subject relapsing.

LDV/SOF was safe and well-tolerated. Most adverse events were mild to moderate in severity and were not considered related to study drug. This study formed the basis for registration of LDV/SOF (Harvoni) in Japan for the treatment of chronic genotype 1 HCV infection {Mizokami et al 2015}.

1.2.2.4. GS-US-337-1468 (LEPTON) Oral Regimens for the Treatment of Chronic HCV Infection

In this multi-cohort study, Cohort 2 Group 1 is comprised of subjects with chronic genotype 2 HCV infection who were assigned to receive LDV/SOF for 12 weeks. Of the 26 subjects enrolled, twenty-five (96%) completed 12 weeks of treatment with LDV/SOF; 1 subject withdrew consent and prematurely discontinued from the study. All 25 subjects who completed treatment achieved SVR12 for an overall rate of 96% (25/26).

Cohort 2 Group 2 is comprised of subjects with chronic genotype 2 HCV infection who were assigned to receive LDV/SOF for 8 weeks. Of the 27 subjects enrolled, 74% (20/27) achieved SVR12. Among subjects who did not achieve SVR, one subject experienced on-treatment virologic breakthrough and 6 subjects relapsed.

These data demonstrate the clinical activity of LDV/SOF in subjects with chronic genotype 2 HCV infection and that 12 weeks of treatment is the optimal treatment length. There were no adverse events of anemia, decreased hemoglobin, nor hyperbilirubinemia reported {Gane et al 2015}.

1.3. Information about Ribavirin

Ribavirin is a guanosine analogue that inhibits the *in vitro* replication of a wide range of RNA and DNA viruses{Roche Laboratories Inc. 2010}, {Roche Products Limited 2010}. Ribavirin monotherapy has little or no effect on the replication of HCV *in vivo* but can result in normalization of serum ALT activity and improvement in liver histology. When combined with IFN or PEG-IFN therapy, RBV decreases substantially the relapse rate seen after cessation of IFN therapy {Poynard et al 1998}, {McHutchison et al 1998}. Ribavirin is a known teratogen. Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment. A comprehensive review of RBV is contained in the REBETOL® package insert.

1.4. Rationale for This Study

This is a Phase 3b study designed to explore the efficacy of LDV/SOF FDC in subjects with chronic genotype 2 HCV infection. The overseas LEPTON study (GS-US-337-1468, Cohort 2 Group 1) has demonstrated that for subjects with genotype 2 HCV infection, 12 weeks of therapy with LDV/SOF FDC resulted in an SVR rate of 96.2% (25/26) and was safe and well-tolerated.

The current study will explore the efficacy and safety of LDV/SOF in two different populations of Japanese subjects with genotype 2 infection. Cohort 1 will determine if LDV/SOF for 12 weeks is non-inferior to SOF+RBV for 12 weeks in Japanese subjects with genotype 2 HCV with or without compensated cirrhosis. Cohort 2 addresses an unmet medical need by treating subjects who are ineligible for, or intolerant of RBV. Under current Japanese Society of Hepatology (JSH) guidelines, the only therapy available to patients ineligible for RBV is PEG-IFN monotherapy for up to 48 weeks, which has poor tolerability and suboptimal virologic response rates {Lai 2000}. All subjects enrolled in Cohort 2 will receive LDV/SOF FDC for 12 weeks.

1.5. Risk/Benefit Assessment for the Study

This study will evaluate a RBV-free treatment option for Japanese patients with genotype 2 HCV infection including those who cannot receive RBV, a population that currently has limited treatment options.

The safety and tolerability of LDV/SOF has been well characterized in overseas studies, Japanese studies, and in real world use both in Japan and abroad. To date, there have been no differences seen in safety and tolerability based on genotype {Afdhal et al 2014a}, {Afdhal et al 2014b}, {Kowdley et al 2014}, {Mizokami et al 2015}. If non-inferiority is demonstrated between LDV/SOF and SOF+RBV, then Harvoni would represent the first RBV-free, single tablet regimen for treatment of genotype 1 and 2 HCV infection.

The safety profile of SOF is based on approximately 7500 chronic HCV-infected study subjects that have been administered SOF in combination with a DAA, PEG-IFN, and/or RBV. No clinical safety issues related to SOF have been identified to date. The safety profile of LDV is based on over 1200 chronic HCV-infected study subjects receiving LDV/SOF in combination with other DAAs, PEG-IFN, and/or RBV. No clinical safety issues related to LDV have been identified to date. Furthermore, there is no expectation of significant overlapping or new, unexpected toxicities upon administration of LDV/SOF together as an FDC. To date, LDV/SOF ± RBV has been administered to over 5000 HCV infected study subjects. No clinical safety issues related to LDV/SOF have been identified to date.

1.6. Compliance

This study will be conducted in compliance with this protocol, ICH Good Clinical Practice (GCP), and J-GCP (Ministerial Ordinance on Good Clinical Practice for Drugs), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objectives of this study are as follows:

- To evaluate the antiviral efficacy of therapy with LDV/SOF FDC as measured by SVR12
- To evaluate the safety and tolerability of each regimen 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 cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of each treatment regimen
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after cessation of treatment

Exploratory objectives of this study are:

3. STUDY DESIGN

3.1. Study Design

This is a multi-center, randomized, open-label study in treatment-naïve and treatment-experienced adults with chronic genotype 2 HCV infection.

3.2. Study Treatments

Cohort 1: approximately 200 subjects will be randomized in a 1:1 ratio to one of the following two treatment groups:

- LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks
- SOF tablet (400 mg) once daily and RBV (600-1000 mg daily as a divided dose) for 12 weeks

Approximately 10% of subjects may have Child-Pugh-A compensated cirrhosis. Approximately 50% of subjects will be treatment-naïve and 50% will be treatment-experienced.

Randomization will be stratified by cirrhosis status (presence/ absence) and prior treatment experience (treatment naïve/treatment-experienced).

Cohort 2: Up to 25 subjects who are ineligible or intolerant for RBV therapy will receive LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks. Approximately 10% of subjects may have Child-Pugh-A compensated cirrhosis.

3.3. Duration of Treatment

Subjects will be treated for 12 weeks.

3.4. Stopping Rules and Discontinuation Criteria

If a subject discontinues study dosing (for example, as a result of an adverse event [AE]), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up procedures (see Section 6.5). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

For subjects who have completed an ET visit, the posttreatment Week 4, 12 and 24 visits will be completed after last dose of any of the study drug.

When medically feasible, the medical monitor must be consulted prior to subject discontinuation. Study drug must be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator

- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Virologic failure (as defined in Section 3.4.1)
- Pregnancy of female subject (refer to Appendix 4)
- Significant protocol violation that impacts subject safety
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason
- Subject noncompliance
- Discontinuation of the study at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

3.4.1. Virologic Response-Based Treatment Stopping Criteria

The following on-treatment Virologic Response-based Treatment Stopping Criteria will be utilized:

- Confirmed HCV RNA $\geq$ LLOQ after 2 consecutive HCV RNA < LLOQ
- Confirmed > 1 $\log_{10}$ increase in HCV RNA from nadir
- HCV RNA $\geq$ 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 during the on-treatment phase.

Subjects who terminate study drug early due to virologic failure as defined above will complete the Early Termination (ET) visit and all posttreatment visits.

3.5. Samples for Optional Genomic Research

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 225 subjects will be enrolled in this study with chronic genotype (GT) 2 HCV infection who are either treatment-naïve or treatment-experienced. Approximately 10% of subjects may have Child-Pugh-A compensated cirrhosis at screening.

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. Criteria apply to all subjects unless otherwise stipulated:

1) Willing and able to provide written informed consent

2) Male or female, age ≥ 20 years

3) Body weight ≥ 40 kg

4) HCV RNA $\geq 10^4$ IU/mL at Screening

5) Genotype 2 HCV at Screening as determined by the central laboratory. Any non-definitive HCV genotype results will exclude the subject from participation.

6) Chronic HCV infection (≥ 6 months) documented by prior medical history or liver biopsy.

7) HCV treatment status defined as one of the following, and with medical records that include sufficient detail to allow for categorization as follows:

    a) HCV treatment-naïve: Subject has had no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agents (DAAs).

    b) HCV treatment-experienced defined as either of the following:

        i) Prior virologic failure after treatment with an approved or experimental DAA-containing, IFN-containing, or RBV-containing regimen. Subjects must not have discontinued prior therapy due to non-compliance. Note: *See Exclusion Criterion #4: if treatment-experienced, prior exposure to any direct acting antiviral agent targeting the HCV NS5A or NS5B is prohibited.*

        ii) Subjects that discontinued HCV treatment due to development or significant worsening of a treatment related adverse event

8) Subjects enrolled in Cohort 2 only must either have contraindications to, or have demonstrated intolerance of ribavirin:

   a) Examples of contraindications to RBV include:

      i) Unable or unwilling to comply with RBV contraception requirements

      ii) Difficult to control cardiac disease (eg, myocardial infarction, cardiac failure, arrhythmia, etc.) *Note: Per Exclusion Criterion #1g, subjects who have had a significant cardiac event in the past year are to be excluded.*

      iii) Hemoglobin <11 g/dL for female subjects or <12 g/dL for male subjects. *Note: Per Exclusion Criterion #7a, all subjects require Hb ≥10 g/dL.*

      iv) Haemoglobinopathy such as thalassaemia or sickle cell anaemia

      v) Porphyria

      vi) Chronic renal dysfunction with $CL_{Cr} \leq 50$ mL/min. *Note: Per Exclusion Criterion #7e, all subjects require a* $CL_{Cr} \geq 30$ mL/min.

      vii) History of severe psychiatric condition. *Note: Per Exclusion Criterion #1i, subjects who have had psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last two years are to be excluded.*

      viii) Other condition, with approval from the Gilead medical monitor

      Note: *The ribavirin package insert should be consulted for additional details concerning contraindications.*

   b) Ribavirin intolerance is defined as: The emergence of RBV-related clinical adverse events or laboratory abnormalities which could not be adequately managed according to dose modification guidance provided in the RBV package insert necessitating permanent discontinuation of RBV therapy.

9) Cirrhosis Determination:

   a) Presence of cirrhosis is defined as either of the following:

      i) Liver biopsy showing cirrhosis (e.g., Metavir score = 4 or Ishak score ≥5)

      ii) Fibroscan showing cirrhosis as reflected by a result >12.5 kPa

   b) Absence of cirrhosis is defined as either of the following, unless the definition of cirrhosis has been met:

      i) Liver biopsy within 2 years of Screening showing absence of cirrhosis

      ii) Fibroscan within 6 months of Day 1 with a result ≤ 12.5 kPa

10) Liver imaging (e.g., ultrasound or CT scan, at the discretion of the investigator) performed within 4-6 months of Day 1 to exclude hepatocellular carcinoma (HCC) is required:

    a) Within 4 months for subjects with cirrhosis

    b) Within 6 months for subjects without cirrhosis

11) 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 Day 1 prior to randomization/enrollment.

12) 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.

13) Male subjects must agree and refrain from sperm donation from the date of screening until at least 6 months after the last dose of RBV, if applicable, or 90 days after the last dose LDV/SOF FDC.

14) Lactating females must agree to discontinue nursing before the study drugs are administered.

15) Subject must be of generally good health, with the exception of chronic HCV infection, as determined by the investigator.

16) Subject must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments, including all required posttreatment visits.

4.3. Exclusion Criteria

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

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

    a) Clinically significant illness or currently under evaluation for a potentially clinically significant illness (other than HCV) or any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol

    b) Gastrointestinal disorder or postoperative 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 (i.e., ascites, encephalopathy or variceal hemorrhage, Child-Pugh-B or C cirrhosis)

    e) Solid organ transplantation

    f) Significant pulmonary disease

g) Unstable cardiac disease or significant cardiac event within the last one year prior to Screening

h) Porphyria (Cohort 1 only)

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

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

k) Prior or current hepatocellular carcinoma (HCC)

l) Significant drug allergy (such as anaphylaxis or hepatotoxicity)

2) Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV)

3) Screening ECG with clinically significant abnormalities

4) If treatment-experienced, prior exposure to any direct acting antiviral agent targeting the HCV NS5A or NS5B. Exposure to IFN and/or any direct acting antiviral agent (e.g., NS3/4A protease inhibitors) within 1 month prior to Screening is prohibited

5) History of clinically significant medical condition associated with other chronic liver disease (e.g., hemochromatosis, autoimmune hepatitis, Wilson's disease, α-1-antitrypsin deficiency, alcoholic liver disease, non-alcoholic steatohepatitis or toxin exposure)

6) Pregnant or nursing female or male with pregnant female partner

7) Subjects with any of the following laboratory parameters at screening:

a) Hemoglobin (Hb)

i) Cohort 1: Hb < 11 g/dL for female subjects; Hb < 12 g/dL for male subjects

ii) Cohort 2: Hb < 10 g/dL

b) Platelets < 50,000/mm^3

c) ALT >10 x upper limit of normal (ULN)

d) AST > 10 x ULN

e) Creatinine Clearance (CL_{Cr}) as calculated by the Cockcroft-Gault equation {Cockcroft et al 1976}.

   i) Cohort 1: CL_{Cr} < 50 mL/min

   ii) Cohort 2: CL_{Cr} < 30 mL/min

f) Albumin < 3g/dL

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

h) Direct bilirubin > 1.5 x ULN

i) HbA1c ≥ 8.5%

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

9) Any other contraindication to LDV/SOF or SOF therapy, or RBV therapy (Cohort 1 only), per the approved package inserts

10) Use of any prohibited concomitant medications as described in Section 5.7

11) Known hypersensitivity to sofosbuvir, ledipasvir, or ribavirin (Cohort 1 only) or the metabolites or formulation excipients

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

This is a randomized, open-label study in adults with chronic genotype 2 HCV infection. This study is an open-label study and no blinding will be required.

Cohort 1 (n = approximately 200):

- LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks
- SOF tablet (400 mg) once daily and RBV (600-1000 mg daily as a divided dose) for 12 weeks

Randomization will be stratified by cirrhosis status (presence/absence) and prior treatment experience (treatment naïve/treatment-experienced).

Cohort 2 (n = up to 25): LDV/SOF FDC tablet (90/400 mg) once daily for 12 weeks

5.2. Description and Handling of LDV/SOF FDC

5.2.1. Formulation

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

5.2.2. LDV/SOF FDC Packaging and Labeling

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

LDV/SOF FDC bottles to be distributed to centers in Japan shall be labeled for clinical use to meet applicable requirements of the Pharmaceuticals and Medical Devices Agency (PMDA), Japan, and/or other local regulations as applicable.

5.2.3. LDV/SOF FDC Storage and Handling

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

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

5.2.4. Dosage and Administration of LDV/SOF FDC

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

If a subject does not take the LDV/SOF FDC dose at the usual time, it may be taken up to 18 hours later; however, no more than one tablet should be taken on any calendar day. The subject should resume the standing dosing schedule on the next day.

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

5.3. Description and Handling of Sofosbuvir (SOF)

5.3.1. Formulation

SOF tablets are yellow, capsule-shaped, film-coated tablets containing 400 mg of sofosbuvir. The tablets are debossed with “GSI” on one side and “7977” on the other side. In addition to the active ingredient, sofosbuvir tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinylalcohol, titanium dioxide, macrogol, talc, and yellow iron oxide.

5.3.2. SOF Packaging and Labeling

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

SOF bottles to be distributed to centers in Japan shall be labeled for clinical use to meet applicable requirements of the Pharmaceuticals and Medical Devices Agency (PMDA), Japan, and/or other local regulations as applicable.

5.3.3. SOF Storage and Handling

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

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

5.3.4. Dosage and Administration of SOF

SOF will be administered as 400 mg once daily by mouth. SOF will be supplied by Gilead Sciences for all subjects.

If a subject does not take the SOF dose at the usual time, it may be taken up to 18 hours later; however, no more than one tablet should be taken on any calendar day. The subject should resume the standing dosing schedule on the next day.

5.4. Description and Handling of Ribavirin (RBV)

5.4.1. Formulation

Ribavirin will be provided in the course of this study as REBETOL® capsules (MSD K.K.). REBETOL® capsules are white opaque hard capsules. Each capsule contains 200 mg of ribavirin. Information regarding commercially available REBETOL® capsules can be found in the current prescribing information {MSD K.K. Kudan-kita Chiyoda-ku 2015}.

5.4.2. RBV Packaging and Labeling

REBETOL® capsules are packaged in blister packaging of 140 capsules. The ribavirin package shall be labeled for clinical use to meet all applicable requirements of the Pharmaceuticals and Medical Devices Agency (PMDA) and/or other local regulations as applicable.

5.4.3. RBV Storage and Handling

Information regarding commercially available REBETOL® capsules can be found in the current prescribing information.

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

5.4.4. Dosage and Administration of Ribavirin (RBV) (Only Cohort 1 Subjects in the SOF + RBV Treatment Group)

RBV will be administered in accordance with approved RBV labeling in Japan, see Table 5-1 below.

Table 5-1. Dosing and Administration of RBV in Japan

Body weight at Day 1	Ribavirin dosage		
	Daily dosage	After morning meal	After evening meal
≤ 60 kg	600 mg	200 mg	400 mg
> 60 kg to ≤ 80 kg	800 mg	400 mg	400 mg
> 80 kg	1,000 mg	400 mg	600 mg

Source: Japan Rebetol® Product Label {MSD K.K. Kudan-kita Chiyoda-ku 2015}

RBV dose modification or discontinuation should be performed in accordance with the RBV package insert.

RBV should be dosed with food and SOF when appropriate.

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

5.5. Co-administration of SOF and RBV

For subjects in Cohort 1 who are randomized to the SOF + RBV treatment group, each subject will be given instructions to maintain approximately the same daily dosing interval between study drug doses.

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

- One SOF tablet: contains 400 mg SOF
- Weight-based RBV (as per Section 5.4.4).

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

- Weight-based RBV (as per Section 5.4.4).

If a subject does not take the SOF dose at the usual time, it may be taken up to 18 hours later; however, no more than one tablet should be taken on any calendar day. The subject should resume the standing dosing schedule on the next day.

RBV should be administered as a divided daily dose (i.e., morning and evening) as per the Rebetol® product label (Section 5.4.4). If the subject misses a dose of ribavirin and remembers the same day, the missed dose should be taken as soon as possible. However, if the subject missed taking the morning dose with lunch or if more than 6 hours have passed since the usual morning dose time, the subject should only take the prescribed evening dose of ribavirin. Subjects should be instructed not to take 2 doses of ribavirin at the same time.

Study medications should not be cut or split. No food restrictions apply to SOF; however, SOF should be taken with the morning dose of RBV which is taken with food.

5.6. Study Drug Adherence and Drug Accountability

Subjects must be instructed to bring back all study medication(s) in the original container at every study visit after Day 1 through the end of treatment.

Study medication(s) will be reconciled using medication pill count at every post-Day 1 visit by the investigator or designee (ie, pharmacist) in order to monitor the subject's adherence with the medication regimen.

5.7. Prior and Concomitant Medications

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

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

- Hematologic stimulating agents (e.g., erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)
- Investigational agents or devices for any indication
- Drugs disallowed per prescribing information of RBV (Cohort 1 only)
- Chronic use of systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab). The Gilead medical monitor will be available to address questions from investigators regarding permissible corticosteroid use for this trial.

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

The use of amiodarone is prohibited from **60 days prior to Day 1** through the end of treatment; other examples of representative medications which are prohibited or are to be used with caution from 21 days prior to Day 1 through the end of treatment are listed below in Table 5-2.

Table 5-2. Disallowed and Concomitant Medications to be Used with Caution for SOF and LDV/SOF

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing Agents[a]		Proton- Pump Inhibitors, H2-Receptor Antagonists, Antacids
Anticonvulsants[c]	Phenytoin, Carbamazepine,	Phenobarbital, Oxcarbazepine
Antimycobacterials[c]	Rifampicin	Rifabutin, Rifapentine,
Cardiac Medications	Amiodarone	Digoxin [b]
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

a LDV plasma concentration may decrease, leading to reduced therapeutic effect of LDV/SOF. In the case of coadministration of H_2RA, the H_2RA dose should not exceed doses comparable to famotidine 40 mg twice daily and should be administered simultaneously with or 12 hours apart from LDV/SOF. PPIs should not be taken before LDV/SOF. In the case of coadministration of PPIs, the PPIs at doses comparable to omeprazole 20 mg should be administered simultaneously with LDV/SOF under fasted conditions.
b The plasma concentration of digoxin may be increased. In case of coadministration the plasma concentration monitoring of digoxin is recommended.
c Plasma concentrations of LDV and SOF may be decreased, leading to reduced therapeutic effect of LDV/SOF.
d The plasma concentration of rosuvastatin may be increased, which is associated with increased risk of myopathy, including rhabdomyolysis.

5.8. Accountability for Investigational Medicinal Product (IMP)

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

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

- Record the lot number, expiration date (if necessary)
- Record the date received and quantity of IMP kits
- Record the date, subject number, the IMP kit number dispensed
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

6. STUDY PROCEDURES

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

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

6.1. Screening Visit

Screening assessments will be completed within 28 days of the Day 1 visit. The screening window can be extended up to 42 days for subjects requiring a liver biopsy, additional HCV genotyping (if initial testing is inconclusive), or for extenuating circumstances with sponsor approval. 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 such as intercurrent infection.

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

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

6.2. Randomization/Enrollment

An Interactive Web Response System (IWRS) will be employed to manage subject enrollment, randomization, and treatment assignment. Randomization stratification factors for Cohort 1 are described in Section 5.1.

6.2.1. Day 1 Assessments

All Day 1 procedures must be performed prior to study drug dosing. When ready to administer drugs to the subject:

- Dispense study drug(s) as directed by the IWRS
- Instruct the subject on the packaging, storage and administration of study drug(s)
- Observe the subject taking the first dose of study drug(s). If the subject is randomized to the SOF + RBV treatment group, the patient should take the study drugs with food

6.3. Treatment Assessments (±3 days)

On-treatment visits will be performed at the end of Weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12.

Study medication will be reconciled at every post-Day 1 visit by the investigator in order to monitor the subject's adherence with the medication regimen.

6.4. Posttreatment Assessments (±5 days)

The posttreatment Week 4, 12, and 24 visits should be timed from the date of last administration of any study drug.

6.5. Early Termination (ET)

For subjects who have completed an ET visit, the posttreatment Week 4, 12, and 24 follow-up visits will be scheduled after last dose of any of the study drug.

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

6.6. Unscheduled Visit

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

6.7. Procedures and Specifications

6.7.1. Clinical Laboratory Analytes

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

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

Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatine Kinase, Creatinine, Direct Bilirubin (at screening and reflexed from total bilirubin at other visits), Total Bilirubin, Glucose, Lipase, Potassium, Sodium;.

Urinalysis: Blood, 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-LiPA2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV genotype should the above assays become unavailable or are not definitive.

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-hCG or Urine β-hCG (if positive, requires immediate confirmation with Serum β-hCG).

Additional Tests: Hemoglobin A1c (HbA1c).

6.7.2. Medical History

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

Obtain HCV treatment history in order to categorize the subject as per Inclusion Criteria #7. Information related to HCV infection will also be collected.

6.7.3. Complete Physical Examination

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

6.7.4. Vital Signs

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

Blood pressure will be measured using the following standardized process:

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

6.7.5. 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. On treatment ECGs should be compared to the subject's Day 1 as part of routine safety monitoring.

6.7.6. Health Related Quality of Life (HRQoL)

Health Related Quality of Life surveys (HRQoL) included in this study are the SF-36, Chronic Liver Disease Questionnaire (CLDQ-HCV), Fatigue Index (FACIT-F), and Work Productivity and Activity Impairment Questionnaire: Hepatitis C, v2.0 (WPAI: Hepatitis C).

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

6.7.7. Viral RNA Sequencing / Phenotyping Sample

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

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

6.7.8. Pregnancy Testing

All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period.

Females of childbearing potential in treatment groups without RBV will have a urine pregnancy test at the posttreatment Week 4 visit only. Females of childbearing potential in the treatment group containing RBV 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 in the treatment group containing RBV after the posttreatment Week 4 visit. 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.

6.7.9. IL28B Testing

A blood sample will be obtained at screening for specific genetic analysis of the rs12979860 (IL28B) genetic variant.

6.7.10. Archive Plasma Sample

The specimens collected for future research will be used to increase our knowledge and understanding of the biology pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These specimens may be used for retesting of the amount of HCV in the blood, clinical laboratory testing to provide additional clinical data and to develop non-genetic biomarker or diagnostic assays and establish the

performance characteristics of these assays. The collection and analysis of future research specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

An archive plasma sample (non-genetic) will be collected at each on-treatment and posttreatment study visit. Samples will be collected and archived for future analysis once approved by local authorities as applicable according to specific local regulations.

Details regarding the collection, processing, and shipping of samples will be included in the lab manual. At the conclusion of this study, these samples may be retained in storage by Gilead Sciences, Inc. for a period up to 15 years after the end of the study. These samples will be destroyed by internationally accepted means (e.g. incineration).

6.7.11. Genomic Testing

The subject's identity will be protected, and the subject's name will not be attached to the sample. The sample may be stored for up to 15 years before being destroyed. The sample will be destroyed by internationally accepted means (e.g. incineration).

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

6.7.12. Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft et al 1976} using actual body weight (ABW).

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

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

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

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 of study drug.

6.9. Poststudy Care

No poststudy ongoing care will be provided.

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

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

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

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

7.2.2. Assessment of Severity

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

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

Requirements for collection prior to study drug initiation:

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

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study IMP and report 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 occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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

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

SAEs will be reported using a paper serious adverse event reporting form or via electronic SAE (eSAE) system.

Serious Adverse Event Paper Reporting Process

- All SAEs will be recorded on the serious adverse event report form and submitted by faxing or emailing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead DSPH or to the designated CRO.

  Gilead DSPH (or CRO): Fax: 1-650-522-5477
  Email: Safety_FC@gilead.com

  Or

  CRO safety Dept. Contact information: TBD

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

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

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

7.5. Toxicity Management

7.5.1. RBV Dose Adjustments (Only Cohort 1)

Dose reduction or discontinuation of RBV due to toxicity should be performed according to the Japanese Rebetol® product label. Information is provided in Table 7-1 and Table 7-2.

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

Table 7-1. RBV Dose Reduction Guidelines for Non-Cirrhotic Subjects

Test items	Value	Ribavirin
Neutrophil count	< 500 /mm^3	Discontinue
Platelet count	< 50,000 /mm^3	Discontinue
	< 25,000/mm^3	Discontinue (resumption of dosing not allowed)
Hemoglobin level (No cardiac disease or history of cardiac disease)	< 10 g/dL	Reduce dose 600 mg/day → 400 mg/day 800 mg/day → 600 mg/day 1,000 mg/day → 600 mg/day
	< 8.5 g/dL	Discontinue
Hemoglobin level (Cardiac disease or history of cardiac disease present)	< 10 g/dL, or during administration, reduction of 2 g/dL or more relative to Day 1 persists for 4 weeks	Reduce dose 600 mg/day → 400 mg/day 800 mg/day → 600 mg/day 1,000 mg/day → 600 mg/day
	< 8.5 g/dL, or after dose reduction, less than 12 g/dL even after 4 weeks	Discontinue

Source: Japan Rebetol® Product Label {MSD K.K. Kudan-kita Chiyoda-ku 2015}

Table 7-2. RBV Dose Reduction Guidelines for Cirrhotic Subjects

Test items	Value	Ribavirin
Neutrophil count	< 500 /mm^3	Discontinue
Platelet count	< 50,000 /mm^3	Discontinue
	< 25,000/ mm^3	Discontinue (resumption of dosing not allowed)
Hemoglobin level (No cardiac disease or history of cardiac disease)	< 11 g/dL at Week 1 to 4 after start of administration	Reduce dose 600 mg/day → 400 mg/day 800 mg/day → 600 mg/day 1,000 mg/day → 600 mg/day
	< 10 g/dL at Week 5 to 12 after start of administration	
	< 8.5 g/dL	Discontinue
Hemoglobin level (Cardiac disease or history of cardiac disease present)	< 11 g/dL at Week 1 to 4 after start of administration or during administration, reduction of 2 g/dL or more relative to Day 1 persists for 4 weeks	Reduce dose 600 mg/day → 400 mg/day 800 mg/day → 400 mg/day 1,000 mg/day → 600 mg/day
	< 10 g/dL at Week 5 to 12 after start of administration or during administration, reduction of 2 g/dL or more relative to baseline persists for 4 weeks	
	< 8.5 g/dL, or after dose reduction, less than 12 g/dL even after 4 weeks	Discontinue

Source: Japan Rebetol® Product Label {MSD K.K. Kudan-kita Chiyoda-ku 2015}

Once RBV has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart RBV at a lower daily dose with subsequent step-wise increase in the daily dose as clinically indicated. However, it is not recommended that the RBV daily dose be increased to the original assigned dose.

7.5.2. Subject Stopping Rules

The Medical Monitor must be consulted prior to dose discontinuation of LDV/SOF FDC or SOF 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 or SOF dose reduction. If LDV/SOF FDC or SOF is stopped due to toxicity, it must not be restarted. If SOF is discontinued then RBV must also be discontinued. If RBV is discontinued permanently, then SOF must also be discontinued. In these cases that study drug(s) are discontinued permanently, the subject must complete an ET visit. Posttreatment 4-Week, 12-Week and 24-Week visits must also be scheduled, 4, 12 and 24 weeks from the last dose of study drug.

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

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

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

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

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

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to the CRO Safety Dept. or 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 Section 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH or the CRO Safety Dept.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to the CRO Safety Dept or 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 the CRO Safety Dept or Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours of the investigator becoming aware of the pregnancy. 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 pregnancies to the Pregnancy Registry at 1 800-593-2214 (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 the CRO Safety Dept or Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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

Refer to Section 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 objective of this study is as follows:

- To evaluate the antiviral efficacy of therapy with LDV/SOF FDC as measured by SVR12
- To evaluate the safety and tolerability of each regimen 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 SVR4 and SVR24
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of each treatment regimen
- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after cessation of treatment

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 any AE leading to permanent discontinuation of study drug(s).

8.1.3. Secondary Endpoint

The secondary efficacy endpoints include the following:

- The proportion of subjects with HCV RNA < LLOQ at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)

- Proportion of subjects who have HCV RNA < LLOQ by visit while on treatment
- HCV RNA change from Baseline
- The proportion of subjects with virologic failure

8.1.4. Other Endpoints of Interest

Additional efficacy evaluations may include the health related quality of life endpoints.

8.2. Analysis Conventions

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

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

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 subjects who took at least 1 dose of study drug.

8.2.1.2. Safety

The primary analysis set for safety analyses will include 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 the analyses of categorical HCV RNA data, missing posttreatment HCV RNA data will have the missing data imputed. Missing on-treatment HCV RNA will have the missing data imputed up to the time of the last dose.

If a data point is missing and is preceded and followed in time by values that are "< LLOQ target not detected (TND)," then the missing data point will be set to "< LLOQ TND." If a data point is missing and preceded and followed by values that are "< LLOQ detected," or preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected," then the missing value will be set to "< LLOQ detected." In

these situations the data point will be termed a bracketed success; otherwise, the data point will be termed a bracketed failure (i.e., ≥ LLOQ detected). If a data point is missing and is not bracketed, the missing data point will also be termed a failure (i.e., ≥ LLOQ detected) except for SVR24, which will be imputed according to the SVR12 status. Success for SVR12 who have no further HCV RNA measurements collected will be counted as a success for SVR24 due to the high correlation between these 2 endpoints.

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

- If a subject took at least 1 dose of study drug, the subject will be included in a summary of AEs according to the treatment received; otherwise, if the subject is not dosed, then they will be excluded from the summary.

- If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a pre-dose value, then the subject will be excluded from the calculation of summary statistics for the pre-dose value and the change from pre-dose values.

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

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

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

8.4. Demographic Data and Baseline Characteristics

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

Demographic summaries will include age, sex, self-identified race and ethnicity. Baseline characteristics data will include body mass index, HCV RNA level (log10 IU/mL), IL28B genotype, and additional endpoints as necessary. The number (proportion) of subjects in each stratum will be summarized for Cohort 1.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint for this study will be the proportion of subjects with SVR12, defined as HCV RNA < LLOQ 12 weeks after cessation of treatment. The primary analysis will be performed after all randomized subjects have been followed through 12 weeks posttreatment or discontinued from study.

In Cohort 1, the primary analyses will consist of a non-inferiority (NI) test of treatment LDV/SOF FDC for 12 weeks versus SOF+RBV for 12 weeks at the 0.05 significance level (two-sided).

Non-inferiority will be assessed using the conventional confidence interval approach, and a clinically meaningful non-inferiority margin of 10% will be applied. The two-sided 95% confidence intervals will be constructed using stratum-adjusted Mantel-Haenszel (MH) proportions, stratified by the randomization stratification factors (ie, cirrhosis status and prior treatment experience).

In the primary efficacy analysis of Cohort 2, the SVR12 rate will be calculated along with the two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method). No statistical hypothesis testing will be performed.

8.5.2. Secondary Analyses

The proportion of subjects with HCV RNA below 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 including HCV RNA values and change from baseline through end of treatment, and subjects who experience virologic failure.

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, and vital signs measurements and AEs will be documented at various time points during the study.

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 cohort and treatment group according to the study drug received.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the eCRF. Exposure data will be summarized by cohort and 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 AE with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of the study drug; or any AE leading to premature discontinuation of the study drug.

Summaries (number and percentage of subjects) or listings, as appropriate, of treatment-emergent adverse events (by SOC, and PT) will be provided by cohort and treatment group for:

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

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 cohort and treatment group and study visit along with corresponding change from baseline.

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

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

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 by cohort and treatment group by incidence of events/abnormalities or descriptive statistical summaries (n, mean, SD, median, Q1, Q3, minimum, and maximum), as appropriate.

8.7. Sample Size

For Cohort 1, a sample size of 100 per treatment group will provide over 90% power to establish non-inferiority in the SVR12 rates between the two groups. It is based on the assumptions that the clinically meaningful non-inferiority margin is 10%, both groups have a SVR12 rate of 96%, and the significance level is 0.025 one-sided.

Sample size for Cohort 2 is based on practical considerations. With a sample size of 25 subjects in Cohort 2, the 2-sided 95% exact CIs for different observed HCV SVR12 rates are presented in the table below:

Cohort	Observed HCV SVR12 rate	2-sided 95% exact CI
Cohort 2	80% (20 out of 25)	[59.3%, 93.2%]
	92% (23 out of 25)	[74.0%, 99.0%]

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.

This protocol is to be conducted in accordance with the guidance stipulated in Article 14, Paragraph 3 and Article 80-2 of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, "MHLW Ordinance on Good Clinical Practice" (MHLW Ordinance No 87 [30 July 2014]) {Ministry of Health and Welfare 2013}.

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

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

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

Before implementation, the investigator will submit to and receive documented approval from the IRB or IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial 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 approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized

representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. The consent form will inform subjects about genomic testing and sample retention.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

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

9.1.5. Study Files and Retention of Records

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

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

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

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

- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log-in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness,

correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

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

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

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB/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 or IEC in accordance with local requirements and receive documented approval before modifications can be implemented.

9.2.2. Study Report and Publications

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

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

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

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

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

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

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

9.3.2. 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.

9.3.3. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3b, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 2 HCV Infection

GS-US-337-1903, Amendment 1, 27 January 2016

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

Stephen Djedjos

Stephen Djedjos, MD

PPD

01/27/2016

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

			Treatment Week (±3 days)										Posttreatment Week (±5 days)		
	Screening	Day1[a]	1	2	3	4	5	6	8	10	12/EOT	ET[b]	4	12	24
Clinical Assessments															
Informed Consent	X														
Determine Eligibility	X	X													
Medical History	X														
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[d]	X	X									X	X			
Adverse Events and Concomitant Medications[e]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling		X									X	X	X	X	X
Health Related Quality of Life[f]		X				X			X		X	X	X	X	X
Imaging for HCC[g]	X														
Review of Study Drug Adherence and Drug Accountability[h]			X	X	X	X	X	X	X	X	X	X			
Study Drug Dispensing[i]		X				X			X						

	Screening	Day1[a]	Treatment Week (±3 days)									ET[b]	Posttreatment Week (±5 days)		
			1	2	3	4	5	6	8	10	12/EOT		4	12	24
Laboratory Assessments															
Hematology & Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation (PT, aPTT and INR)	X	X	X	X	X	X	X	X	X	X	X	X			
HCV RNA (Plasma)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral RNA Sequencing /Phenotyping Sample (Plasma)[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Test[j]	X	X				X			X		X	X	X	X	X
Urinalysis	X	X				X			X		X	X			
HCV Genotype, IL28B Genotype	X														
HCV Ab, HIV Ab and HBsAg	X														
HbA1c	X														
Archive plasma sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single Genomic Sample[k]		X													

a Day 1 assessments must be performed prior to dosing.
b ET = Early Termination; at all unscheduled visits initiated for the purpose of confirmatory testing, a viral sequence analysis plasma sample must be obtained.
c Vital signs include resting blood pressure, pulse, respiratory rate and temperature.
d 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 signficant abnormalities. On treatment ECGs should be compared to the subject's Day 1 as part of routine safety monitoring.
e Adverse events and Concomitant Medications will be collected up to 30 days after the last dose of all study drug.
f Health Related Quality of Life (HRQoL) Surveys (e.g. SF-36, CLDQ-HCV, FACIT-F and WPAI) will be conducted for all subjects where the surveys are available at Day 1.
g Liver imaging (e.g., ultrasound or CT scan, at the discretion of the investigator) should be performed to exclude the presence of hepatocellular carcinoma (HCC) in all subjects. For subjects without cirrhosis, imaging must have been performed within 6 months prior to Day 1. For subjects with cirrhosis, imaging must have been performed within 4 months of Day 1.
h Study medication will be reconciled at every post- Day 1 visit by the investigator in order to monitor the subject's adherence with the medication regimen. Subjects must be instructed to bring back all bottles of study medication(s) in the original container at every post- Day 1 visit through the end of treatment.
i Dispense study drugs as directed by the IWRS

j All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period. Females of childbearing potential in treatment groups without RBV will have a urine pregnancy test at the posttreatment Week 4 visit only. Females of childbearing potential in the treatment group containing RBV 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 in the treatment group containing RBV after the posttreatment Week 4 visit. 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.

k Only for subjects who have provided separate consent for this sample and testing. This sample can be obtained at a subsequent visit if not obtained at Day 1.

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	2.5 to < 3.0 mg/dL	2.0 to < 2.5 mg/dL	< 2.0 mg/dL
	0.74 mmol/L to < LLN	0.62 to < 0.74 mmol/L	0.49 to < 0.62 mmol/L	< 0.49 mmol/L
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/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) Adult	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
LDL (Fasting) Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

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

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

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

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

Notes:

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

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

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

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

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

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

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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24-48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

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

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

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

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

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

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

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

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

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

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

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

1) Definitions

a. Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

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

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Ribavirin is contraindicated in pregnancy as significant teratogenic and embryocidal effects have been demonstrated in all animal species tested. Data from clinical pharmacokinetic interaction studies of Ribavirin have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception or that the effect on hormonal contraception is insignificant. Please refer to the latest version of the product insert for additional information

Data from clinical pharmacokinetic interaction studies of SOF, LDV/SOF FDC have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical toxicity studies of SOF, LDV/SOF FDC have demonstrated no adverse effect on fertility or embryo-fetal development. However, there are no clinical studies of SOF or LDV/SOF in pregnant women. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Day 1 visit prior to randomization/enrollment. Pregnancy tests will be performed every 4 weeks thereafter. Female subjects must agree to one of the following from screening until 6 months after last dose of RBV or 30 days after last dose of LDV/SOF FDC:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below:
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Or

- Consistent and correct use of one hormonal method and one barrier method:
  - Barrier methods
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Male condom (with or without spermicide) (Female condom and male condom should not be used together)
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone

- Implants of levonorgestrel
- Transdermal contraceptive patch
- Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until 6 months after last dose of RBV or 30 days after last dose of LDV/SOF FDC.

3) Contraception Requirements for Male Subjects

Male subjects with female partners of childbearing potential must use condoms during treatment and until 6 months after last dose of RBV or 90 days after last dose of LDV/SOF FDC. If their female partner is of childbearing potential (as defined above), their female partner must use 1 of the methods of birth control listed above from the date of Screening until 6 months after the last dose of RBV or 90 days after the last dose of LDV/SOF.

Male subjects must agree to refrain from sperm donation for at least 6 months after last dose of RBV or 90 days after the last dose of LDV/SOF FDC.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

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

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.