CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 Weeks in Subjects with Chronic HCV Infection and Child-Pugh-Turcotte Class C Cirrhosis
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
IND Number:	118605
EudraCT Number:	2016-003066-10
Clinical Trials.gov Identifier:	Not Available
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-342-4022

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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 Weeks in Subjects with Chronic HCV Infection and Child-Pugh-Turcotte Class C Cirrhosis
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	118605 2016-003066-10 Not Available
Study Centers Planned:	Approximately 20 centers in United States and Europe
Objectives:	The primary objectives of this study are: • To evaluate the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL) fixed-dose combination (FDC) with ribavirin (RBV) for 12 weeks in subjects with chronic hepatitis C virus (HCV) infection and Child-Pugh-Turcotte (CPT) class C cirrhosis as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12) • To evaluate the safety and tolerability of the treatment regimen The secondary objectives of this study are: • To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of the study treatment regimen (SVR4 and SVR24) • To evaluate the proportion of subjects with virologic failure • To evaluate therapeutic efficacy as measured by the change of CPT score and Model for End Stage Liver Disease (MELD) score • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation treatment • To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

The exploratory objectives of this study are:

PPD

Study Design:

Approximately 50 subjects with chronic HCV infection and CPT Class C cirrhosis will be enrolled and treated with SOF/VEL Fixed-Dose Combination (FDC) tablet with RBV for 12 weeks.

Substudies and Registry Studies:

PPD

Sequence Registry Study (GS-US-248-0123)

Subjects who do not achieve SVR will be eligible for enrollment in an Observational Sequence Registry Study. The purpose of the Sequence Registry Study will be to monitor the persistence of HCV resistant mutations. The Sequence Registry Study is described in a separate protocol.

Cirrhosis SVR Registry Study (GS-US-337-1431)

Cirrhotic subjects who achieve SVR will be eligible for enrollment in the Cirrhosis SVR Registry Study. The purpose of the Cirrhosis SVR Registry Study will be to evaluate durability of SVR and the progression or regression of liver disease for up to 5 years posttreatment. The Cirrhosis SVR Registry Study is described in a separate protocol.

Number of Subjects Planned:

Approximately 50 subjects

Target Population:

Adults with chronic HCV infection and CPT C cirrhosis.

Duration of Treatment:

12 weeks

Diagnosis and Main Eligibility Criteria:

Chronic HCV infected, male and non-pregnant/non-lactating female subjects aged 18 years or older with CPT C cirrhosis.

See the Sections 4.2 and 4.3 for full eligibility criteria.

Study Procedures/ Frequency:	Screening assessments will be completed within 28 days of the Day 1 visit. The screening window can be extended to 42 days for subjects in extenuating circumstances with Sponsor approval. All subjects will complete the following study visits: Screening, Day 1, on-treatment visits at the end of Weeks 2, 4, 8, and 12, and posttreatment visits at Week 4 and 12, after completion of treatment. Subjects who achieve SVR12 will complete the posttreatment Week 24 visit. Screening assessments will include obtaining informed consent, physical examination, medical history, height, weight, vital signs, 12-lead electrocardiogram (ECG), adverse events (AEs) related to screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), calculation of CPT and MELD scores, HCV RNA, HCV genotyping, serology (HIV, HCV, HBV), hemoglobin A1c (HbA1c), screening for hepatocellular carcinoma (HCC), serum β-hCG (females of child bearing potential only), IL28B genotyping, urinalysis and urine drug screen. On-treatment assessments include AEs, concomitant medications, calculation of CPT and MELD scores, study drug pill count, physical examination, weight, vital signs, safety laboratory tests, HCV RNA, HRQoL surveys, urinalysis and urine pregnancy tests (females of child bearing potential only). Single 12-lead ECGs will be collected at Screening and Day 1 (prior to study drug administration). At the time of ECG collection, printed copies (paper) will be reviewed by qualified study staff (as determined by the Investigator). Posttreatment assessments include AEs, concomitant medications, vital signs, weight, safety laboratory tests, calculation of CPT and MELD scores, pregnancy prevention counseling, physical examination, HCV RNA, HRQoL surveys, and urine pregnancy tests (females of child bearing potential only). HRQoL surveys (SF-36, CLDQ-HCV, FACIT-F, and WPAI) will be conducted at Day 1, on-treatment Week 12, Early Termination (ET) (if applicable), and posttreatment Weeks 12 (if applicable). Samples for viral RNA sequencing/phenotyping will be collected at Day 1 and every visit thereafter. Samples will be collected during on-treatment visits for pharmacokinetic (PK) analysis of study drugs. For subjects who are Hepatitis B core antibody positive (HBcAb+), HBV DNA will be measured at Day 1, on-treatment Weeks 4, 8, 12, and posttreatment Weeks 4, 12, and 24.

	PPD PPD
Test Product, Dose, and Mode of Administration:	SOF/VEL FDC is manufactured as a 400 mg/100 mg FDC tablet for oral administration. Subjects will take 1 tablet daily with or without food. RBV is manufactured as a 200 mg tablet for oral administration. Subjects will take a starting dose of 600 mg RBV with food in a divided daily dose. If the starting dose is well-tolerated, RBV can be titrated up to a maximum of 1000-1200 mg daily (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg) divided twice daily. If the starting dose is not well tolerated, the dose should be reduced as necessary.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	AEs and laboratory tests will be collected throughout the study.
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0. Efficacy will also be assessed based on MELD and CPT scores on-treatment and posttreatment.
Pharmacokinetics:	A single PK blood sample will be collected at each on-treatment visit for all subjects. The PK of SOF (and metabolites), VEL and RBV may be assessed.

Statistical Methods:	The primary efficacy endpoint for the study is SVR12 in all enrolled and treated subjects. In the primary efficacy analysis, point estimate and 95% confidence interval (using the Clopper-Pearson method) of SVR12 will be computed. Secondary endpoints include SVR4 and SVR24; proportion of subjects who have HCV RNA < LLOQ by visit while on study treatment; absolute and change from Day 1 in HCV RNA; virologic failure; and change from Day 1 in MELD and CPT scores. With a sample size of approximately 50 subjects, a 2-sided 95% exact confidence interval of the SVR12 rate will extend at most 29% in length.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
ACR	acute cellular rejection
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
BMI	body mass index
CK	creatine kinase
CT	computed tomography
Cl_{Cr}	creatinine clearance
CRF	case report form(s)
CRO	contract (or clinical) research organization
CPT	Child-Pugh-Turcotte
CSA	colony stimulating agents
DAA	direct acting antiviral
DCV	daclatasvir
dL	deciliter
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
eCRF	electronic case report form(s)
ESA	erythropoiesis stimulating agent
ET	early termination
EU	European Union
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FDC	Fixed-Dose Combination
FEV_1	forced expiratory volume in one second
GCP	Good Clinical Practice (Guidelines)
GM-CSF	granulocyte-macrophage colony stimulating factor
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
Hb	hemoglobin
HbA1c	hemoglobin A1c
HBcAb	Hepatitis B core antibody

HBcAb+	Hepatitis B core antibody positive
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBsAg+	Hepatitis B surface antigen positive
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
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL28B	IL28B gene
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
kg	kilogram
L	liter
LDV	ledipasvir, GS-5885
LLN	lower limit of the normal range
LLOQ	lower limit of quantification
LLT	Lower-Level Term
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
mg	milligram
mL	milliliter
min	minute
mmHg	millimeters mercury
MRI	magnetic resonance imaging
NS (3/4A/5A/5B)	non-structural protein
PBMC	peripheral blood mononuclear cell(s)
PPD	
P-gp	P-glycoprotein
PK	pharmacokinetic
PPI	proton pump inhibitor
RBC	red blood cell count
RBV	ribavirin

RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SmPC	Summaries of Product Characteristics
SOC	System Organ Class
SOF	sofosbuvir, GS-7977
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
TIPS	transjugular intrahepatic portosystemic shunt
ULN	upper limit of the normal range
US	United States
US PI	United States Package Insert
VEL	velpatasvir, GS-5816
WBC	white blood cell

1. INTRODUCTION

1.1. Background

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

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

Recently, there has been a transformation in the treatment of HCV infection with the development of DAAs targeting viral proteins essential to viral replication. DAA based treatment regimens are generally well tolerated and result in high rates of sustained virologic response at 12 weeks following completion of all treatment (SVR12) across most patient populations {Gilead Sciences Inc 2013, Gilead Sciences Inc 2016a, Gilead Sciences Inc 2016b}. Sofosbuvir-based regimens (Sovaldi® and Harvoni®) are the most widely prescribed treatments for HCV infection due to the efficacy, tolerability, and simplicity of the dosing regimens. In addition, sofosbuvir-based regimens offer the advantages of having relatively few drug-drug interactions, strong concordance between clinical trial and "real world" data, and absence of a requirement for baseline NS5A polymorphism testing{Ioannou et al 2016} The recent approvals in the US and EU of Epclusa®, a fixed dose combination of sofosbuvir and velpatasvir is an important advance in HCV drug development as Epclusa® is highly efficacious across all HCV genotypes whereas previously approved regimens were HCV genotype specific {Arias et al 2016, Gilead Sciences Inc 2013, Gilead Sciences Inc 2016a, Gilead Sciences International Ltd 2016, Ioannou et al 2016}.

Despite the progress made in the development of effective treatments for HCV infection, many challenges remain. These include the evaluation of DAA based regimens in patient populations not evaluated in registration clinical studies, such as patients with advanced hepatic disease, or advanced renal disease and pediatric populations. In addition, the treatment of populations with high HCV prevalence such as the incarcerated or injection drug users will require the

development of treatment models tailored to these specific populations. Finally, as the highest prevalence of HCV infection occurs in low and middle income countries, the development of treatment algorithms that can be implemented in resource limited settings will be necessary to decrease the global prevalence and burden of HCV.

1.2. Sofosbuvir/Velpatasvir Fixed-Dose Combination

Sofosbuvir (SOF) is a nucleotide analog HCV NS5B polymerase inhibitor. Velpatasvir (VEL) is a pangenotypic HCV NS5A inhibitor. SOF/VEL (Epclusa®) is a co-formulation of SOF 400 mg and VEL 100 mg that is approved in the US, EU and other regions for the treatment of HCV infection in adults.

1.2.1. General Information

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

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

1.3. Ribavirin (RBV)

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.

Ribavirin is a known teratogen (FDA category X). Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 7 months following completion of treatment, and in the case of males, impregnating a female while on RBV and up to 7 months following completion of therapy.

A comprehensive review of RBV is contained in the US PI or SmPC.

1.4. Rationale for This Study

The GS-US-342-4022 study is a Phase 2 multicenter, open-label study evaluating SOF/VEL +RBV for 12 weeks in subjects with HCV infection and Child-Pugh-Turcotte (CPT) class C (CPT C) cirrhosis. Approximately 50 subjects will be enrolled.

SOF/VEL with RBV for 12 weeks is approved in the US and EU (as Epclusa®) for the treatment of HCV infection in patients with decompensated cirrhosis based on the results of the ASTRAL-4 study {Curry et al 2015}. However, of the 87 HCV infected subjects treated with SOF/VEL and RBV for 12 weeks in the ASTRAL-4 study, 77 (89%) had CPT B cirrhosis and only 4 (5%) had CPT C cirrhosis at baseline. The regimen was efficacious with all 4 subjects with CPT C cirrhosis achieving SVR12. However 3 of 4 subjects with CPT C cirrhosis required dose reduction of RBV suggesting that weight-based dosing of RBV may not be appropriate for subjects with CPT C cirrhosis. An additional limitation of the ASTRAL-4 study was that subjects who had received a liver transplant were not eligible.

Given the small number of subjects with CPT C cirrhosis evaluated with SOF/VEL+RBV in the ASTRAL-4 study, this study will more comprehensively evaluate the safety and efficacy of SOF/VEL+RBV in subjects with CPT C cirrhosis including patients who have received a liver transplant.

1.5. Rationale for Dose Selection of SOF/VEL

Subjects in this study will be administered SOF/VEL, a co-formulation of SOF 400 mg and VEL 100 mg that is approved in the US, EU and other regions as Epclusa® for the treatment of HCV infection in adults.

In the Phase 3 ASTRAL 1-3 studies, treatment of HCV infected subjects without cirrhosis or with compensated cirrhosis for 12 weeks with SOF/VEL was well tolerated and resulted in high SVR12 rates. In the ASTRAL-4 study, treatment of HCV infected subjects with decompensated Child Pugh Turcotte class B cirrhosis with SOF/VEL and ribavirin for 12 weeks was well tolerated and resulted in high SVR12 rates across all HCV genotypes evaluated.

Based on these data, the results of Phase 1 studies in subjects with hepatic impairment and population PK analyses from studies of HCV infected subjects, no dose adjustment of SOF/VEL is recommended in patients with CPT C cirrhosis. Refer to the SOF/VEL Investigator's Brochure for additional information.

1.6. Rationale for Dose Selection of Ribavirin

Data from the ASTRAL-4 and SOLAR studies support a starting dose of RBV 600 mg in combination with SOF/VEL for subjects with CPT C cirrhosis in this study.

The ASTRAL-4 study evaluated the safety and efficacy of SOF/VEL with and without weight based RBV (1000-1200 mg) for 12 weeks and SOF/VEL for 24 weeks in patients with decompensated cirrhosis. Of 87 subjects treated with SOF/VEL and RBV for 12 weeks, 77 (89%) had CPT B cirrhosis and 4 (5%) had CPT C cirrhosis at baseline. RBV dose reduction was required by approximately one third of subjects with CPT B cirrhosis compared with 3 of 4 subjects with CPT C cirrhosis suggesting that weight based (1000-1200 mg) RBV dosing was less tolerated in patients with CPT C cirrhosis compared with patients with CPT B cirrhosis.

The SOLAR-1 and SOLAR -2 studies evaluated ledipasvir (LDV) /SOF and RBV 600mg for 12 or 24 weeks in pre- and posttransplant patients including patients with decompensated cirrhosis{Charlton et al 2015, Manns et al 2016}. In these studies, treatment of subjects with CPT C cirrhosis with LDV/SOF and RBV 600mg for 12 or 24 weeks was well tolerated and resulted in high SVR12 rates. Based on the SOLAR data, the US PI and EU SmPC for Harvoni recommended a 600 mg starting dose of RBV in HCV infected patients with decompensated cirrhosis {Gilead Sciences Inc 2016b, Gilead Sciences International Ltd. 2016}.

1.7. Risk/Benefit Assessment for the Study

This study will provide information of the safety and efficacy of the combination of SOF/VEL plus RBV for 12 weeks in patients with CPT C decompensated cirrhosis.

The safety profile of SOF/VEL has been established in 3126 subjects, including 1558 subjects in the Phase 3 studies, 802 in the Phase 2 studies, 499 in the Phase 1 studies, and 267 subjects with decompensated cirrhosis in the Phase 3 Study GS-US-342-1137 (ASTRAL-4). No clinical safety issues specifically related to the combination of SOF/VEL have been identified to date. No clinical safety issues specifically related to the NS5A inhibitor class including daclatasvir (DCV) and LDV have been identified to date {Afdhal et al 2014a, Afdhal et al 2014b, Kowdley et al 2014}. Overall, SOF/VEL plus RBV for 12 weeks was safe and well tolerated in patients with CPT B cirrhosis.

During the conduct of the study, the sponsor will perform ongoing safety review.

In summary, safety and efficacy of SOF/VEL plus RBV for 12 weeks has been evaluated in subjects with CPT B decompensated cirrhosis. This study will evaluate this regimen in patients with more advanced liver disease.

1.8. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL) fixed-dose combination (FDC) with ribavirin (RBV) for 12 weeks in subjects with chronic HCV infection and Child-Pugh-Turcotte (CPT) class C cirrhosis as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of the treatment regimen

The secondary objectives of this study are:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of the study treatment regimen (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate therapeutic efficacy as measured by the change of CPT score and MELD score
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation treatment
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

The exploratory objectives of this study are:

PPD

3. STUDY DESIGN

3.1. Study Design

This is a multicenter, open-label study evaluating the efficacy and safety of SOF/VEL and RBV for 12 weeks in chronic HCV infected subjects with CPT C cirrhosis.

3.2. Visit Schedule

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

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

3.3. Duration of Treatment

Approximately 50 subjects will be enrolled and treated with SOF/VEL tablet once daily and 600-1200 mg RBV in a divided daily dose with food.

The total time to complete all study visits is approximately 40 weeks (42 weeks for those requiring extension of the Screening period):

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

3.4. Treatment Discontinuation

3.4.1. Treatment 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 6.4). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

There is no option for SOF/VEL dose reduction due to toxicity. If SOF/VEL is withheld due to toxicity, the subject must discontinue treatment and complete an Early Termination (ET) visit. Subjects that require discontinuation of only RBV for RBV-related events should continue with SOF/VEL for the remainder of the treatment period and complete all scheduled study visits.

For subjects who have completed an ET visit, the posttreatment Week 4, and 12 visits will be completed after the last dose of the study drug. Subjects who achieve SVR12 will complete a posttreatment Week 24 visit.

The Medical Monitor should be consulted prior to subject discontinuation when medically feasible.

Study drug must be discontinued in the following instances:

- Unacceptable toxicity, as defined in Section 3.4.2, or toxicity that in the opinion of the investigator compromises that ability of the subject to participate in the study or is considered to not be in the best interest of the subject
- Virologic failure (as defined in Section 3.5)
- Pregnancy of female subject or female partner of male subject
- Significant protocol violation including non-compliance with study assessments
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason
- Discontinuation of the study at the request of Gilead, regulatory agency, or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

3.4.2. Toxicity-Based Stopping Criteria

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

- Confirmed total bilirubin > 3x Day 1 or nadir and ALT and/or AST > 3x Day 1 or nadir
- Elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 10x Day 1 or nadir, confirmed by immediate repeat testing
- Elevation of ALT >15x ULN, confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any non-laboratory Grade 4 event assessed as related to administration of SOF/VEL, study drugs should be discontinued immediately

3.5. Virologic Response-Based Stopping Criteria

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

- Confirmed HCV RNA ≥LLOQ after 2 consecutive HCV RNA <LLOQ

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

3.6. Substudies and Registry Studies

PPD

3.6.2. Sequence Registry Study (GS-US-248-0123)

Subjects who do not achieve SVR will be eligible for enrollment in an observational Sequence Registry Study. The purpose of the Sequence Registry Study will be to monitor the persistence of HCV resistant mutations. The Sequence Registry Study is described in a separate protocol.

3.6.3. Cirrhosis SVR Registry Study (GS-US-337-1431)

Cirrhotic subjects who achieve SVR will be eligible for enrollment in the Cirrhosis SVR Registry Study. The purpose of the Cirrhosis SVR Registry Study will be to evaluate durability of SVR and the progression or regression of liver disease for up to 5 years posttreatment. The Cirrhosis SVR Registry Study is described in a separate protocol.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 50 subjects will be enrolled in this study.

In order to manage the total study enrollment, Gilead Sciences, Inc. at its sole discretion, may suspend screening and/or discontinue the enrollment at any site or study-wide at any time (upon written notice to the site). Discontinuation of the enrollment phase may result in the immediate ineligibility of all subjects screened but not yet enrolled, regardless of the progress or outcome of the screening assessments performed.

4.2. Inclusion Criteria

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

1) Willing and able to provide written informed consent

2) Males and females, age ≥ 18 years old

3) A body mass index (BMI) of ≥ 18 kg/m^2

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

5) Quantifiable HCV RNA at Screening

6) Subjects may be non-transplanted or with recurrent HCV post-liver transplant.

    a. If listed for liver transplant, then the projected date of transplant must be ≥12 weeks after Day1 of treatment

    b. If post-liver transplant, then Day1 must be ≥ 6 months from date of transplant

7) CPT score of 10 to 12, inclusive, as determined at Screening

8) Liver imaging within 6 months of Day 1 to exclude HCC

9) If treatment-experienced, the most recent HCV treatment must have been completed at least 8 weeks prior to Screening

10) 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

11) 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

12) Female subjects must agree to refrain from egg donation and in vitro fertilization during treatment until at least 30 days after the last dose of SOF/VEL or 6 months after the last dose of RBV, whichever occurs last

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

14) Male subjects must agree to refrain from sperm donation from the date of Screening until at least 7 months after the last dose of RBV or 30 days after the last dose of SOF/VEL, whichever occurs last

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

4.3. 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 medical or psychiatric illness or subjects is currently under evaluation for a potentially clinically significant illness (other than HCV or co-morbidities associated with advanced liver disease except as noted below) or any other medical or psychiatric disorder that may interfere with subject treatment, assessment or compliance with the protocol

   b) Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug

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

   d) Significant pulmonary disease, significant cardiac disease or porphyria

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

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

2) Any history of organ transplant other than liver or kidney

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

4) Inability to exclude HCC by imaging within 6 months of Day 1 (including indeterminate hepatic nodule meeting OPTN Class 5 criteria, defined by arterial enhancement with washout on portal venous/delayed phase OR rate of growth maximum diameter increase in the absence of ablative therapy by 50% or more documented on serial magnetic resonance imaging (MRI) or computed tomography (CT) obtained <6 month apart)

5) Alpha-fetoprotein (AFP) > 50 unless negative imaging for hepatic masses within the last 6 months or during screening

6) Active spontaneous bacterial peritonitis at Screening

7) Infection requiring systemic antibiotics at the time of Screening

8) Evidence of fibrosing cholestatic hepatitis at Screening

9) Life threatening SAE during Screening

10) Active variceal bleeding within 6 months of Screening

11) Prior placement of a portosystemic shunt (such as TIPS)

12) ECG with clinically significant abnormalities

13) Laboratory parameters at Screening:

    a) Hemoglobin < 10 g/dL

    b) Platelets < 30,000/μL

    c) ALT > 10 × the upper limit of normal (ULN)

    d) AST > 10 × ULN

    e) Alkaline phosphatase > 10 x ULN

    f) Sodium <125 mEq/L

    g) Total bilirubin > 10 mg/dL

    h) Creatinine clearance (CL_{cr}) < 30 mL /min, as calculated by the Cockcroft-Gault equation {Cockcroft et al 1976} using actual body weight

14) Hepatitis B surface antigen positive (HBsAg+) at Screening

15) Infection with human immunodeficiency virus (HIV)

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

17) Prior exposure to any HCV NS5A inhibitor

18) Current use of corticosteroids at any dose >10 mg of prednisone/day (or equivalent dose of corticosteroid)

19) Use of any prohibited concomitant medications as described in Section 5.5

20) Use of GM-CSF, epoetin alfa or other hematopoietic stimulating agents within 2 weeks of Screening.

21) Male with pregnant female partner.

22) History of clinically significant hemoglobinopathy (eg, sickle cell disease, thalassemia)

23) Contraindications to RBV therapy

24) Known hypersensitivity to VEL, RBV, SOF, the metabolites, or formulation excipients

25) Participation in a clinical study with an investigational drug or biologic within 3 months prior to Day 1

Exclusion criteria that are specific to subjects who have not had a liver transplant

26) Medical justification for any MELD exception points (such as for HCC, current hepatopulmonary syndrome, intractable encephalopathy, or any other reason)

27) History of hepatopulmonary syndrome

Exclusion criteria that are specific to subjects who have had a liver transplant

28) Recipient of ABO incompatible organ

29) Histological evidence of unresolved rejection of liver transplant

30) Patients who had evidence of HCC at time of transplant must be 5 years posttransplant with no evidence of recurrence at Screening

31) Use or planned use of T-cell depleting/masking antibodies, systemic antineoplastic agents or cyclosporine >300mg/day, or use of any prohibited medications listed in Section 5.4

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

This is a multicenter, open label study. All subjects enrolled will receive SOF/VEL and RBV for 12 weeks. There will be no randomization or blinding.

5.2. Description and Handling of SOF/VEL FDC

5.2.1. Formulation

The SOF/VEL (400/100 mg) tablets are pink, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side. In addition to the active ingredients, the SOF/VEL tablets contain copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

5.2.2. Packaging and Labeling

SOF/VEL (400/100 mg) tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

SOF/VEL bottles to be distributed to centers in participating countries shall be labeled to meet all applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

SOF/VEL tablets 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 SOF/VEL tablets.

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

5.3. Description and Handling of Ribavirin (RBV)

5.3.1. Formulation

RBV tablets, 200 mg, are light blue, capsule-shaped, film-coated tablets debossed with "3RP" on one side and "200" on the other side. See package insert for further information.

The RBV tablets being supplied by Gilead Sciences are a US marketed formulation of RBV.

5.3.2. Packaging and Labeling

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

All RBV bottles to be distributed to centers in the participating countries and shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practices- Annex 13 (Investigational Medicinal Products), and/or other local regulations as applicable.

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

5.3.3. Storage and Handling

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

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

5.4. Dosage and Administration of SOF/VEL and RBV

SOF/VEL 400/100 mg tablets will be administered once daily. RBV 200 mg tablets will be administered twice daily at a starting dose of 600 mg. RBV should be taken in a divided daily dose with food (Table 5-1). If the starting dose is well-tolerated and the subject maintains a hemoglobin level above 10 g/dL without the need for significant growth factor support, the dose can be titrated up to a maximum of 1000-1200 mg daily (1000 mg for subjects weighing <75 kg and 1200 mg for subjects weighing ≥75 kg). If the starting dose is not well-tolerated, the dose should be reduced as necessary.

Table 5-1. Suggested Dose Administration of RBV

Total Daily RBV dose	AM dose	PM dose
200 mg	1 tablet	--
400 mg	1 tablet	1 tablet
600 mg	1 tablet	2 tablets
800 mg	2 tablets	2 tablets
1000 mg	2 tablets	3 tablets
1200 mg	3 tablets	3 tablets

All subjects should be instructed to maintain approximately the same daily dosing interval between study drug doses. To aid compliance, it is suggested that SOF/VEL is administered with either the morning or evening dose of RBV with food.

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

For missed dose(s) of RBV, subjects should be instructed to take the missed dose(s) of study drug as soon as possible, unless more than 6 hours has elapsed since the scheduled time of the missed dose. In this case, the subject should be instructed to wait and take the next dose at the regularly scheduled time. No more than the daily dose of RBV should be taken on any calendar day. Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

No food restrictions apply to SOF/VEL. However as RBV must be taken with food hence it is suggested that when SOF/VEL is taken with RBV, both drugs should be taken together and with food for optimal adherence.

5.5. 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 eCRFs (including all blood products).

For subjects on a calcineurin inhibitor (eg, tacrolimus, sirolimus, everolimus) for posttransplant immunosuppression, drug levels should be measured as per the standard schedule (or as clinically indicated) for dose management at the clinical site, and processed at the local laboratory. Management of the immunosuppression is not part of the clinical protocol, but levels and resulting dose adjustments will be recorded to assess whether the regimens required adjustment in correlation with resolution of the HCV infection.

Chronic use of corticosteroids at any dose > 10mg of prednisone/day (or equivalent dose of corticosteroid) for maintenance of immunosuppression is prohibited from 28 days prior to the Day 1 visit through the end of study drug dosing. Use of steroids for the short term treatment of Acute Cellular Rejection (ACR) or other reasons is up to the discretion of the Investigator.

Investigational agents or devices for any indication are prohibited from **28 days prior to the Day 1** visit through the end of study drug dosing.

Concomitant use of certain medications or herbal/natural supplements (such as moderate to potent inducers of drug transporters or metabolizing enzymes, eg, P-gp, CYP2B6, CYP2C8, or CYP3A) with the study drug may result in pharmacokinetic interactions resulting in increases or decreases in exposure of the study drug or these medications.

Table 5-2 below contains examples of medications that are prohibited from **21 days prior to Day 1** through the end of treatment and those medications which may be used with caution. The use of amiodarone is prohibited from **60 days prior to Day 1** through the end of treatment. Additionally, Investigators should refer to the product/package inserts of other medications for age-related recommendations or contraindications related to their use.

Table 5-2. Disallowed and Concomitant Medications to be Used with Caution

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing Agents[a]		Proton Pump Inhibitors, H2-Receptor Antagonists, Antacids
Anticonvulsants[b]	Phenytoin, Carbamazepine, Phenobarbital, Oxcarbazepine	
Antimycobacterials[b]	Rifampicin, Rifabutin, Rifapentine	
Cardiac Medications	Amiodarone[d]	Digoxin[e]
Herbal/Natural Supplements[b]	St. John's Wort, Echinacea, Milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[f]		Rosuvastatin (≤10 mg/day), Atorvastatin
Other	Bosentan[b], Modafinil [b], Sulfasalazine[c], Methotrexate[c]	

a Co-administration with proton pump inhibitors (PPIs) is not recommended. If it is considered necessary to co-administer, then SOF/VEL should be administered with food and taken 4 hours before PPI at max doses comparable to omeprazole 20 mg. H2-receptor antagonists must not exceed a dose of 40 mg famotidine or equivalent and can be taken simultaneously with SOF/VEL and/or staggered by 12 hours. Antacids that directly neutralize stomach acid (ie, Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/VEL administration.
b May result in a decrease in the concentration of study drugs.
c May result in an increase in the concentration of study drugs and/or concomitant medications
d May result in symptomatic bradycardia. Mechanism is not currently known. The use of amiodarone is prohibited from 60 days prior to Day 1 through the end of treatment
e Monitor for signs and symptoms of digoxin toxicity.
f Use with SOF/VEL may result in an increase in the concentration of rosuvastatin Titrate rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. Use atorvastatin with caution and at the lowest necessary dose. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis

Medications for disease conditions **excluded** from the protocol (eg, HIV infection) are not listed under this Concomitant Medication section and are disallowed in the study. Should subjects have a need to initiate treatment with any excluded concomitant medication, the Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication.

Subjects may not take any approved HCV medications during their participation in the study period.

5.5.1 Colony Stimulating Agents

Potential subjects may not be treated with colony stimulating agents (CSA) within 2 weeks of Screening to elevate hematology laboratory parameters to facilitate entry into the study. Use during the study is allowed as clinically indicated. Use should be captured as a concomitant medication.

If erythropoiesis-stimulating agents (ESAs) are used during the study, the following guidelines should be adhered to:

- ESAs should not be initiated until the hemoglobin falls below 10 g/dL,
- Iron studies should be obtained prior to and during treatment with ESA,
- Iron supplementation should be initiated for deficient patients and to maintain transferrin saturation at a level that will support erythropoiesis,
- Once an ESA is initiated, hemoglobin levels and blood pressure must be monitored weekly until the hemoglobin level stabilizes,
- Treatment should target a hemoglobin level sufficient to avoid transfusion.
- ESA dose should be titrated to treatment response,
- ESA dose should be reduced if the hemoglobin increases by more than 1 g/dL in a 2 week period,
- ESA dose should not exceed those recommended for currently approved indications,
- ESAs should not be used in patients at increased risk for thromboembolic events, cardiovascular events, including those with inadequately controlled hypertension, and in patients diagnosed with malignancies.

5.6. Accountability for SOF/VEL+RBV

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

SOF/VEL + RBV accountability records will be provided to each study site to:

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

5.6.1. Study Drug Return or Disposal

Refer to Section 9.1.7 for information on return and disposal of study drugs.

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. Subject Enrollment and Treatment Assignment

This is an open-label study. An Interactive Web Response System (IWRS) will be employed to manage subject screening, subject enrollment, and study drug dispensation and resupply.

6.1.1. Screening Visit (Day -28 to Day 0)

Subjects will be screened within 28 days prior to enrollment to determine eligibility for participation in the study. The screening window can be extended to 42 days with Sponsor approval for subjects with extenuating circumstances. The following will be performed and documented at screening:

- Obtain written informed consent
  - PPD [redacted]
- Determine inclusion and exclusion eligibility
- Obtain medical history, including:
  - Hepatitis C treatment history:
    - Regimen(s)
    - Dates of previous treatment(s)
    - Response to previous treatment (eg, nonresponder, relapse, discontinuation including reason)
  - Liver transplant history
- Perform 12-lead ECG
- Liver Disease Assessment
  - Liver biopsy and/or Fibroscan results (if available)

  - Assess presence and severity of ascites and hepatic encephalopathy for CPT score
  - Diagnostic imaging (eg, ultrasound or CT scan) should be performed to exclude the presence of HCC
- Perform complete physical examination
- Vital signs
- Body weight and height
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form
- Review of concomitant medications
- Pregnancy prevention counseling
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Determination of genotype and subtype of HCV infection
  - Serum β-hCG pregnancy test for females of childbearing potential only
  - HCV antibody, HIV 1/2 antibody, HBsAg, HBcAb, and Hepatitis B surface antibody (HBsAb)
  - HbA1c
  - IL28B
  - Fibrotest®
- Obtain urine sample for:
  - Urinalysis
  - Urine Drug Screen

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

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

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

6.2. Treatment Phase: Treatment Assessments

6.2.1. Day 1 Assessments

After confirmation of eligibility has been evaluated, the following tests and procedures must be completed on Day 1 prior to enrollment and dosing/dispensing:

- Confirm eligibility
- Perform complete physical examination
- Vital signs
- Body weight
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Perform 12-lead ECG
- Subject completes Health Related Quality of Life Questionnaire: SF-36, CLDQ-HCV, FACIT-F, and WPAI
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests

— HCV RNA

— Viral sequencing

PPD [redacted]

PPD [redacted]

— HBV DNA (only in subjects who are HBcAb+ at Screening)

- Obtain urine samples for the following procedures:

  — Urinalysis

  — Urine pregnancy test for females of childbearing potential only

6.2.2. Study Drug Administration

- Dispense study drugs as directed by the IWRS
- Instruct the subject on the packaging, storage and administration of study drug
- Observe the subject taking the first dose of study drugs and record the time of first dose and whether it was taken with or without food

6.2.3. Week 2 (± 3 days)

The following procedures/assessments are to be completed at this visit:

- Vital signs
- Body Weight
- Assessment of AEs and concomitant medications
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Obtain blood samples for:

  — Hematology

  — Chemistry

  — Coagulation

- HCV RNA
- Viral sequencing
- Single PK

- Assess adherence with the study drug dosing regimen including pill count

6.2.4. Weeks 4 and 8 (± 3 days)

- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Vital signs
- Body Weight
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation
  - HCV RNA
  - Viral sequencing
  - Single PK
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only
- Review study drug compliance with subject (subject should return all study drug at these visits)
- Dispense study drug as directed by the IWRS

6.2.5. Week 12 (± 3 days) or Early Termination

- Perform complete physical examination
- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Vital signs
- Body weight
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes Health Related Quality of Life Questionnaire: SF-36, CLDQ-HCV, FACIT-F, and WPAI
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral sequencing
  - PPD [redacted]
  - Single PK
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
- Obtain urine samples for the following procedures:
  - Urinalysis
  - Urine pregnancy test for females of childbearing potential only
- Review study drug compliance
- Subjects should return all bottles of study drug at the Week 12 Visit

6.3. Posttreatment Assessments

6.3.1. 4-Week Posttreatment Visit (± 5 days)

- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Vital signs
- Body Weight
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation
  - HCV RNA
  - Viral sequencing
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only

6.3.2. 12 & 24 Week Posttreatment Visit (± 5 days)

- Assess presence and severity of ascites and hepatic encephalopathy for CPT score
- Vital signs
- Body Weight
- Perform symptom-directed physical examination
- Pregnancy prevention counseling
- Subject completes Health Related Quality of Life Questionnaire: SF-36, CLDQ-HCV, FACIT-F, and WPAI at posttreatment Week 12 only

- Obtain blood samples for:
  - Hematology
  - Chemistry
  - Coagulation
  - HCV RNA
  - Viral sequencing
  - HBV DNA (only in subjects who are HBcAb+ at Screening)
- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only

6.4. Assessments for Premature Discontinuation from Study

If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 3.4.1, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study.

6.5. Procedures and Specifications

6.5.1. Clinical Laboratory Analytes

Hematology: Hematocrit, hemoglobin (Hb), platelet count, red blood cell count (RBC), white blood cell count (WBC) with differential (absolute and percentage) including lymphocytes, monocytes, neutrophils, eosinophils, basophils, reticulocyte count and mean corpuscular volume (MCV).

Coagulation: International normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT)

Chemistry: Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), albumin, alkaline phosphatase, creatinine, total bilirubin and direct bilirubin, glucose, lipase, potassium, sodium, phosphate, uric acid, and creatine kinase (CK),

Urinalysis: blood, glucose, leukocyte esterase, pH, protein, urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal.

Virological Tests: Serologies for HCV and HBV. HBV DNA (only in subjects who are HBcAb+ at Screening). Serology and/or antigen testing for HIV (including reflex testing) as

necessary, HCV RNA will be measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 for Use with the High Pure System. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV genotype should the above assays become unavailable or the results are inconclusive.

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

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

Additional Tests: Urine drug screen (for amphetamines, cocaine, methadone, opiates), hemoglobin A1c (HbA1c), Fibrotest.

6.5.2. 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 as per Section 4.

6.5.3. Complete Physical Examination

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

6.5.4. Height & Weight Measurement

Height will be collected at Screening. Weight measurement will be collected at each study visit. The difference in body weight measurements between Day 1 and End of Treatment will be calculated.

6.5.5. 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.

6.5.6. Body Mass Index (BMI)

BMI is calculated by the following equation.

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

6.5.7. MELD and CPT Score Calculations

MELD score and CPT score will be calculated from the central laboratory values attained at each visit. Assessment of ascites and hepatic encephalopathy will be determined by the site as in below table and will be entered into the CRF. Besides calculating the CPT score at Screening (using central laboratory values) to determine eligibility, sites will not need to calculate these scores for subsequent visits.

6.5.7.1. MELD Score

The MELD score is calculated using the following formula {MELD/PELD 2009}:

MELD = 3.8[serum bilirubin (mg/dL)] + 11.2[INR] + 9.57[serum creatinine* (mg/dL)] + 6.43

Round to the nearest whole number. Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD score calculation.

* If subject has had dialysis twice within a week prior to the serum creatinine measurement, or is within 24 hours of continuous venovenous hemodiafiltration, then default to 4 mg/dL for serum creatinine value in MELD calculation.

6.5.7.2. CPT Score

Child-Pugh-Turcotte score should be assessed at all visits per Table 6-1.

Table 6-1. Child-Pugh-Turcotte Classification of the severity of cirrhosis

	1	2	3
Hepatic Encephalopathy	**None** No encephalopathy and not on any treatment for hepatic encephalopathy	**Medication-Controlled** Subject is lethargic, may have moderate confusion Subject is receiving medical therapy for HE	**Medication-Refractory** Marked confusion/incoherent, rousable but sleeping unless aroused or comatosed
Ascites	**None** No ascites and not on treatment for ascites	**Mild/Moderate** Cross sectional imaging showing ascites Abdominal distension Medication for ascites	**Severe (diuretic-refractory)** Visible clinically
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3

CPT score is obtained by adding the score for each parameter.

CPT class: A = 5-6 points
B = 7-9 points
C = 10-15 points

Records of concomitant medications for ascites and hepatic encephalopathy will be collected in the CRF.

6.5.8. Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft et al 1976}.

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

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

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

Actual body weight will be used for the CL_{Cr}.

6.5.9. 12-Lead ECG

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

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

6.5.10. Viral Sequencing (Archive)

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

6.5.11. Single Pharmacokinetic (PK) Sample

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

6.5.12. HBV DNA Sample

A sample for HBV DNA testing will be collected at on-treatment visits at Day 1 and at Weeks 4, 8, and 12 or Early Termination and all posttreatment visits. HBV DNA will only be tested in subjects who are HBcAb+ at Screening to monitor for HBV re-activation.

6.5.13. IL28B Testing

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

6.5.14. Archive Plasma Sample

6.5.16. Pregnancy Testing

Female subjects of childbearing potential should be provided with Urine Pregnancy test kits, instructed on their use, and requested to continue to self-monitor for pregnancy between scheduled study visits, every 4 weeks, for 6 months after their last dose of RBV. If required by regulations, additional pregnancy tests beyond 6 months may be added. The subject will be contacted every 4 weeks and asked to report results of the urine pregnancy tests. If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

6.5.17. Health Related Quality of Life Survey

A health related quality of life survey, SF-36, CLDQ-HCV, FACIT-F, and WPAI, will be completed by patients at Day 1, Week 12 and posttreatment Week 12, and Early Termination (if appropriate). The subject should read the questionnaire by himself/herself and write/mark answers directly onto the questionnaire.

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 (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

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

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

- A congenital anomaly/birth defect

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

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No**: Evidence exists that the adverse event has an etiology other than the study drug. 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 drug, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs, regardless of cause or relationship, and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug and report to the CRF/eCRF database as instructed.

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

7.3.2. 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 posttreatment follow-up period, must be reported to the CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically (ie, the eCRF database is not functioning) record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

  Gilead Sciences, DSPH: Fax: PPD
  E-mail: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

Medical Monitor contact information is as follows:

Gilead Medical Monitor: PPD
Telephone: PPD
Fax: PPD
Email: PPD

7.4. Gilead Reporting Requirements

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

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

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

7.5. Toxicity Management

7.5.1. Dose Adjustments

There is no option of SOF/VEL dose reduction due to toxicity. If SOF/VEL is withheld due to toxicity, the subject must discontinue treatment and complete an Early Termination (ET) visit.

Dose reduction or discontinuation of RBV due to toxicity is allowed at the discretion of the investigator. Once discontinued or reduced, the RBV dosing may be restarted or increased to the starting dose at the discretion of the investigator. RBV may be permanently discontinued due to toxicity without stopping SOF/VEL FDC.

7.5.2. Management of Rejection

The diagnosis of ACR, based on liver biopsy, and the decision to treat are important concerns due to the potential interactions between immunosuppression and the success of HCV treatment. It is expected that this will not be a common occurrence in this study, given that subjects must be stable and at least 6 months from transplant at study entry. Sites will be asked to follow their institutional guidelines for the management of organ rejection, but to also give consideration to the following issues as related to this study protocol. (This information is provided for guidance and consistency across subjects, but variations will not be considered protocol violations if the treatment is consistent with the guidelines of the institution).

- It is important to use standard criteria for diagnosis of rejection, to avoid over-treatment of milder grades of rejection with corticosteroids whenever possible, and to standardize the exposure to corticosteroids when treatment for rejection is necessary

- Episodes of rejection will be recorded on the CRF and severity will be graded (grading by Banff criteria, Appendix 3)
- It is preferred that mild ACR is to be treated with upward adjustment of maintenance immunosuppression rather than the addition of corticosteroids
- Cases of moderate or severe ACR may require treatment with corticosteroids
- Cases of presumptive rejection should be confirmed by liver biopsy (as per standard practice) if more than one dose of corticosteroid is required
- Subjects with steroid-resistant ACR should be discontinued from the study so that management of their organ rejection can be the primary focus of treatment.

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, occupational exposure with an AE, pregnancy reports regardless of an associated AE and AE in an infant following exposure from breastfeeding.

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

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

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

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

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

Occupational exposure with an AE is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

Refer to Section 7.3 and the CRF/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.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: PPD and Fax: PPD

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

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

7.6.2.2. Reporting Requirements for Liver Transplant and Complications of Liver Transplant

If the liver transplant procedure occurs within the AE collection window (30 days after the last dose of study drug), due to the nature of the subject population and the inclusion criteria, events that are clearly related to liver transplant should not be collected as an AE or SAE. In addition, these events will be exempt from global expedited reporting requirements for the duration of the study. These include:

a) The liver transplant procedure itself (and related hospitalization)

b) Events that are direct sequelae of the liver transplant (such as surgical complications) or peri-operative care (central line insertions, etc.)

c) Planned hospitalizations for testing or procedures that are part of the liver transplant assessment and preparation process

These events should be reported as AEs/SAEs only if it is assessed that the events were not an anticipated or predictable part of the transplant process or procedure. In addition, concomitant medications related to the transplant procedure do not need to be recorded (anesthetics, peri-operative pain medication, etc). If there are any questions about how an event should be reported, please contact the study Medical Monitor.

7.6.2.3. Reporting Other Special Situations

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To evaluate the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL) fixed-dose combination (FDC) with ribavirin (RBV) for 12 weeks in subjects with chronic HCV infection and Child-Pugh-Turcotte (CPT) class C cirrhosis as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of the treatment regimen

The secondary objectives of this study are:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of the study treatment regimen (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate therapeutic efficacy as measured by the change of CPT score and MELD score
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation treatment
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

The exploratory objectives of this study are:

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8.1.2. Primary Endpoint

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

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

8.1.3. Secondary Endpoint

The secondary efficacy endpoints include the proportion of subjects who attain sustained virologic response at 4 and 24 weeks after cessation of the study treatment regimen (SVR4 and SVR24); the proportion of subjects who have HCV RNA < LLOQ by visit while on study treatment; CPT and MELD score changes from Day 1; absolute and change from Day 1 in HCV RNA through Week 12; and the proportion of subjects with virologic failure.

8.1.4. Other Endpoints of Interest

Other endpoints of interest may include ALT normalization and change in HRQoL parameters.

8.2. Analysis Conventions

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

The study drugs in this study are SOF/VEL + RBV. Last dose of the study drug refers to the last dose of SOF/VEL and RBV and will be used in the definition of treatment-emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various posttreatment timepoints.

8.2.1. Analysis Sets

8.2.1.1. Efficacy Analysis Set

The analysis set for antiviral activity analyses is defined as the Full Analysis Set (FAS) which includes all enrolled subjects who received at least 1 dose of the study drug.

8.2.1.2. Safety Analysis Set

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

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

8.2.1.3. Pharmacokinetics Analysis Sets

The Pharmacokinetic (PK) Analysis Set includes all enrolled subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value for the corresponding analyte in plasma. The analytes of interest may include SOF (and its metabolites GS-566500 and GS-331007), VEL, and RBV. The PK Analysis Set will be used for analysis of general PK.

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

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 predose value and the change from predose values.

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

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

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

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

8.3. Demographic Data and Baseline Characteristics

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

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

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

8.4. Efficacy Analysis

8.4.1. 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 the study treatment regimen in the FAS population. Point estimate and 95% confidence interval (using the Clopper-Pearson method) of SVR12 will be computed.

8.4.2. Secondary Analyses

The proportion of subjects with HCV RNA below the LLOQ over time (including SVR4 and SVR24) will be presented in tabular and graphical form. Descriptive summaries and listings will be provided for additional efficacy evaluations of the proportion of subjects who experience virologic failure, serum HCV RNA actual values and change from baseline, and other endpoint of interest including ALT normalization.

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

8.5. Safety Analysis

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

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

8.5.1. Extent of Exposure

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

8.5.2. Adverse Events

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

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event 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 adverse event leading to premature discontinuation of the study drug.

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

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

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

8.5.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the laboratory toxicity grading scheme defined in Appendix 3.

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 and including the date of last dose of study drug plus 30 days will be summarized.

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

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

8.5.4. Other Safety Evaluations

Individual data and change from baseline for vital signs measurements will be listed by subject and summarized by descriptive statistical summaries (n, mean, SD, median, Q1, Q3, minimum, and maximum).

8.6. Pharmacokinetic Analysis

Concentrations of SOF (and its metabolites GS-566500 and GS-331007), VEL, and RBV in plasma may be determined using validated bioanalytical assays and listed.

8.7. Sample Size

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The sample size is selected for practical reasons.

With a sample size of approximately 50 subjects, a 2-sided 95% exact confidence interval of the SVR12 rate will extend at most 29% in length.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

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

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

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

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

9.1.3. Informed Consent

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

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

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

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

- Documentation of the reason(s) a consented subject is not enrolled;
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, 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 (eg, 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

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

The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any

expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page
Appendix 2. Study Procedures Table
Appendix 3. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities
Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 Weeks in Subjects with Chronic HCV Infection and Child-Pugh-Turcotte Class C Cirrhosis

GS-US-342-4022, Protocol Amendment 1, 22 November 2016

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

PPD

PPD (Printed)

PPD

Nov 22, 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

			On-treatment Study Week (± 3 days)				Posttreatment Study Week (± 5 days)		
	Screen	Day 1[a]	2	4	8	12/ET	4	12	24
Informed Consent	X								
Determine Eligibility	X	X							
Medical History	X								
Physical Examination	X	X				X		X	X
Assess ascites and hepatic encephalopathy	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X							
AEs	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling	X	X		X	X	X	X	X	X
Health Related Quality of Life[c]		X				X		X	
Study Drug Dispensing[d]		X		X	X				
Review of Study Drug Compliance[e]			X	X	X	X			
Hematology, Chemistry	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X	X	X	X	X	X	X	X
Urinalysis	X	X				X			

	Screen	Day 1[a]	On-treatment Study Week (± 3 days)				Posttreatment Study Week (± 5 days)		
			2	4	8	12/ET	4	12	24
HCV RNA	X	X	X	X	X	X	X	X	X
HBV DNA[f]		X		X	X	X	X	X	X
Viral Sequencing		X	X	X	X	X	X	X	X
Single PK			X	X	X	X			
Serum β-hCG or Urine Pregnancy Test[g]	X	X		X	X	X	X	X	X
Urine Drug Screen	X								
HbA1c	X								
HCV & IL28B Genotyping	X								
HCV, HIV, HBV Serology	X								
Fibrotest®	X								
PPD									

a Day 1 assessments must be performed prior to dosing.
b Vital signs include resting blood pressure, pulse, respiratory rate and temperature.
c There are four Health Related Quality of Life surveys to provide to subjects: SF-36, CLDQ-HCV, FACIT-F, and WPAI.
d The IWRS will provide direction on the specifics of each subject's study drug dispensing.
e Instruct the subject to bring back all study drugs and study drug containers (used/unused).
f Only for subjects who are HBcAb+ at Screening
PPD

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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to <LLN 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 mmol/L	2.0 to < 2.5 mEq/L 2.0 to <2.5 mmol/L	< 2.0 mEq/L <2.0 mmol/L
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 mmol/L	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric** **> 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric** **> 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric** **≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine[**]	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/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** **≥ 16 years**	-	2.0 to < LLN g/dL 20 to < LLN g/L	< 2.0 g/dL < 20 g/L	NA
	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 (eg, 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
Pruritus (itching – no skin lesions) (See also Injection Site Reactions: Pruritus associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

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

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

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

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

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

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

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

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **Necrosis (involving dermis and deeper tissue)**
Pruritus Associated with Injection See also Skin: Pruritus (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 antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial 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) Background

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

a. Definition of Childbearing Potential

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

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

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

b. Definition of Male Fertility

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

2) Study Drug Effects on Pregnancy and Hormonal Contraception

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

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

However, the risks of treatment with SOF/VEL during pregnancy in humans have not been evaluated. Please refer to the latest version of the investigator's brochure for additional information.

3) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Day 1 visit prior to enrollment. Pregnancy tests will be performed at monthly intervals thereafter. They must also agree to one of the following from Screening until 30 days of the last dose of SOF/VEL or 6 months after the last dose of RBV, whichever occurs last.

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom from the date of Screening until 30 days after the last dose of SOF/VEL or 6 months after the last dose of RBV, whichever occurs last.
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Tubal sterilization
  - Essure micro-insert system
  - Vasectomy in the male partner
  - Barrier methods
    - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel or etonogestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment until at least 30 days after the last dose of SOF/VEL or 6 months after the last dose of RBV, whichever occurs last.

4) Contraception Requirements for Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms until 30 days after the last dose of SOF/VEL or 7 months after the last dose of RBV, whichever comes last, when engaging in intercourse of reproductive potential. If their female partner is of childbearing potential (as defined above), their female partner must use 1 of the methods of birth control listed above from the date of Screening until 30 days after the last dose of SOF/VEL or 7 months after last dose of RBV, whichever comes last.

Male subjects must agree to refrain from sperm donation until 30 days after the last dose of SOF/VEL or 7 months after the last dose of RBV, whichever comes last.

5) Unacceptable Methods of Contraception

Birth control methods that are unacceptable include periodic abstinence (eg, 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.

6) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of the last dose of SOF/VEL or if they become pregnant within 6 months (7 months for partners of male subjects) of the last dose of RBV. 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 within 30 days of the last dose of SOF/VEL or 7 months after the last dose of RBV, whichever occurs last must report the information to the investigator.

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