CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 or 24 Weeks in Subjects with Chronic Genotype 1 or 2 HCV Infection Who Have Previously Failed a Direct-Acting Antiviral-Containing Regimen	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA	
IND Number:	This is a non-IND study	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	Not Available	
Indication:	Hepatitis C Virus Infection	
Protocol ID:	GS-US-342-3921	
Gilead Study Director:	Name: Telephone: Fax: Email:	PPD PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax: Email:	Brian McNabb, MD PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3:	01 April 2016 04 May 2016 02 June 2016 13 June 2016

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title:	A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 or 24 Weeks in Subjects with Chronic Genotype 1 or 2 HCV Infection Who Have Previously Failed a Direct-Acting Antiviral-Containing Regimen
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	This is a non-IND study Not Applicable Not Available
Study Centers Planned:	Approximately 20 centers in Japan.
Objectives:	The primary objectives of this study are follows: • To evaluate the antiviral efficacy of therapy with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) and ribavirin for 12 or 24 weeks as measured by the proportion of subjects with sustained virologic response 12 weeks after cessation of treatment (SVR12) • To evaluate the safety and tolerability of each regimen as assessed by review of the accumulated safety data The secondary objectives of this study are as follows: • To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24) • To evaluate the proportion of subjects with virologic failure • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of each treatment regimen • To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

Exploratory objectives of this study are:

Study Design:

This is a multicenter, randomized, open-label study in subjects who previously failed a DAA-containing regimen with chronic HCV infection with or without cirrhosis.

Approximately 110 subjects will be randomized in a 1:1 ratio to one of the following two groups:

- SOF/VEL FDC tablet (400/100 mg) plus ribavirin for 12 weeks
- SOF/VEL FDC tablet (400/100 mg) plus ribavirin for 24 weeks

Randomization will be stratified by cirrhosis status (presence/absence) and HCV genotype (genotype 1/genotype 2). Approximately 20 subjects will have Child-Pugh-A compensated cirrhosis.

The number of subjects by HCV genotype to be enrolled in the study is presented below:

HCV Genotype	Number of Subjects Enrolled
1	approximately 90
2	approximately 20
Total	approximately 110

Number of Subjects Planned: Approximately 110 subjects

Target Population: Adults with chronic genotype 1 or 2 hepatitis C virus (HCV) infection who have previously been treated with a DAA-containing regimen.

Duration of Treatment: Subjects will be treated for 12 or 24 weeks.

Diagnosis and Main Eligibility Criteria: DAA-experienced chronic genotype 1 or 2 HCV-infected male and non-pregnant/non-lactating female subjects, aged 20 years or older.

Optional Substudies: Intensive Pharmacokinetic (PK) Substudy

All subjects, with a target of ~20 subjects, will be eligible to participate in an optional PK substudy if consent is obtained. An intensive serial PK sample collection (i.e., samples obtained over

	24 hours post-dose) will be performed at either the Week 2, Week 3, or Week 4 on-treatment visit to determine the steady-state pharmacokinetics of SOF, its metabolites GS-566500 and GS-331007, VEL and RBV (if appropriate).
Study Procedures/ Frequency:	Screening assessments will be completed within 28 days prior to the Day 1 visit. The screening window can be extended up to 42 days in extenuating circumstances, including the need for a liver biopsy or additional HCV genotyping (if initial testing is inconclusive). Study visits will occur at Screening, Day 1, and on-treatment at the end of Weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12 for subjects randomized to receive 12 weeks of study treatment. Study visits will occur at Screening, Day 1, and on-treatment at the end of Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20 and 24 for subjects randomized to receive 24 weeks of study treatment. Following the last dose of study drugs, all subjects will complete posttreatment Week 4, Week 12, and Week 24 visits. Screening assessments will include medical history, physical examination, height, weight, vital signs, 12-lead electrocardiogram (ECG), adverse events (AEs) related to screening procedures, concomitant medications, liver imaging to exclude hepatocellular carcinoma (HCC) within 6 months for non-cirrhotics and within 4 months for cirrhotics, safety laboratory tests (including hematology, chemistry, coagulation, urinalysis), HCV RNA, serum β-hCG (females of child bearing potential only), HCV genotype, host IL28B genotype, serology (HIV, HCV, HBV), hemoglobin A1c (HbA1c), and assessment of the presence or absence of cirrhosis (including FibroTest®). On-treatment assessments include physical examination, weight, vital signs, AEs, concomitant medications, pregnancy prevention counseling, review of study drugs adherence and drug accountability, study drugs dispensing, safety laboratory tests (including hematology, chemistry, coagulation), HCV RNA, viral RNA sequencing/phenotyping and/or HBV DNA sample, pharmacokinetic samples, urine pregnancy tests (females of child bearing potential only). Posttreatment assessments include physical examination, weight, vital signs, AEs and concomitant medications, pregnancy prevention counseling, safety laboratory tests (including hematology and chemistry), HCV RNA, viral RNA sequencing/phenotyping and/or HBV DNA, and urine pregnancy tests (females of childbearing potential only).

Study Procedures/ Frequency:	For subjects who provide their additional and specific consent, a single blood sample will be collected at the Day 1 visit for human genomic testing (this sample may be drawn after Day 1, if necessary). Health Related Quality of Life (HRQoL) surveys will be conducted at Day 1, on-treatment Weeks 12 and 24 (if applicable), and Posttreatment Week 12 visits. For subjects who provide consent, archive plasma samples will be collected at Day 1 and End of Treatment (Week 12 or Week 24) Visits for potential future testing. For subjects who provide consent, an intensive PK collection will be performed at the on-treatment Week 2, Week 3, or Week 4 visit.
Test Product, Dose, and Mode of Administration:	1. SOF/VEL fixed dose combination (FDC) is manufactured as a 400/100 mg FDC tablet for oral administration. Subjects will take 1 tablet daily with or without food. 2. Ribavirin (REBETOL®, RBV) is manufactured as a 200 mg capsule. Subjects will take weight-based RBV every day (600-1000 mg/day in a divided daily dose) in accordance with RBV product labeling. The morning dose of RBV will be taken with the SOF/VEL tablet and with food. The evening dose of RBV will be taken alone with food. Ribavirin dose reductions and modifications will be performed according to the approved RBV labeling.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	AEs and safety laboratory tests will be collected throughout the study.
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® Ampliprep/ COBAS® TaqMan® HCV Quantitative Test, version 2.0.
Pharmacokinetics:	A single PK blood sample will be collected at each on-treatment visit for all subjects. An optional intensive PK substudy may also be performed at the Week 2, Week 3, or Week 4 on-treatment visit in a subset of subjects (target ~20 subjects). Serial PK samples will be collected over 24 hours post-dose. The PK of SOF, its metabolites GS-566500 and GS-331007, VEL, and RBV may be assessed.

Statistical Methods:

The primary efficacy endpoint for the study is SVR12 in all randomized and treated subjects.

Approximately 110 subjects will be randomized in this study with approximately 90 subjects with genotype 1 HCV infection and approximately 20 subjects with genotype 2 HCV infection. Due to the limited number of genotype 2 subjects in this study, the sample size justification will be based on genotype 1 subjects only.

Genotype 1 Subjects

In the primary efficacy analysis, the SVR12 rate for genotype 1 subjects in each of the two treatment groups will be compared to the historical control rate of 50% using the two-sided exact one-sample binomial test with Bonferroni alpha adjustment (each at significance level 0.025).

The 50% SVR null rate is a weighted average rate derived from SVR rates of 43% (59/137) and 59% (57/96) for treatment naive genotype 1 HCV-infected patients and high viral loads treated with PEG IFN and RBV for 48 weeks cited in the Japanese package inserts for REBETOL® Capsules 200 mg (MSD, July 2015, 19th version) and COPEGUS® Tablets 200 mg (Chugai Pharmaceuticals, July 2015, 6th version,) respectively.

A sample size of 45 genotype 1 subjects in each treatment group will provide over 90% power to detect at least 27% improvement in SVR12 rate from the historical control rate of 50% using a two-sided exact one-sample binomial test at significance level of 0.025.

Genotype 2 Subjects

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

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

This study will be conducted in accordance with ICH Good Clinical Practice (GCP), and J-GCP (Ministerial Ordinance on Good Clinical Practice for Drugs), and all applicable regulatory requirements, including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
Ab	antibody
ABW	actual body weight
ADD	Attention deficit disorder
AE(s)	adverse event(s)
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
ASV	asunaprevir
AUC	area under the curve
AV	atrioventricular
BLQ	below limit of quantification
BMD	bone mineral density
BMI	body mass index
BW	body weight
CD4+	cluster of differentiation 4+
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CL_{Cr}	creatinine rate
CLDQ-HCV	Chronic Liver Disease Questionnaire
cm^2	square centimeter
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CNS	Central nervous system
Cr_{cl}	creatinine clearance
CRO	contract (or clinical) research organization
CSR	clinical study report
CVA	Cerebral vascular accident
DAA	direct-acting antiviral
DCV	daclatasvir
dL	deciliter
DNA	deoxyribonucleic acid
DSPH	(Gilead) Drug Safety and Public Health
ECG	electrocardiogram
eCRF	electronic case report form

EDC	electronic data capture
eg	example given
ER	emergency room
eSAE	electronic serious adverse event
ESLD	end stage liver disease
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FACIT-F	Fatigue Index
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed-dose combination
FEV1	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
g	grams
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	giga
GMR	geometric mean ratio
GS-7977	sofosbuvir, formerly PSI-7977
GSI	Gilead Sciences, Inc.
GT	genotype
h	hour
H2	histamine
Hb	hemoglobin
HbA_{1c}	hemoglobin A_{1c}
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HMG-CoA	3-hydroxy-3-methyl-glutaryl coenzyme A
HPF	high power field
HRQoL	Health Related Quality of Life
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonization

IEC	independent ethics committee
IFN	interferon
LH	luteinizing hormone
IL28B	interleukin-28B gene
IMB	intermenstrual bleeding
IND	Investigational New Drug (Application)
INR	international normalized ratio of prothrombin time
IRB	institutional review board
IU	International Units
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWRS	interactive web response system
J-GCP	Ministerial Ordinance on Good Clinical Practice for Drugs
kg	kilogram
kPA	kilopascal
L	liter
LAM	lactational amenorrhea method
LDL	low-density lipoprotein
LDV	ledipasvir
LLN	lower limit of the normal range
LLOQ	lower limit of quantification
LLT	lower-level term
m^2	square meter
MCV	mean corpuscular volume or mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalents
mg	milligram
MGB	minor groove binder
MH	Mantel-Haenszel
MHLW	Ministry of Health, Labour and Welfare
mL	milliliter
mm^3	cubic millimeter
mmHg	millimeters mercury
mmol	millimole
n	number
NGM/EE	norgestimate/ethinyl estradiol
NS (3/4A/5A/5B)	non-structural protein
OC	hormonal contraceptive
PCR	polymerase chain reaction

Peg-IFN	pegylated interferon
P-gp	p-glycoprotein
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPIs	proton-pump inhibitor
PR	P and R waves (in electrocardiography)
PT	preferred term or prothrombin time
Q1	quartile 1
Q3	quartile 3
QTc	corrected QT
RAV	resistance-associated variants
RBC	red blood cell count
RBV	ribavirin
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
S_{cr}	serum creatinine (mg/dL)
SD	standard deviation
sec	seconds
SF-36	36-Item Short Form Health Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SNP	single nucleotide polymorphism
SOC	system Organ Class
SOF	sofosbuvir, formerly GS-7977
SOP	standard operating procedure
STR	single tablet regimen
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	sustained virologic response
SVR12	sustained virologic response 12 weeks after cessation of treatment
SVR24	sustained virologic response 24 weeks after cessation of treatment
SVR4	sustained virologic response 4 weeks after cessation of treatment
TEN	toxic epidermal necrolysis
TND	target not detected
ULN	upper limit of normal
US	United States
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment
VEL	velpatasvir
β-hCG	β-human chorionic gonadotropin

µg	microgram
µL	microliter
µmol	micromole

1. INTRODUCTION

1.1. Background

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

The advent of direct-acting antivirals (DAAs) that target the NS5A and NS5B regions of the HCV virus offer higher response rates and improved safety and tolerability than the previous therapies based on pegylated interferon (PEG-IFN) and ribavirin (RBV). Though DAA-containing therapies provide SVR rates >80%, those who fail these regimens often develop resistance associated variants (RAVs) thereby limiting future treatment options. There are no approved therapies for patients who have failed DAA-containing regimens and these patients are typically excluded from clinical trials of next generation HCV drugs. Therefore development of salvage therapies will address the unmet medical need of patients who have previously failed DAA-containing regimens.

1.1.1. HCV Infection in Japan

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

1.1.2. Treatment Options in Japan

Until recently, the standard of care in Japan for chronic genotype 1 and genotype 2 HCV infection was 24-48 weeks of interferon-based therapy, according to HCV genotype and virologic response. However, the standard of care therapy for chronic HCV infection has been evolving rapidly since the first DAA agent, telaprevir (TVR) administered in combination with Peg-IFNα+RBV was approved in 2011. Since then, the all-oral, IFN-free regimen of the HCV NS5A inhibitor daclatasvir (DCV) plus the HCV NS3/4A protease inhibitor asunaprevir (ASV) has been approved for patients with chronic genotype 1 HCV infection. This regimen was initially indicated for patients who were ineligible for, or intolerant of IFN-based therapy, with subsequent label modifications to include prior non-responders and finally treatment-naïve patients and relapsers. Although the DCV+ASV combination has provided a new treatment option in Japan, the overall efficacy associated with this regimen is suboptimal. In the Japanese Phase 3 study, overall 15% (34/222) of subjects experienced virologic failure, which was associated with the emergence of resistance associated mutations to both DCV and ASV (predominantly NS5A:L31M/V and Y93H and NS3:D168E). Failure rates are high in patients with baseline NS5A RAVs, where the SVR rates were 40.5% (15/37) overall with 43.3% (13/30) and 25.0% (2/8) in subjects with baseline Y93H and L31M/V, respectively {Kumada et al 2014}. This finding is particularly important since the Y93H and L31M variants have been reported to occur in 8.2-19.6% and 1.8-2.7% of untreated Japanese patients with chronic genotype 1b HCV infection respectively {Suzuki et al 2012}. More recent studies have demonstrated that among patients who fail treatment with DCV+ASV for 24 weeks, 91% develop NS5A RAVs {Lio et al 2016}. Results from the clinical studies are consistent with post-marketing data, with an estimated 6,000 patients having failed the DCV+ASV regimen at this time largely due to the emergence of multi-class drug resistance.

In July 2015, Harvoni®, the single tablet regimen (STR) comprised of the NS5A inhibitor ledipasvir (LDV) and the NS5B nucleotide analogue polymerase inhibitor sofosbuvir (SOF), was approved for patients with chronic genotype 1 HCV infection. In the Japanese Phase 3 clinical trial (GS-US-337-0113), treatment with Harvoni® (LDV/SOF) administered for 12 weeks resulted in a 100% SVR rate (171/171) in treatment-naive and treatment-experienced subjects, irrespective of cirrhosis status {Mizokami et al 2015}. In this study, patients who had previously received treatment with a regimen containing an HCV NS5A inhibitor were prohibited from participation yet 22% (76/341) of subjects enrolled had HCV NS5A RAVs at baseline largely L31 and Y93 variants {Mizokami et al 2015}. In those patients with pre-existing HCV NS5A RAVs the SVR rate in LDV/SOF recipients was 100% (42/42).

In September 2015, Viekirax®, the combination of the NS5A inhibitor ombitasvir, the NS3/4A protease inhibitor paritaprevir, and ritonavir, taken for 12 weeks was approved for the treatment of chronic genotype 1 HCV infection. In the Japanese Phase 3 trial, the overall SVR12 rate among patients without cirrhosis was 94.9% (204/215) and 90.5% (38/42) in those with compensated cirrhosis {Kumada et al 2015}. RAVs were observed in both the NS3 and NS5A regions at the time of virologic failure in 10 out of the 11 patients who experienced on-treatment virologic failure or relapse. In NS5A, the Y93H was found at both baseline and the time of

virologic failure in 8 patients; Y93H alone or in combination with L28M, R30Q, L31M, L31V, and/or P58S were observed in 91% (10/11) of patients; L31F was observed in one patient.

The all-oral, IFN-free regimen of SOF+RBV was approved in March 2015 for the treatment of chronic genotype 2 HCV infection with or without compensated cirrhosis. In the Japanese Phase 3 clinical trial (GS-US-334-0118), SOF+RBV administered for 12 weeks resulted in SVR12 rates of 97.6% in treatment-naïve patients and 94.7% in treatment-experienced patients. The SVR12 rates in patients with and without cirrhosis were similar at 93.3% (14/15) and 96.8 % (121/125), respectively {Omata et al 2014}.

1.2. Sofosbuvir/Velpatasvir FDC

The sofosbuvir/velpatasvir fixed-dose combination (SOF/VEL FDC) combines two HCV specific DAAs into a single tablet for the treatment of chronic HCV infection. Phase 3 studies have demonstrated that SOF/VEL FDC administered for 12 weeks is well tolerated and results in high SVR rates across HCV genotypes 1-6.

The development of SOF/VEL+RBV may have a major impact on the burden of HCV in Japan as it may provide a salvage regimen for the growing population of HCV infected patients who have failed DAA-containing regimens. Efficacy of this regimen in HCV-infected subjects who have failed DAA-containing regimens is described in Section 1.2.3.3.

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

1.2.2. Clinical Pharmacology Studies

1.2.2.1. Study GS-US-367-1905

Study GS-US-367-1905 evaluated the pharmacokinetics of SOF/VEL/GS-9857 in healthy Japanese (N=20) and Caucasian (N=20) subjects following administration of SOF/VEL 400/100 mg + GS-9857 100 mg administered with food (Japanese diet) for 10 days. Intensive pharmacokinetic assessments were conducted on Day 1 and Day 10. Additionally, blood samples were collected for OATP1B1 genotype analysis.

Preliminary results from the OATP1B1 genotype analysis (including *1A, *1B, *5, and *15 variants) indicate that the Japanese subjects enrolled in this study adequately represent the

broader Japanese population with respect to OATP1B1 genotype prevalence {Nozawa et al 2002}.

Preliminary pharmacokinetic results are available for all 40 subjects. Percent geometric mean ratios (%GMRs: Japanese/Caucasian) for PK parameters are presented in Table 1-1. Single dose and steady-state exposures of SOF, and its metabolites (GS-566500 and GS-331007), were similar between healthy Japanese and Caucasian subjects. These data agree with previously conducted studies demonstrating similar SOF and metabolite exposure when administered as SOF single-agent or as LDV/SOF in Japanese and Caucasian subjects (GS-US-334-0111). Single-dose and steady-state VEL exposures were also similar between healthy Japanese and Caucasian subjects. For GS-9857, AUC_{tau} and C_{max} were higher following a single dose (Day 1 AUC_{tau}: 109%, C_{max}: 194%) or at steady-state (Day 10 AUC_{tau}: 75%, C_{max}: 123%) in Japanese compared to Caucasian subjects.

Table 1-1. GS-US-367-1905: Preliminary %Geometric Mean Ratios of SOF/VEL/GS 9857 PK Parameters Observed (Japanese / Caucasian)

PK Parameter	% Geometric Mean Ratios (90% CI) (Japanese / Caucasian)	
	Day 1	Day 10
SOF		
AUC_{tau}	114 (99.4, 130)	90.4 (76.4, 107)
C_{max}	156 (122, 201)	94.5 (73.5, 122)
GS-566500		
AUC_{tau}	125 (110, 142)	118 (105, 134)
C_{max}	146 (123, 175)	128 (112, 146)
GS-331007		
AUC_{tau}	91.3 (81.1, 103)	86.9 (76.9, 98.2)
C_{max}	92.9 (77.9, 111)	89.7 (79.5, 101)
VEL		
AUC_{tau}	116 (94.1, 143)	104 (78.0, 138)
C_{max}	129 (109, 154)	116 (92.4, 145)
C_{tau}	111 (84.6, 145)	95.5 (67.2, 136)
GS-9857		
AUC_{tau}	209 (143, 305)	175 (110, 277)
C_{max}	294 (191, 454)	223 (152, 327)
C_{tau}	127 (92.9, 174)	149 (85.2, 259)

Preliminary data presented to 3 significant figures.

1.2.2.2. Study GS-US-281-1058

GS-US-281-1058 is an open-label, Phase 1, multiple-dose drug-drug interaction study in healthy female subjects of childbearing age evaluating the effect of VEL on the pharmacokinetics of a representative hormonal contraceptive medication, norgestimate/ethinyl estradiol (NGM/EE, OC). Following screening, eligible subjects were enrolled in a lead-in period (Part A) of 28 days during which they completed dosing with the hormonal contraceptive (OC) prior to baseline assessments and initiation of Cycle 1 (Part B). Subjects with a documented history of taking OC for at least 1 menstrual cycle could be enrolled directly into Cycle 1. The PK, safety, and tolerability of OC and OC+VEL were assessed in Part B of the study, which consisted of 2 cycles: subjects received OC alone during Cycle 1, and OC plus VEL 100 mg once daily during days 8-14 of Cycle 2. Fifteen subjects were enrolled, and 13 completed the study. Two subjects were discontinued from the study prior to initiation of Cycle 2 (OC+VEL) for laboratory abnormalities.

Table 1-2 presents the steady-state PK parameters and statistical comparisons of NGM metabolites norelgestromin (NGMN) and norgestrel (NG) and EE following administration alone or in combination with VEL. Steady-state VEL PK parameters were also assessed. Norgestimate was not quantifiable for all subjects at most time points. Similar systemic exposure of NGMN and NG were achieved following NGM/EE administration with VEL relative to administration of NGM/EE alone. A modest increase in EE C_{max} was observed when administered with VEL with no change in overall exposure (AUC) or C_{tau}. The magnitude of increase in EE C_{max} when administered with VEL is similar to that observed with the concomitant administration of other drugs such as voriconazole and etravirine, which did not warrant dose adjustment {Andrews et al 2008}, {Janssen Pharmaceuticals Inc. 2013}. VEL exposures were consistent with historical data (GS-US-281-0115, GS-US-342-0104).

Table 1-2. NGMN, NG, EE, and VEL Plasma PK Parameters Following Administration of NGM/EE alone or with VEL

PK Parameter	Mean (%CV)		GLSM Ratio (90% CI) NGM/EE + VEL vs. NGM/EE
	NGM/EE Alone (N = 15)	NGM/EE + VEL (N = 13)	
Norelgestromin			
AUC_{tau} (pg•h/mL)	17,700 (16.7)	15,700 (11.2)	0.90 (0.82, 0.98)
C_{max} (pg/mL)	1650 (16.8)	1600 (13.7)	0.97 (0.88, 1.07)
C_{tau} (pg/mL)	454 (18.5)	416 (14.3)	0.92 (0.83, 1.03)
Norgestrel			
AUC_{tau} (pg•h/mL)	47,000 (34.4)	43,000 (32.4)	0.91 (0.73, 1.15)
C_{max} (pg/mL)	2410 (30.6)	2330 (31.5)	0.96 (0.78, 1.19)
C_{tau} (pg/mL)	1760 (34.4)	1640 (35.7)	0.92 (0.73, 1.18)

PK Parameter	Mean (%CV)		GLSM Ratio (90% CI) NGM/EE + VEL vs. NGM/EE
	NGM/EE Alone (N = 15)	NGM/EE + VEL (N = 13)	
Ethinyl Estradiol			
AUC_{tau} (pg•h/mL)	666 (30.7)	686 (27.3)[a]	1.04 (0.87, 1.24)
C_{max} (pg/mL)	57.5 (27.3)	80.0 (28.4)[a]	1.39 (1.17, 1.66)
C_{tau} (pg/mL)	14.8 (39.3)	12.4 (43.9)[a]	0.83 (0.65, 1.06)
Velpatasvir			
AUC_{tau} (ng•h/mL)	–	4680 (35.1)	–
C_{max} (ng/mL)	–	626 (22.0)	–
C_{tau} (ng/mL)	–	68.3 (47.6)	–

Note: preliminary data presented to 3 significant figures.
a N = 12

Luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone concentrations were similar in both treatment cycles, as presented in Table 1-3. Luteinizing hormone and progesterone median values were lower than those expected for ovulatory or luteal phases, respectively {Quest Diagnostics 2013b}, {Quest Diagnostics 2013a}, {Barditch-Crovo et al 1999}. Follicle stimulating hormone was lower or within the expected range for the ovulatory phase {Quest Diagnostics 2013a}. These results are consistent with a possible decrease in serum LH and FSH by hormonal contraceptives and absence of ovulation, as assessed by very low progesterone values on cycle Day 21.

Table 1-3. Summary of LH, FSH, and Progesterone Concentrations Following Administration of NGM/EE alone or with VEL

PD Analyte	Median (Q1, Q3)	
	OC Alone (N = 15)	OC + VEL (N = 13)
LH (mIU/mL)	8.0 (2.9, 12.7)	9.3 (5.4, 14.4)
FSH (mIU/mL)	3.6 (2.0, 5.9)	2.6 (2.2, 5.1)
Progesterone (ng/mL)	0.24 (0.17, 0.39)	0.27 (0.18, 0.80)

Based on these results, no loss in contraceptive efficacy is expected upon administration of combined oral contraceptives containing norgestimate/ethinyl estradiol with VEL.
Study GS-US-334-0146 previously demonstrated that the use of SOF with contraceptives (eg, norgestimate/ethinyl estradiol) is permitted. Accordingly, the use of hormonal contraceptives with VEL as a single agent or as part of SOF/VEL FDC is permitted.

1.2.2.3. Drug-Drug Interaction Studies with SOF/VEL and Gastric Acid Suppressants

GS-US-342-1346 and GS-US-342-1709 were open-label, Phase 1, single-dose drug-drug interaction studies in healthy volunteers evaluating the effect of gastric acid suppressants (histamine-2 receptor antagonists and proton pump inhibitors) on the PK of SOF/VEL. These studies were conducted because VEL has demonstrated pH-dependent solubility in vitro. A summary of results from these studies is presented in the table below.

Study GS-US-342-1346 demonstrated that simultaneous or staggered (12 hour) administration of SOF/VEL, administered under fasting conditions, with famotidine 40 mg resulted in no change to the AUC of SOF or VEL, suggesting that SOF/VEL can be administered simultaneously or staggered with H2RAs at doses comparable to famotidine 40 mg. Study GS-US-342-1346 also demonstrated that simultaneous or staggered (12 hour) administration of SOF/VEL, administered under fasting conditions, with omeprazole 20 mg resulted in a reduction in VEL AUC of 37% and 56%, respectively. The AUC of SOF also decreased 29% to 44%, respectively, though these effects are secondary to the impact of PPIs on VEL, as SOF does not demonstrated pH-dependent solubility. Based on these data, the use of SOF/VEL under fasting conditions with PPIs is not recommended.

Study GS-US-342-1709 evaluated the effect of omeprazole 20 mg or 40 mg on the PK of SOF/VEL when SOF/VEL is administered with food. Administration of SOF/VEL with food and omeprazole did not alter the overall exposure (AUC) of SOF or its metabolites, regardless of timing or dose of omeprazole. Administration of SOF/VEL with food and omeprazole resulted in a decrease in VEL exposure. The smallest decrease in VEL exposure (AUC: 26%, C_{max}: 33%) was observed following administration of SOF/VEL with food 4 hours before omeprazole 20 mg. A slightly greater decrease in VEL exposure (AUC: 38%, C_{max}: 48%) was observed when SOF/VEL was administered with food 2 hours after omeprazole 20 mg. The largest decline in VEL exposure (AUC: 53%, C_{max}: 56%) was observed following SOF/VEL administration with food 4 hours before the higher dose of omeprazole 40 mg.

Collectively, these studies indicate that PPIs can impact the PK of SOF/VEL. Administration of SOF/VEL with food reduces the effect of omeprazole on SOF/VEL PK. The overall exposure of SOF and its metabolites were not affected by omeprazole 20 mg when SOF/VEL was administered with food, and the reduction in VEL exposure was less when administered with food (26% to 38%) compared to fasted administration (37% to 56%). Staggering timing of omeprazole 20 mg and SOF/VEL administration also modestly impacted VEL exposure; VEL AUC was least impacted when administered 4 hours before omeprazole 20 mg (equivalent to 20 hours after the previous omeprazole dose).

Study GS-US-342-1709 also demonstrates that the nature of VEL exposure decrease was not uniform across the study population. The largest decreases were observed in subjects with the highest exposure at the reference condition of dosing, with SOF/VEL fasted without an acid reducing agent, and those with low exposure at the reference condition were generally unaffected by administration with a PPI. These data suggests that gastric pH is a contributor to the natural variability of VEL, and the range of exposure for HCV-infected subjects on PPIs is expected to be within that observed in Phase 3 ASTRAL studies. Accordingly, PPI doses comparable with

omeprazole 20 mg can be administered with SOF/VEL when SOF/VEL is administered with food.

Table 1-4. Summary of Changes in SOF/VEL PK following administration with Representative H2RAs and PPIs

Study	Dosing Scheme	SOF PK Parameters			GS-331007 PK Parameters			VEL PK Parameters		
		AUC_{last}	AUC_{inf}	C_{max}	AUC_{last}	AUC_{inf}	C_{max}	AUC_{last}	AUC_{inf}	C_{max}
GS-US-342-1346 (N=60)	SOF/VEL (fasted) with simultaneous FAM 40 mg	↔	↔	↔	↔	↔	↔	↔	↔	↔
	SOF/VEL (fasted) with 12 hours after FAM 40 mg	↔	↔	↓23%	↔	↔	↔	↔	↔	↔
	SOF/VEL (fasted) with simultaneous OME 20 mg	↓29%	↓29%	↓34%	↔	↔	↔	↓37%	↓36%	↓37%
	SOF/VEL (fasted) 12 hours after OME 20 mg	↓44%	↓44%	↓45%	↔	↔	↔	↓56%	↓55%	↓57%
GS-US-342-1709 (N=40)	SOF/VEL (fed) 2 hours After OME 20 mg	↔	↔	↓16%	↔	↔	↔	↓38%	↓38%	↓48%
	SOF/VEL (fed) 4 hours Before OME 20 mg	↔	↔	↓21%	↔	↔	↔	↓26%	↓26%	↓33%
	SOF/VEL (fed) 4 hours Before OME 40 mg	↔	↔	↓30%	↔	↔	↔	↓53%	↓53%	↓56%

FAM = famotidine; OME = omeprazole. The 90% CIs of the %GLSM ratios were within (↔), or extended below (↓) the predetermined PK alteration boundary of 70%.

1.2.3. Clinical Trials of SOF/VEL

Two Phase 3 studies evaluated the efficacy and safety of SOF/VEL in subjects with genotype 1a, 1b, 2, 4, 5, 6 HCV infection, without cirrhosis or with compensated cirrhosis, GS-US-342-1138 (ASTRAL-1) and GS-US-342-1139 (ASTRAL-2). Summaries of interim results from the individual Phase 3 studies are presented below. Also summary of interim results from study GS-US-342-1553 is presented below.

1.2.3.1. Study GS-US-342-1138 (ASTRAL-1)

1.2.3.1.1. Design

This Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study is assessing the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL treatment compared with 12 weeks of SOF/VEL placebo treatment in subjects with chronic genotype 1, 2, 4, 5, or 6 hepatitis C virus (HCV) infection. This study was conducted in Belgium, Canada, France, Germany, Hong Kong, Italy, United Kingdom, and United States.

Subjects with genotype 1, 2, 4, or 6 HCV infection were randomized in a 5:1 ratio to treatment with SOF/VEL for 12 weeks (SOF/VEL 12 Week group) or SOF/VEL placebo for 12 weeks (Placebo 12 Week group). Subjects with genotype 5 HCV infection were enrolled to the SOF/VEL 12 Week group. Randomization was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) and the presence or absence of cirrhosis at screening.

1.2.3.1.2. Disposition

A total of 740 subjects were enrolled and treated; 624 subjects in the SOF/VEL 12 Week group and 116 subjects in the Placebo 12 Week group.

The majority of subjects (99.3%) completed study treatment. Five subjects (0.7%) prematurely discontinued study treatment; 2 subjects in the SOF/VEL group and 3 subjects in the placebo group. In the SOF/VEL 12 Week group, 1 subject prematurely discontinued due to an AE and 1 subject was lost to follow-up; in the Placebo 12 Week group, 2 subjects prematurely discontinued due to AEs and 1 subject discontinued based on investigator discretion.

1.2.3.1.3. Demographics and Baseline Characteristics

Demographics and baseline disease characteristics were generally balanced between the SOF/VEL 12 Week and Placebo 12 Week groups.

In the SOF/VEL 12 Week group, the majority of subjects were male (59.9%), and 21.6% of subjects had a body mass index (BMI) ≥ 30 kg/m^2, 19.4% had cirrhosis and most subjects (73.9%) had baseline HCV RNA $\geq$ 800,000 IU/mL. Of the 624 subjects who received SOF/VEL, 328 subjects (52.6%) had genotype 1 HCV infection (210 subjects [33.7%] with HCV genotype 1a and 118 subjects [18.9%] with HCV genotype 1b), 104 subjects (16.7%) had genotype 2 HCV infection, 116 subjects (18.6%) had genotype 4 HCV infection, 35 subjects (5.6%) had genotype 5 HCV infection, and 41 subjects (6.6%) had genotype 6 HCV infection.

1.2.3.1.4. Efficacy Results

The SOF/VEL 12 Week group met the primary endpoint of an SVR12 rate that was statistically superior relative to the prespecified performance goal of 85% ($p < 0.001$). The SVR12 rate was as follows:

- SOF/VEL 12 Week group: 99.0% (95% CI: 97.9% to 99.6%) of subjects (618 of 624) achieved SVR12.

Table 1-5 presents the SVR12 results for the SOV/VEL 12 Week group overall and by HCV genotype. A total of 6 of 624 subjects (1.0%) who received SOF/VEL did not achieved SVR12. Two subjects had relapse determined at Posttreatment week 4; one treatment-naive subject with genotype 1a HCV infection without cirrhosis and one treatment experienced subject with genotype 1b infection and cirrhosis. Four additional subjects (3 with genotype 1 and 1 with genotype 5) did not achieve SVR12 (1 subject withdrew consent, 2 subjects had not returned for the Post-treatment Week 12 visit, and 1 subject died prior to the Post-treatment Week 4 visit).

Table 1-5. GS-US-342-1138: SVR12 Overall and by HCV Genotypes

	SOF/VEL 12 Weeks							
	Total (All Genotypes) (N = 624)	**GT-1a (N = 210)**	**GT-1b (N = 118)**	**GT-1 Total (N = 328)**	**GT-2 (N = 104)**	**GT-4 (N = 116)**	**GT-5 (N = 35)**	**GT-6 (N = 41)**
SVR12	618/624 (99.0%)	206/210 (98.1%)	117/118 (99.2%)	323/328 (98.5%)	104/104 (100.0%)	116/116 (100.0%)	34/35 (97.1%)	41/41 (100.0%)

GT = genotype

The SVR4 results for subjects with genotype 1, 2, 4, 5, or 6 HCV infection were the same as the SVR12 results with the exception of 1 subject with genotype 1a HCV infection who achieved SVR4 but had not returned for his Post-treatment Week 12 visit at the time of the interim analysis.

HCV RNA declined rapidly with similar decreases in HCV RNA observed across all HCV genotypes in the SOF/VEL 12 Week group. Consistent with the rapid and sustained decline in HCV RNA, > 88.5% of subjects in the SOF/VEL 12 Week group had HCV RNA < LLOQ at Week 4. Time to virologic suppression was not associated with treatment outcome overall or in any genotype.

1.2.3.1.5. Virologic Resistance

Deep sequence analyses indicated that subjects in the SOF/VEL 12 Week group had a diverse population of HCV with more than 30 subtypes across genotypes 1, 2, 4, 5, 6, and 7.

Approximately 42% and 9% of subjects in the SOF/VEL 12 Week group had baseline NS5A resistance-associated variants (RAVs) and NS5B RAVs, respectively. Baseline NS5A or NS5B RAVs had no impact on SVR12, with high SVR12 across all subtypes/genotypes regardless of the presence of NS5A RAVs or NS5B RAVs. Two subjects had virologic failure and both had baseline NS5A RAVs. At virologic failure time points, both subjects developed additional NS5A RAVs (Y93N and Y93H) that conferred a high (> 700) fold shift in EC_{50} to VEL. No NS5B RAVs were detected at baseline or Post-treatment in either subject with virologic failure.

1.2.3.1.6. Safety Results

Treatment with SOF/VEL was well tolerated. Subjects in the SOF/VEL 12 Week treatment group had similar type, incidence, and severity of AEs as subjects in the Placebo 12 Week group.

Grade 3 (severe) and Grade 4 (life-threatening) AEs were rare, 19 of 624 (2.9%) in the SOF/VEL 12 Week group and 1 of 116 (0.9%) in the Placebo 12 Week group. Two subjects (0.3%) in the SOF/VEL 12 Week group had Grade 4 AEs. One subject had a Grade 4 AE of malignant lung neoplasm and 1 subject had a Grade 4 AE of sudden death. Both events were assessed by the investigators as unrelated to study drugs.

SAEs were rare and occurred in 15 subjects (2.4%) in the SOF/VEL 12 Week group. All SAEs were assessed by the investigators as unrelated to study drugs. No placebo treated subjects had SAEs. No trends in SAE type or onset time were observed, and no SAE was reported in > 1 subject. No SAEs led to treatment discontinuation. One subject death was reported in the study. This subject completed 12 weeks of treatment with SOF/VEL and died in his sleep on Post-treatment Day 8. The death was assessed as not related to study drugs by the investigator. One subject (0.2%) in the SOF/VEL 12 Week group discontinued study treatment due to a Grade 3 AE of anxiety and 2 subjects (1.7%) in the Placebo 12 Week group discontinued study treatment due to meeting the prespecified stopping criteria of elevated ALT and/or AST levels $\geq 5 \times$ nadir.

Most laboratory abnormalities were Grade 1 or 2 in severity. Subjects in the SOF/VEL 12 Week group had Grade 3 or 4 chemistry abnormalities of elevated AST (Grade 3; 1 subject [0.2%]), elevated creatine kinase (Grade 3; 2 subjects [0.3%], Grade 4; 2 subjects [0.3%]), hyperglycemia (Grade 3, 15 subjects [2.4%]), and elevated lipase (Grade 3; 14 subjects [2.2%], Grade 4, 2 subjects [0.3%]). Among subjects in the SOF/VEL 12 Week, all Grade 3 or 4 creatinine kinase elevations were transient, all Grade 3 or 4 lipase elevations were asymptomatic and generally transient, and Grade 3 or 4 hyperglycemia occurred in subjects with a medical history of diabetes. The most frequently observed Grade 3 or 4 laboratory abnormalities observed in placebo treated subjects were elevated ALT (Grade 3; 6 subjects [5.2%] and Grade 4; 2 subjects [1.7%]) consistent with ongoing HCV infection.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study. No trends in ECG findings suggestive of cardiotoxicity were observed.

1.2.3.1.7. Conclusions

The conclusions were as follows:

- The study met its primary efficacy endpoint demonstrating that the SVR12 rate of 99.0% (95% CI: 97.9% to 99.6%) in genotype 1, 2, 4, 5, and 6 HCV-infected subjects treated for 12 weeks with SOF/VEL was statistically superior to the prespecified SVR12 performance goal of 85% ($p<0.001$).

- High SVR12 rates were achieved across all HCV genotypes and subgroups
  - — Among subjects with cirrhosis, the SVR rate was 99.2%
  - — Among subjects with prior treatment failure, the SVR rate was 99.5%
  - — Among subjects with baseline NS5A RAVs, the SVR12 rate was 98.8%
- Treatment with SOF/VEL for 12 Weeks was generally well tolerated with a safety profile similar to that of placebo treatment. There was a low incidence of SAEs, discontinuations due to AEs and no clinically relevant laboratory abnormalities.

1.2.3.2. Study GS-US-342-1139 (ASTRAL-2)

1.2.3.2.1. Study Design

This Phase 3, randomized, open-label, multicenter study is assessing the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL treatment compared with 12 weeks of SOF+RBV treatment in subjects with chronic genotype 2 HCV infection. The study was conducted in the United States (US).

Subjects with genotype 2 HCV infection were randomized (1:1) to treatment with SOF/VEL for 12 weeks (SOF/VEL 12 Week group) or SOF+RBV for 12 weeks (SOF+RBV 12 Week group). Randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience (treatment naive vs. treatment experienced).

1.2.3.2.2. Disposition

A total of 266 subjects were randomized and treated; 132 in the SOF/VEL 12 Week group and 134 in the SOF+RBV 12 Week group. The majority of subjects (99.2%) completed study treatment. Two subjects (0.8%), 1 in each treatment group, prematurely discontinued study treatment. One subject in the SOF/VEL 12 Week group discontinued study treatment on Day 1 (after receiving 1 dose of study drugs) due to AEs of disturbance in attention, headache, and anxiety. One subject in the SOF+RBV 12 Week group completed the Week 10 study visit, but did not return for any subsequent study visits and was assumed to be lost to follow-up; the last confirmed dosing date was Day 71.

1.2.3.2.3. Demographics and Baseline Characteristics

Overall, demographics and baseline disease characteristics were balanced across both treatment groups. The majority of subjects were male (59.4%), and 32.7% of subjects had a BMI ≥ 30 kg/m^2. A total of 38 subjects (14.3%) had cirrhosis at screening. Overall, the majority of subjects had HCV RNA $\geq$ 800,000 IU/mL (79.7%). Overall, 14.7% (39 subjects) were treatment experienced.

1.2.3.2.4. Efficacy Results

The SOF/VEL 12 Week group met the primary endpoint of an SVR12 rate that was noninferior to the SVR12 rate in the SOF+RBV 12 Week group. The SVR12 rates were as follows:

- SOF/VEL 12 Week group: 99.3% (95% CI: 95.9% to 100%) of subjects (133 of 134) achieved SVR12
- SOF+RBV 12 Week group: 93.9% (95% CI: 88.4% to 97.3%) of subjects (124 of 132) achieved SVR12

The strata-adjusted difference (95% CI) in the proportions was 5.2% (0.2% to 10.3%). Since the lower bound of the 2-sided 95% CI for the difference between groups was greater than the prespecified noninferiority margin of −10%, the efficacy of SOF/VEL for 12 weeks was demonstrated to be statistically noninferior to SOF+RBV for 12 weeks. There was sufficient evidence to demonstrate the statistical superiority of treatment with SOF/VEL for 12 weeks over SOF+RBV for 12 weeks for SVR12 ($p = 0.018$; CMH test stratified by cirrhosis status and prior treatment experience).

In the SOF/VEL 12 Week group, 1 of 134 subjects (0.7%) did not achieve SVR12: the subject discontinued study treatment on Day 1 (after receiving 1 dose) due to AEs of difficulty concentrating, headache, and anxiety. The subject never achieved HCV RNA < LLOQ. In the SOF+RBV 12 Week group, 8 of 132 subjects (6.1%) did not achieve SVR12. Of these, 6 subjects relapsed and 2 were lost to follow-up. Four relapses occurred by the Post-treatment Week 4 visit and 2 relapses occurred between the Post-treatment Week 4 and 12 visits. The low number of virologic failures in the study precluded meaningful subgroup analysis of SVR.

The SVR4 results were similar to the SVR12 results with the exception of 3 subjects in SOF+RBV 12 Week group: 1 subject was lost to follow-up after Post-treatment Week 4 and 2 subjects relapsed between the Post-treatment Week 4 and Week 12 visits.

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly with similar decreases in HCV RNA observed in both treatment groups. After 1 week of treatment, the mean change from baseline in HCV RNA levels was –4.51 $\log_{10}$ IU/mL in both treatment groups. The decreases in HCV RNA were maintained from Weeks 2 through 12. Consistent with the rapid and sustained decline in HCV RNA, 90.2% of subjects in both treatment groups had HCV RNA < LLOQ at Week 4. There was a lack of correlation of time to suppression with virologic outcome in the SOF/VEL 12 week group as all subjects who completed treatment achieved SVR regardless of the time to suppression.

1.2.3.2.5. Virologic Resistance

Deep sequencing analyses indicated that genotype 2a and 2b were the predominant HCV subtypes in subjects who were randomized and treated in this study. Approximately 60% and 10% of subjects in the SOF/VEL 12 Week group had pretreatment NS5A and NS5B RAVs, respectively. The most prevalent NS5A RAV observed was L31M in 51% of subjects. Despite

the presence of pretreatment NS5A and NS5B RAVs, no subjects in the SOF/VEL 12 Week group experienced virologic failure in this study. Two of the 6 subjects who relapsed in the SOF+RBV 12 Week group had low levels of the NS5B NI RAV L159F detectable at failure.

1.2.3.2.6. Safety Results

Overall, treatment with SOF/VEL or SOF+RBV for 12 weeks was generally safe and well tolerated. A smaller percentage of subjects in the SOF/VEL 12 Week group experienced any AE (68.7%, 92 of 134) compared with the SOF+RBV 12 Week group (76.5%, 101 of 132), including treatment-related AEs (SOF/VEL, 33.6%; SOF+RBV, 56.8%) and AEs leading to modification or interruption of any study drugs (SOF/VEL, 0; SOF+RBV, 9.8%).

The most common AEs (ie, AEs reported in > 10% of subjects in either group) were reported by a smaller percentage of subjects in the SOF/VEL 12 Week group compared with the SOF+RBV 12 Week group, including fatigue (14.9% vs. 35.6%), headache (17.9% vs. 22.0%), nausea (10.4% vs. 14.4%), and insomnia (4.5% vs. 13.6%).

Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Grade 3 (severe) AEs were rare (SOF/VEL, 2.2%; SOF+RBV, 2.3%). No Grade 4 (life-threatening) AEs were reported. Anxiety was the only Grade 3 AE reported in > 1 subject in the SOF/VEL 12 Week group (n = 2, 1.5%).

Serious adverse events (SAEs) were also rare (1.5%, 4 of 266 subjects [2 in each treatment group]). No SAE was reported in > 1 subject. All SAEs were considered by the investigators to be not related to study drugs. Two non-treatment-emergent deaths were reported during the study (metastatic lung cancer and cardiac arrest after treatment completion). No pregnancies were reported during the study. Only 1 subject permanently discontinued any study drugs (SOF/VEL) due to AEs. After receiving 1 dose of SOF/VEL, the subject, who had a medical history of depression, insomnia and post-traumatic stress disorder, discontinued study treatment due to Grade 3 AEs of difficulty concentrating, headache, and anxiety that were assessed as related to study drugs by the investigator.

Most subjects had at least 1 laboratory abnormality reported, with the majority being Grade 1 (104 of 266 subjects, 39.1%) or Grade 2 (70 of 266 subjects, 26.3%) in severity. A smaller percentage of subjects had Grade 3 laboratory abnormalities in the SOF/VEL 12 Week group (7.5%, 10 subjects) compared with the SOF+RBV 12 Week group (13.6%, 18 subjects). This difference was accounted for primarily by the expected decreases in hemoglobin observed with RBV therapy. No subjects in the SOF/VEL 12 Week group had a Grade 3 or 4 hematology laboratory abnormality. The only Grade 3 hematology laboratories abnormality in the SOF+RBV 12 Week group were decreased hemoglobin (5.3%, 7 subjects) and increased lymphocytes (0.8%, 1 subject). The most common Grade 3 or 4 chemistry laboratory abnormalities in both treatment groups were increased serum glucose (hyperglycemia) and increased lipase. Grade 3 increases in lipase were reported for 7 subjects (5.3%) in the SOF/VEL 12 Week group and 2 subjects (1.5%) in the SOF+RBV 12 Week group. Grade 4 increases in lipase were reported for 1 subject (0.8%) in each treatment group. All of the Grade 3 lipase elevations were transient and asymptomatic, with no cases of clinical pancreatitis. In the SOF/VEL 12 Week group, 1 subject

each experienced a Grade 3 or 4 increase in creatine kinase following workout sessions. Grade 3 hyperbilirubinemia was only observed in the SOF+RBV 12 Week group and was consistent with RBV-associated hemolysis. Grade 4 chemistry laboratory abnormalities were reported for lipase and creatine kinase.

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) or ECGs were reported during the study.

1.2.3.2.7. Conclusions

The conclusions were as follows:

- The study met its predefined primary efficacy endpoint, demonstrating that the SVR12 rate of 99.3% with SOF/VEL for 12 weeks was noninferior to the SVR12 rates of 93.9% with SOF+RBV for 12 weeks.
- Treatment with SOF/VEL for 12 weeks led to a statistically superior SVR12 rate compared with SOF+RBV for 12 weeks ($p = 0.018$).
- No subjects treated with SOF/VEL experienced virologic failure, including subjects with cirrhosis (14%), prior treatment failure (14%), and baseline NS5A RAVs (60%).
- SOF/VEL was generally well tolerated and, compared with SOF+RBV, lacked toxicities associated with RBV. No treatment-emergent deaths, Grade 4 AEs, treatment-related SAEs, or clinically relevant laboratory abnormalities were observed.

1.2.3.3. GS-US-342-1553

Study GS-US-342-1553 is an ongoing, Phase 2b, open-label, multicenter study to evaluate the antiviral efficacy, safety, and tolerability of 24 weeks of SOF/VEL+ribavirin (RBV) in HCV infected subjects that have failed treatment with SOF (400 mg) and VEL (25 mg or 100 mg) with or without RBV for 8 or 12 weeks in a prior Gilead-sponsored HCV study. Cohort 1 includes subjects who participated in the Phase 2 studies GS-US-342-0102, GS-US-342-0109, or GS-US-337-0122; Cohort 2 includes subjects with virologic failure to SOF/VEL+GS-9857 treatment for 4, 6, or 8 weeks in Study GS-US-337-1468. As of 25 March 2016, subjects in Cohort 1 have completed study treatment and are in the post-treatment phase while Cohort 2 is in the treatment phase; therefore, only efficacy and safety data for cohort 1 is provided below.

1.2.3.3.1. Disposition

A total of 41 subjects were enrolled in Cohort 1; all enrolled subjects received at least 1 dose of SOF/VEL+RBV. Of the 41 subjects in the Safety Analysis Set, 39 subjects (95.1%) have completed study treatment; and 2 subjects (4.9%) have discontinued study treatment (1 due to lack of efficacy, 1 due to protocol violation.

- Subject PPD was a PPD 52-year-old male subject with genotype 3a HCV infection with cirrhosis who had relapse determined at the posttreatment Week 4 visit.
- Subject PPD was a PPD 62-year-old male subject with genotype 3a HCV infection without cirrhosis who was a non-responder at the Week 8 visit and was taken off study drug due to meeting the virologic stopping criteria.

The 1 subject with virologic outcomes characterized as "Other" is described below.

- Subject PPD was a PPD 54-year-old male subject with genotype 3a HCV infection with cirrhosis who achieved SVR4. He was subsequently diagnosed with hepatocellular carcinoma and withdrew consent from the study.

1.2.3.3.4. Safety

Table 1-7 presents a brief overall summary of adverse events (AEs). A total of 34 subjects (82.9%) experienced at least 1 AE. The majority of AEs were Grade 1 or Grade 2 in severity. Three subjects (7.3%) had Grade 3 or above AEs, 1 of which was assessed as related to study drug by the investigator (Grade 3 headache). No Grade 4 AEs were reported. One subject (1.4%) had an SAE (Grade 3 nephrolithiasis) which was assessed as unrelated to study drug. There were no AEs leading to premature discontinuation of SOF/VEL+RBV. Adverse events led to premature discontinuation of RBV for 1 subjects (2.4%) and modification or interruption of RBV for 5 subjects (12.2%). There were no subject deaths.

Table 1-7. GS-US-342-1553: Brief Summary of Adverse Events (Cohort 1)

Event, n (%)	SOF/VEL+RBV 24 Weeks (N = 41)
Subjects Experiencing Any	
Adverse Event	34 (82.9%)
Grade 3 or Above Adverse Event	3 (7.3%)
Treatment-Related Adverse Event	28 (68.3%)
Grade 3 or Above Treatment-Related Adverse Event	1 (2.4%)
Serious Adverse Event	1 (2.4%)
Treatment-Related Serious Adverse Event	0
Adverse Event Leading to Premature Discontinuation of SOF/VEL	0
Adverse Event Leading to Discontinuation of RBV	1 (2.4%)
Adverse Event Leading to Modification or Interruption of Any Study Drug[a]	5 (12.2%)
Death	0

a All dosing modifications or interruptions were to RBV. Percentages were calculated based on the number of subjects in the Safety Analysis Set.

- Subject PPD was a PPD 52-year-old male subject with genotype 3a HCV infection with cirrhosis who had relapse determined at the posttreatment Week 4 visit.
- Subject PPD was a PPD 62-year-old male subject with genotype 3a HCV infection without cirrhosis who was a non-responder at the Week 8 visit and was taken off study drug due to meeting the virologic stopping criteria.

The 1 subject with virologic outcomes characterized as "Other" is described below.

- Subject PPD was a PPD 54-year-old male subject with genotype 3a HCV infection with cirrhosis who achieved SVR4. He was subsequently diagnosed with hepatocellular carcinoma and withdrew consent from the study.

1.2.3.3.4. Safety

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Table 1-7. GS-US-342-1553: Brief Summary of Adverse Events (Cohort 1)

Event, n (%)	SOF/VEL+RBV 24 Weeks (N = 41)
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Treatment-Related Adverse Event	28 (68.3%)
Grade 3 or Above Treatment-Related Adverse Event	1 (2.4%)
Serious Adverse Event	1 (2.4%)
Treatment-Related Serious Adverse Event	0
Adverse Event Leading to Premature Discontinuation of SOF/VEL	0
Adverse Event Leading to Discontinuation of RBV	1 (2.4%)
Adverse Event Leading to Modification or Interruption of Any Study Drug[a]	5 (12.2%)
Death	0

a All dosing modifications or interruptions were to RBV. Percentages were calculated based on the number of subjects in the Safety Analysis Set.

In summary, retreatment with SOF/VEL+RBV for 24 weeks was safe and effective in the majority of subjects who failed prior treatment with SOF/VEL. There were no virologic failures in subjects with genotype 1 and 2 HCV infection who completed 24 weeks of treatment with SOF/VEL+RBV. Additional analysis is ongoing and will be available at a later date.

1.3. Information about Ribavirin

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

1.4. Rationale for This Study

The population of this study will be genotype 1 NS5A inhibitor-experienced subjects and genotype 2 DAA-experienced subjects. At this time there are no approved retreatment options for these patients who have failed DAA-containing treatment. Re-treatment with currently available DAA-containing regimens does not yield high SVR rates. Subjects with HCV genotype 1 that failed 8 or 12 weeks of LDV/SOF-containing regimens that were retreated with 24 weeks of LDV/SOF had an SVR12 rate of 71% and in this population, the presence of baseline NS5A RAVs was associated with virologic failure {Lawitz et al 2015}. As more DAA agents are approved and available, this unmet medical need for effective retreatment options for patients who fail these regimens, especially those with RAVs, will increase. Combination regimens with highly potent DAAs that have activity against commonly observed resistance-associated variants (RAVs) may be effective in these patients.

Sofosbuvir is an approved pan-genotypic nucleotide analog HCV NS5B polymerase inhibitor, which, when combined with VEL, a second generation NS5A inhibitor, in a fixed-dose combination was well-tolerated and resulted in high SVR rates in a broad range of HCV genotypes after 12 weeks of treatment in Phase 3 studies.

Sofosbuvir 400 mg, once daily, when dosed in combination with RBV with or without Peg-IFN has demonstrated broad genotypic efficacy and favorable safety profile in over 1700 HCV-infected subjects across multiple patient populations in Phase 2 and 3 trials. This dose is the approved marketed dose of sofosbuvir for the treatment of HCV-infection and, as such, was selected for co-formulation with VEL into a fixed-dose combination tablet.

VEL 100 mg was administered in combination with SOF 400 mg for 12 weeks to 237 HCV-infected subjects in Phase 2 studies. VEL 100 mg was selected for co-formulation with SOF based on the Phase 2 safety, PK and antiviral activity (studies GS-US-342-0102,

GS-US-342-0109, and GS-US-337-0122 [Cohort 4]). The Phase 1 study GS-US-281-0102 established the anti-HCV activity of VEL and indicated that the exposures achieved following administration of doses > 25 mg provide at least 80% of maximal antiviral response in all HCV genotypes. SOF/VEL (400 mg /100 mg) as a FDC tablet was evaluated in the Phase 3 ASTRAL program.

The favorable safety and efficacy profiles of SOF 400 mg and VEL 100 mg support further evaluation of this combination and doses in clinical development.

1.5. Risk/Benefit Assessment for the Study

The regimen to be assessed in this study combines a potent HCV nucleotide inhibitor with a potent HCV NS5A inhibitor and RBV in patients who have previously failed a DAA-containing regimen. The potential benefit of treatment with SOF/VEL+RBV in this population is the HCV regimen would offer a retreatment option for genotype 1 patients who have failed an NS5A inhibitor-containing regimen and genotype 2 patients who have failed a DAA-containing regimen.

The safety profile of SOF in clinical studies includes over 1700 chronic HCV-infected subjects that have been administered ≥ 12 weeks of SOF and RBV+/-Peg-IFN. No clinical safety issues specifically related to SOF have been identified to date.

The safety profile of SOF + VEL 25 mg or VEL 100 mg administered for 8 or 12 weeks has been established in over 800 subjects in Phase 2 studies. The safety profile of the proposed therapeutic regimen of SOF 400 mg and VEL 100 mg administered for 12 weeks has been established in 237 subjects enrolled in Phase 2 studies. No clinical safety issues specifically related to VEL or SOF + VEL have been identified to date.

The safety profile of SOF/VEL has been studied in 4 Phase 3 trials (ASTRAL 1-4) in 1302 subjects. Twelve weeks of SOF/VEL was generally well tolerated, and led to a similar incidence of AEs and SAEs compared to placebo in subjects with GT 1, 2, 4, 5, or 6 HCV (See Section 1.2.3.1). When 12 weeks of SOF/VEL was compared to SOF + RBV for 12 weeks in subjects with genotype 2 or 3 HCV, therapy with SOF/VEL was again well tolerated with few differences in AEs or SAEs, minus the avoidance of RBV associated toxicities.

In summary, there is currently no approved treatment for patients who have failed DAA-containing therapies, especially those who have developed RAVs. There is an urgent need to develop salvage therapies that are safe and highly efficacious for this growing population.

During the conduct of this study, the sponsor together with the investigator will perform ongoing safety reviews.

1.6. Compliance

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

2. OBJECTIVES

The primary objectives of this study are as follows:

- To evaluate the antiviral efficacy of therapy with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) and ribavirin for 12 or 24 weeks as measured by the proportion of subjects with sustained virologic response 12 weeks after cessation of treatment (SVR12)

- To evaluate the safety and tolerability of each regimen as assessed by review of the accumulated safety data

The secondary objectives of this study are as follows:

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

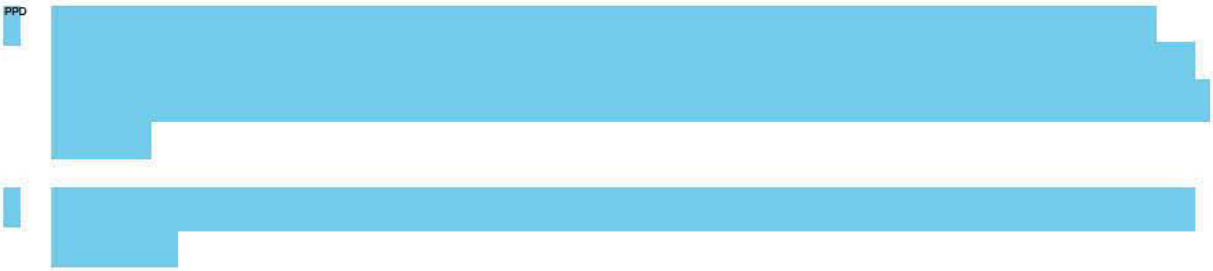
- To evaluate the proportion of subjects with virologic failure

- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of each treatment regimen

- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

Exploratory objectives of this study are:

PPD



3. STUDY DESIGN

3.1. Study Design

This is a multicenter, randomized, open-label study in subjects who previously failed a DAA-containing regimen with chronic HCV infection with or without cirrhosis. All subjects with HCV genotype 1 will have failed prior treatment with an NS5A inhibitor. Subjects with HCV genotype 2 can have failed any DAA-containing treatment regimen.

3.2. Study Treatments

Approximately 110 subjects will be randomized in a 1:1 ratio to one of the following two groups:

- SOF/VEL FDC tablet (400/100 mg) plus RBV for 12 weeks
- SOF/VEL FDC tablet (400/100 mg) plus RBV for 24 weeks

Randomization will be stratified by cirrhosis status (presence/absence) and HCV genotype (genotype 1/genotype 2). Approximately 20 subjects will have Child-Pugh-A compensated cirrhosis.

The number of subjects by HCV genotype to be enrolled in the study is presented below:

HCV Genotype	Number of Subjects Enrolled
1	approximately 90
2	approximately 20
Total	approximately 110

3.3. Duration of Treatment

Subjects will be treated for 12 or 24 weeks.

3.4. Stopping Rules and Discontinuation Criteria

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

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

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

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

3.4.1. Virologic Response-Based Treatment Stopping Criteria

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

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

Confirmation should be performed as soon as possible and must occur no later than 2 weeks after an initial observation indicating virologic failure during the on-treatment phase.

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

PPD

[redacted]

3.6. Samples for Optional Future Research

PPD

[redacted]

PPD

3.7. Intensive Pharmacokinetic (PK) Substudy

PPD

PPD

3.7. Intensive Pharmacokinetic (PK) Substudy

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 110 subjects who have previously failed a DAA-containing regimen with chronic genotype 1 (approximately 90 subjects) or genotype 2 (approximately 20 subjects) HCV infection with or without cirrhosis will be enrolled.

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

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study. Criteria apply to all subjects unless otherwise stipulated:

1) Willing and able to provide written informed consent

2) Male or female, age ≥ 20 years at Screening

3) Body weight ≥ 40 kg at Screening

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

5) Genotype 1 or 2 HCV at Screening as determined by the central laboratory. Any non-definitive HCV genotype results will exclude the subject from participation.

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

7) Treatment experienced with a DAA-containing regimen of at least a 4-week duration.

   a) The most recent treatment must have been completed at least 8 weeks prior to Screening.

   b) Prior treatments

      i) For subjects with genotype 1: Treatment(s) must have included an NS5A inhibitor

      ii) For subjects with genotype 2: Treatment(s) must have included at least one DAA

   c) Subjects must not have discontinued the most recent regimen due to virologic failure as a result of noncompliance. The subject's medical records must include sufficient detail of prior treatment(s) to confirm eligibility.

   d) Subjects cannot have previously discontinued SOF+RBV due to intolerance

8) Cirrhosis Determination:

   a) Presence of cirrhosis is defined as any one of the following:

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

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

      iii) In the absence of liver biopsy or availability of Fibroscan, FibroTest® score ≥ 0.75 at screening

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

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

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

      iii) In the absence of liver biopsy or availability of Fibroscan, FibroTest® score < 0.75 at screening

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

   a) Within 4 months for subjects with cirrhosis

   b) Within 6 months for subjects without cirrhosis

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) Male subjects must agree and refrain from sperm donation from the date of screening until at least 6 months after the last dose of RBV or 30 days after the last dose SOF/VEL FDC.

13) Lactating females must agree to discontinue nursing before the study drugs are administered and through at least 12 weeks after the last dose of study drug.

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

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

4.3. Exclusion Criteria

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

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

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

   b) Gastrointestinal disorder or postoperative condition that could interfere with the absorption of the study drugs

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

   d) Clinical hepatic decompensation (eg, ascites, encephalopathy, variceal hemorrhage, Child-Pugh-B or C cirrhosis)

   e) Solid organ transplantation

   f) Significant pulmonary disease

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

   h) Porphyria

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

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

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

   l) Prior or current hepatocellular carcinoma (HCC)

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

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

3) Screening ECG with clinically significant abnormalities

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

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

6) Women who wish to become pregnant or males with female partners who wish to become pregnant during study treatment and through 6 months after the last dose of study drug

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

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

   b) AST > 10 x ULN

   c) Direct bilirubin > 1.5 × ULN

   d) Platelets < 50,000/μL

   e) HbA1c > 8.5%

   f) Creatinine clearance (Cr_{cl}) < 50 mL/min as calculated by the Cockcroft-Gault equation {Cockcroft et al 1976}

   g) Hemoglobin < 10 g/dL

   h) Albumin < 3 g/dL

   i) International Normalized Ratio of prothrombin time (INR) > 1.5 × ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR

   j) Neutrophil count < 500/μL

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

9) Use of any prohibited concomitant medications as described in Section 5.6

10) Known hypersensitivity to sofosbuvir, velpatasvir, or ribavirin or the metabolites or formulation excipients

11) Known contraindication to sofosbuvir and/or ribavirin

5. STUDY DRUG

5.1. Randomization, Blinding and Treatment Codes

This is a randomized, open-label study in subjects who have previously failed a DAA-containing regimen with chronic HCV infection with or without cirrhosis. No blinding will be required.

Subjects will be randomized in a 1:1 ratio to one of the following two groups:

- SOF/VEL FDC tablet (400/100 mg) plus RBV for 12 weeks
- SOF/VEL FDC tablet (400/100 mg) plus RBV for 24 weeks

Randomization will be stratified by cirrhosis status (presence/absence) and HCV genotype (genotype 1/genotype 2). Approximately 20 subjects will have Child-Pugh-A compensated cirrhosis.

5.2. Description and Handling of SOF/VEL FDC

5.2.1. Formulation

The SOF/VEL (400/100 mg) FDC 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. SOF/VEL FDC 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 Japan shall be labeled for clinical use to meet applicable requirements of the J-GCP (Ministerial Ordinance on Good Clinical Practice for Drugs).

5.2.3. SOF/VEL FDC Storage and Handling

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

5.2.4. Dosage and Administration of SOF/VEL FDC

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

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

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

5.3. Description and Handling of Ribavirin (RBV)

5.3.1. Formulation

Ribavirin will be provided in the course of this study as REBETOL® capsules (MSD K.K.). REBETOL® capsules are white opaque hard capsules. Each capsule contains 200 mg of ribavirin. Information regarding commercially available REBETOL® capsules can be found in the current prescribing information {MSD K.K. Kudan-kita Chiyoda-ku 2016}.

5.3.2. RBV Packaging and Labeling

REBETOL® capsules are packaged in blister packaging of 140 capsules. The ribavirin package shall be labeled for clinical use to meet all applicable requirements of the J-GCP (Ministerial Ordinance on Good Clinical Practice for Drugs).

5.3.3. RBV Storage and Handling

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

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures

that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling RBV.

5.3.4. Dosage and Administration of Ribavirin (RBV)

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

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

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

Source: Japan Rebetol® Product Label {MSD K.K. Kudan-kita Chiyoda-ku 2016}

RBV dose modification or discontinuation should be performed in accordance with the RBV package insert (refer to Section 7.5.1).

RBV should be dosed with food and SOF/VEL FDC when appropriate.

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

5.4. Co-administration of SOF/VEL FDC and RBV

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

- One SOF/VEL FDC Tablet: contains 400 mg of SOF and 100 mg of VEL
- Weight-based RBV (as per Section 5.3.4).

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

- Weight-based RBV (as per Section 5.3.4).

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

RBV should be administered as a divided daily dose (i.e., morning and evening) as per the Rebetol® product label (Section 5.3.4). If the subject misses a dose of ribavirin and remembers the same day, the missed dose should be taken as soon as possible. However, if the subject missed taking the morning dose with lunch or if more than 6 hours have passed since the usual

morning dose time, the subject should only take the prescribed evening dose of ribavirin. Subjects should be instructed not to take 2 doses of ribavirin at the same time.

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

5.5. Study Drug Adherence and Drug Accountability

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

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

5.6. 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 drugs need to be recorded in the source documents and eCRFs.

The following medications are prohibited from **28 days prior to the Day 1** visit through the end of treatment:

- Investigational agents or devices for any indication
- Drugs disallowed per prescribing information for RBV

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

Table 5-2 below contains medications that are prohibited from **21 days prior to Day 1** through the end of treatment and those medications that may be used with caution. The use of amiodarone is prohibited from **60 days prior to Day 1** through the end of treatment.

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[g]	
Antimycobacterials[b]	Rifampicin, Rifabutin, Rifapentine[g]	
Cardiac Medications[c]	Amiodarone[d]	Diltiazem, Verapamil, Dronedarone[g], Quinidine, Ranolazine[g], Bosentan, Olmesartan, Valsartan, Digoxin[e]
Herbal/Natural Supplements[b]	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[f]		Rosuvastatin (≤10 mg/day)
Other	Modafinil [b], Sulfasalazine[c, g], Methotrexate[c]	

a Proton pump inhibitor (PPI) doses comparable with omeprazole 20 mg can be administered with SOF/VEL when SOF/VEL is administered with food. 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 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 HMG-CoA Reductase Inhibitor, rosuvastatin. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.
g Unapproved in Japan

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.

5.7. Accountability for Study Drug

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

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

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

6. STUDY PROCEDURES

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

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

6.1. Screening Visit

Screening assessments will be completed within 28 days of the Day 1 visit. The screening window can be extended up to 42 days for subjects requiring a liver biopsy, additional HCV genotyping (if initial testing is inconclusive), or for extenuating circumstances with sponsor approval. A single retest of screening labs is permitted only if there is reason to believe the retest value will be within accepted parameters if the initial value was either due to a sample processing error or due to an extenuating circumstance such as intercurrent infection.

The following procedures will be performed and documented:

- Obtain written informed consent
  - Separate informed consent(s) will be required from subjects participating in any of the following:PPD
- Determine inclusion and exclusion eligibility
- Obtain medical history (refer to Section 6.7.2)
- Perform complete physical examination (refer to Section 6.7.3)
- Obtain height and weight
- Obtain vital signs (refer to Section 6.7.4)
- Perform 12-Lead ECG (refer to Section 6.7.5)
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form
- Obtain details of concomitant medications
- Perform imaging for HCC, if needed. Liver imaging (eg, ultrasound or CT scan, at the discretion of the investigator) should be performed to exclude the presence of hepatocellular carcinoma (HCC) in all subjects. For subjects without cirrhosis, imaging must have been performed within 6 months prior to Day 1. For subjects with cirrhosis, imaging must have been performed within 4 months of Day 1.

- Obtain blood samples for tests (approximately 35 mL of blood will be drawn):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Serum β-hCG pregnancy test for females of childbearing potential only
  - HCV Genotype
  - IL28B Genotype
  - HCV antibody, HIV antibody, HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), HBV core antibody (HBcAb)
  - HbA1c
  - Fibrotest®
- Obtain urine sample for:
  - Urinalysis
- A single retest of Screening labs is permitted only if there is reason to believe the retest value will be within accepted parameters, for example, if the initial exclusionary value was either due to a sample processing error or due to an extenuating circumstance such as intercurrent illness.

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

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

6.2. Randomization

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

6.2.1. Day 1 Assessments

The following Day 1 tests and procedures must be performed prior to enrollment and dosing/dispensation of study drugs:

- Determine inclusion and exclusion eligibility (refer to Section 4.2 and 4.3)
- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Subject completes Health Related Quality of Life (HRQoL) surveys (refer to Section 6.7.6)
- Obtain blood samples for tests (approximately 35 mL of blood will be drawn for required tests):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Archive plasma sample (for subjects who have consented) (an additional 12 mL of blood will be drawn)
  - Single genomic sample (for subjects who have consented) (an additional 6 mL of blood will be drawn)
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

When ready to administer study drugs to the subject:

- Dispense study drugs as directed by the IWRS

- Instruct the subject on the packaging, storage, and administration of study drugs
- Instruct the subject on how to complete the subject diary
- Observe the subject taking the first dose of study drugs. The subject should take the study drugs with food.

6.3. Treatment Assessments (± 3 days)

On-treatment visits will be performed at the end of Weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12 for subjects randomized to receive 12 weeks of study treatment.

On-treatment visits will be performed at the end of Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20 and 24 for subjects randomized to receive 24 weeks of study treatment.

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

6.3.1. Week 1 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 1:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Assess adherence with study drug dosing regimen including pill count
- Obtain blood samples for tests (approximately 35 mL of blood will be drawn total):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Single PK sample

6.3.2. Weeks 2 and 3 (± 3 days)

The following procedures/assessments are to be completed at the end of Weeks 2 and 3:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Assess adherence with study drug dosing regimen including pill count
- Obtain blood samples for tests (approximately 35 mL of blood will be drawn for required tests):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Single PK sample
  - If applicable, collect intensive PK Substudy samples at either the Week 2, 3, or 4 visit (for subjects who have consented) (an additional 55mL of blood will be drawn)

6.3.3. Week 4 (± 3 days)

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

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Assess adherence with study drug dosing regimen including pill count
- Dispense study drugs as directed by the IWRS

- Obtain blood samples for tests (approximately 35 mL of blood will be drawn for required tests):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Single PK sample
  - If applicable, collect intensive PK Substudy samples at either the Week 2, 3, or 4 visit (for subjects who have consented) (an additional 55 mL of blood will be drawn)
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

6.3.4. Weeks 5 and 6 (± 3 days)

The following procedures/assessments are to be completed at the end of Weeks 5 and 6:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Assess adherence with study drug dosing regimen including pill count
- Obtain blood samples for tests (approximately 35 mL of blood will be drawn total):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Single PK sample

6.3.5. Week 8 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 8:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Assess adherence with study drug dosing regimen including pill count
- Dispense study drugs as directed by the IWRS
- Obtain blood samples for tests (approximately 35 mL of blood will be drawn total):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Single PK sample
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

6.3.6. Week 10 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 10:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Assess adherence with study drug dosing regimen including pill count

- Obtain blood samples for tests (approximately 35 mL of blood will be drawn total):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Single PK sample

6.3.7. Week 12 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 12:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Subject completes Health Related Quality of Life (HRQoL) surveys (refer to Section 6.7.6)
- Assess adherence with study drug dosing regimen including pill count
- Dispense study drugs as directed by the IWRS (for subjects on the 24-week treatment group only)
- Collect any remaining study drug from the subject (for subjects on the 12-week treatment group only)
- Obtain blood samples for tests (approximately 35 mL of blood will be drawn for all required tests):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA

- Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
- Single PK sample
- Archive plasma sample (for subjects who have consented) (an additional 12 mL of blood will be drawn)

- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

6.3.8. Weeks 16 and 20 (± 3 days) [for Subjects on the 24-week Treatment Group Only]

The following procedures/assessments are to be completed at the end of Weeks 16 and 20:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Assess adherence with study drug dosing regimen including pill count
- Dispense study drugs as directed by the IWRS
- Obtain blood samples for tests (approximately 35 mL of blood will be drawn total):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Single PK sample
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

6.3.9. Week 24 (± 3 days) [for Subjects on the 24-week Treatment Group Only]

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

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Subject completes Health Related Quality of Life (HRQoL) surveys (refer to Section 6.7.6)
- Assess adherence with study drug dosing regimen including pill count. Collect any remaining study drug from the subject
- Obtain blood samples for tests (approximately 35 mL of blood will be drawn for required tests):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Single PK sample
  - Archive plasma sample (for subjects who have consented) (an additional 12 mL of blood will be drawn)
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

6.4. Posttreatment Assessments (± 5 days)

The posttreatment Week 4, 12, and 24 visits should be timed from the date of last administration of any study drugs for all subjects, regardless of whether they are a virologic failure or discontinued study drugs early.

6.4.1. Posttreatment Week 4 (± 5 days)

The following procedures/assessments are to be completed for all subjects, 4 weeks after taking the last dose of study drug:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Obtain blood samples for tests (approximately 25 mL of blood will be drawn total):
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

Females 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 a minimum of 6 months following last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. In the event of a positive urine pregnancy result, subjects will be instructed to return to the clinic as soon as possible for a serum pregnancy test. The subject will be contacted by telephone monthly to confirm that urine pregnancy testing has been performed posttreatment and to record the outcome. Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine pregnancy tests.

6.4.2. Posttreatment Week 12 (± 5 days)

The following procedures/assessments are to be completed for all subjects, 12 weeks after taking the last dose of study drug:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Conduct pregnancy prevention counseling
- Subject completes Health Related Quality of Life (HRQoL) surveys (refer to Section 6.7.6)

- Obtain blood samples for tests (approximately 25 mL of blood will be drawn total):
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

Females 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 a minimum of 6 months following last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. In the event of a positive urine pregnancy result, subjects will be instructed to return to the clinic as soon as possible for a serum pregnancy test. The subject will be contacted by telephone monthly to confirm that urine pregnancy testing has been performed posttreatment and to record the outcome. Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine pregnancy tests.

6.4.3. Posttreatment Week 24 (± 5 days)

The following procedures/assessments are to be completed for all subjects, 24 weeks after taking the last dose of study drug:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Conduct pregnancy prevention counseling
- Obtain blood samples for tests (approximately 25 mL of blood will be drawn total):
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

6.5. Early Termination (ET)

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

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

The following procedures/assessments are to be completed at an Early Termination visit:

- Perform complete physical examination (refer to Section 6.7.3)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Subject completes Health Related Quality of Life (HRQoL) surveys (refer to Section 6.7.6)
- Assess adherence with study drug dosing regimen including pill count. Collect any remaining study drug from the subject
- Obtain blood samples for tests (approximately 35 mL of blood will be drawn for required tests):
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample and/or HBV DNA Sample
  - Single PK sample
  - Archive plasma sample (for subjects who have consented) (an additional 12 mL of blood will be drawn)
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

6.6. Unscheduled Visit

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

6.7. Procedures and Specifications

6.7.1. Clinical Laboratory Analytes

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

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

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

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 (reflex testing done when ALT > 2x Day 1 value in subjects who are HBsAb or HBcAb positive 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 Quantitative Test, version 2.0. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV genotype should the above assays become unavailable or are not definitive.

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

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

Additional Tests: Hemoglobin A1c (HbA1c, screening only).

6.7.2. Medical History

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

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

6.7.3. Complete Physical Examination

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

6.7.4. Vital Signs

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

Blood pressure will be measured using the following standardized process:

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

6.7.5. 12-Lead 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.

6.7.6. Health Related Quality of Life (HRQoL)

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

The Health Related Quality of Life surveys (HRQoL) will only be administered to subjects if available at Day 1, Week 12, Week 24 (if applicable), and Posttreatment Week 12. The subject should read the questionnaire by himself/herself and record the answers by himself/herself.

6.7.7. Viral RNA Sequencing / Phenotyping Sample

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

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

6.7.8. 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, its metabolites, VEL, and RBV (if appropriate). Approximately 6 mL of whole blood will be collected for each sample (which is included in the total blood volume amounts in Sections 6.1, 6.2, 6.3, and 6.5). The exact time the study drugs were taken and whether or not the study drugs were taken with food on PK assessment days will be recorded in the source documents and eCRF.

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

6.7.9. Intensive Pharmacokinetic (PK) Substudy

PPD

6.7.10. Pregnancy Testing

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

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

6.7.11. IL28B Testing

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

6.7.12. Archive Plasma Sample

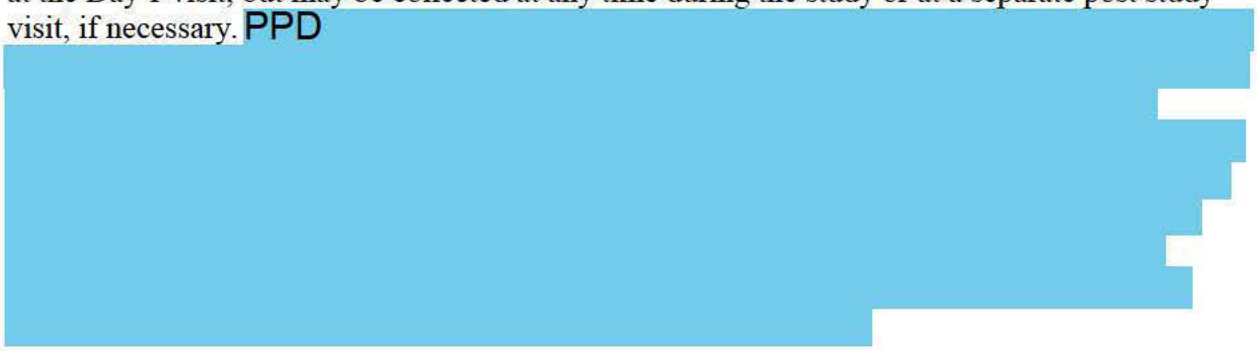
For subjects who provide consent, an archive plasma sample (non-genetic) will be collected at Day 1, Week 12, Week 24 (if applicable) and Early Termination (if applicable) Visits. Approximately 12 mL of whole blood will be collected for each sample. The specimens collected will be used to increase our knowledge and understanding of the biology pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These specimens may be used for retesting of the amount of HCV in the blood, clinical laboratory testing to provide additional clinical data and to develop non-genetic biomarker or diagnostic assays and establish the performance characteristics of these assays.

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

6.7.13. Genomic Testing

This study also includes the optional collection of a whole blood sample for human genomic testing. This sample may only be collected following approval of site IRB or Ethical Committees. In addition to the study-specific informed consent to be signed by each subject participating in the study, a separate, specific signature will be required to document a subject's agreement to provide this additional sample for optional genomic research. Provision of the genomic sample is optional and is not required in order for a subject to participate in the study.

From subjects who agree to participate and provide their additional specific consent, one blood sample of approximately 6 mL of whole blood will be collected. This sample should be collected at the Day 1 visit, but may be collected at any time during the study or at a separate post study visit, if necessary. PPD



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

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

6.7.14. Creatinine Clearance

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

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

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

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

6.8. End of Study

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

6.9. Poststudy Care

No poststudy ongoing care will be provided.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (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 eCRF.

7.1.2. Serious Adverse Events

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

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

- A congenital anomaly/birth defect

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No**: Evidence exists that the adverse event has an etiology other than the study drugs. 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 study drugs.

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 drugs initiation:

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

Adverse Events

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

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

Serious Adverse Events

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

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

Prior treatment history is collected as part of the study entry criteria and evaluation of individual patient characteristics and will not be generating lack of effect reports as this is outside the scope of the present clinical study. However, investigators should report any cases of lack of effect that they feel appropriate regarding the previous treatment regimen as spontaneous reports to the relevant authorities or marketing authorisation holders.

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

Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

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

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

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

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

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

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

7.5. Toxicity Management

7.5.1. RBV Dose Adjustments

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

In the event a female partner of a male subject becomes pregnant, the male subject must permanently discontinue RBV, however they can continue SOF/VEL FDC.

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

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

Source: Japan Rebetol® Product Label {MSD K.K. Kudan-kita Chiyoda-ku 2016}

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

Test items	Value	Ribavirin
Neutrophil count	< 500 /mm^3	Discontinue
Platelet count	< 50,000 /mm^3	Discontinue
	< 25,000/ mm^3	Discontinue (resumption of dosing not allowed)
Hemoglobin level (No cardiac disease or history of cardiac disease)	< 11 g/dL at Week 1 to 4 after start of administration	Reduce dose 600 mg/day → 200 mg/day 800 mg/day → 400 mg/day 1,000 mg/day → 400 mg/day
	< 10 g/dL at Week 5 to 12 after start of administration	
	< 8.5 g/dL	Discontinue
Hemoglobin level (Cardiac disease or history of cardiac disease present)	< 11 g/dL at Week 1 to 4 after start of administration or during administration, reduction of 2 g/dL or more relative to Day 1 persists for 4 weeks	Reduce dose 600 mg/day → 200 mg/day 800 mg/day → 400 mg/day 1,000 mg/day → 400 mg/day
	< 10 g/dL at Week 5 to 12 after start of administration or during administration, reduction of 2 g/dL or more relative to baseline persists for 4 weeks	
	< 8.5 g/dL, or after dose reduction, less than 12 g/dL even after 4 weeks	Discontinue

Source: Japan Rebetol® Product Label {MSD K.K. Kudan-kita Chiyoda-ku 2016}

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

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

Abuse is defined as persistent or sporadic intentional excessive use of study drugs by a subject.

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to 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 of the investigator becoming aware of the pregnancy.

Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com.

Clinical staff should also report any pregnancies to the Pregnancy Registry at 1 800-593-2214 (see also http://www.ribavirinpregnancyregistry.com). Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

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

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

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

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

8.1.3. Secondary Endpoint

The secondary efficacy endpoints include the following:

- The proportion of subjects with HCV RNA < LLOQ at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- Proportion of subjects who have HCV RNA < LLOQ by visit while on treatment
- HCV RNA change from Baseline
- The proportion of subjects with virologic failure

8.1.4. Other Endpoints of Interest

PPD

8.2. Analysis Conventions

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

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

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

8.2.1.2. Safety

The primary analysis set for safety analyses will include all subjects who took at least 1 dose of study drugs. Treatment-emergent data will be analyzed and defined as data collected from the first dose of study drugs through the date of last dose of study drugs plus 30 days.

8.2.1.3. Pharmacokinetic

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

The PK Substudy Analysis Set includes all subjects who are enrolled in the PK substudy, have been administered at least 1 dose of the study drugs, and have at least 1 nonmissing postdose concentration value for the corresponding analyte in plasma. The analytes of interest may include SOF, GS-566500, GS-331007, VEL, and/or RBV (if appropriate). The PK Substudy Analysis Set will be used for intensive PK profiles of these analytes.

8.3. Data Handling Conventions

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

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

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

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

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

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

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

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

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

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

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

8.4. Demographic Data and Baseline Characteristics

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

Demographic summaries will include age, sex, self-identified race and ethnicity. Baseline characteristics data will include body mass index, HCV RNA level ($\log_{10}$ IU/mL), IL28B genotype, and additional endpoints as necessary. The number (proportion) of subjects in each stratum will be summarized.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

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

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

Genotype 1 Subjects

In the primary efficacy analysis, the SVR12 rate for genotype 1 patients in each of the two treatment groups will be compared to the historical control rate of 50% using two-sided exact one-sample binomial test with Bonferroni alpha adjustment (each at significance level 0.025): ie, for each treatment group, the hypothesis for superiority is as follows:

- H0: SVR12 rate = 50%
- H1: SVR12 rate $\neq$ 50%

The 50% SVR null rate is derived from SVR rates of 43% (59/137) and 59% (57/96) for treatment naive patients with genotype 1 HCV infection and high viral loads treated with PEG IFN and RBV for 48 weeks cited in the Japanese package inserts for REBETOL® Capsules 200 mg (MSD, July 2015, 19th version) and COPEGUS® Tablets 200 mg (Chugai Pharmaceuticals, July 2015, 6th version,) respectively. The weighted average rate then is 50% ((59+57)/(137+96) = 50%).

It is important to note that this historical control rate is a conservative estimate. Because there are no currently available IFN-free treatment options for these subjects and because many of these subjects will have a history of treatment failure with IFN-based therapy and/or medical comorbidities precluding the use of IFN, the actual response rate of this population would likely be much lower than 50%.

Genotype 2 Subjects

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

8.5.2. Secondary Analyses

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

Descriptive summaries and listings will be provided for additional efficacy evaluations including HCV RNA values and change from baseline through end of treatment, and subjects who experience virologic failure.

Exploratory analyses may be performed to assess the relationship between PPD

PPD

8.6. Safety Analysis

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

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

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

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

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

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

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- All treatment-related SAEs

PPD

8.6. Safety Analysis

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

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

8.6.1. Extent of Exposure

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

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

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

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

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- All treatment-related SAEs

- AEs leading to premature discontinuation of any study drugs
- AEs leading to modification or interruption of any study drugs

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

8.6.3. Laboratory Evaluations

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

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

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

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

8.6.4. Other Safety Evaluations

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

8.7. Pharmacokinetic Analysis

In the PK analysis set, concentrations of SOF, its metabolites GS-566500 and GS-331007, VEL, and RBV (if appropriate) in plasma may be determined using validated bioanalytical assays and listed. Details of the analyses will be provided in the pharmacokinetic reporting and analysis plan.

In the Intensive PK substudy analysis set, plasma concentrations of the study drugs over time will be summarized using descriptive statistics. PK parameters (eg, AUC_{tau}, C_{max}) may be listed and summarized (as appropriate) for all analytes using descriptive statistics. Details of the analysis will be provided in the pharmacokinetic reporting and analysis plan.

8.8. Sample Size

Approximately 110 subjects will be randomized in this study with approximately 90 subjects with genotype 1 HCV infection and approximately 20 subjects with genotype 2 HCV infection. Due to the limited number of genotype 2 subjects in this study, the sample size justification will be based on genotype 1 subjects only.

A sample size of 45 genotype 1 subjects in each treatment group will provide over 90% power to detect at least 27% improvement in SVR12 rate from the historical control rate of 50% using a two-sided exact one-sample binomial test at significance level of 0.025.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

This protocol is to be conducted in accordance with the guidance stipulated in Article 14, Paragraph 3 and Article 80-2 of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, "MHLW Ordinance on Good Clinical Practice" {Ministry of Health and Welfare 2013}.

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

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

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

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

9.1.3. Informed Consent

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

investigator must use the most current approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. The consent form will inform subjects about genomic testing and sample retention.

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

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

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

Gilead recommends that used and unused study drugs supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's study drugs disposal procedures and provide appropriate instruction for destruction of unused study drugs supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drugs 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 drugs are destroyed on site, the investigator or designee (ie, pharmacist) must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drugs. Upon study completion, copies of the study drugs accountability records must be filed at the site. Another copy will be returned to Gilead.

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

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

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to

verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.2. Access to Information for Auditing or Inspections

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

9.3.3. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavirin for 12 or 24 Weeks in Subjects with Chronic Genotype 1 or 2 HCV Infection Who Have Previously Failed a Direct-Acting Antiviral-Containing Regimen

GS-US-342-3921, Protocol Amendment 3, 13 June 2016

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

Brian McNabb

Brian McNabb, MD

PPD

Signature

13- Jun -2016

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

			Treatment Week (±3 days)												ET[c]	Posttreatment Week (±5 days)		
	Screening	Day 1[a]	1	2	3	4	5	6	8	10	12	16[b]	20[b]	24[b]		4	12	24
Clinical Assessments																		
Informed Consent	X																	
Determine Eligibility	X	X																
Medical History	X																	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X																	
Adverse Events and Concomitant Medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling		X									X			X	X	X	X	X
Health Related Quality of Life[g]		X									X			X	X		X	
Imaging for HCC[h]	X																	
Review of Study Drug Adherence and Drug Accountability[i]			X	X	X	X	X	X	X	X	X	X	X	X	X			
Study Drug Dispensing[j]		X				X			X		X[b]	X	X					
Laboratory Assessments																		
Hematology & Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation (PT, aPTT and INR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
HCV RNA (Plasma)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Day 1[a]	Treatment Week (±3 days)												ET[c]	Posttreatment Week (±5 days)		
			1	2	3	4	5	6	8	10	12	16[b]	20[b]	24[b]		4	12	24
Viral RNA Sequencing /Phenotyping and/or HBV DNA Sample (Plasma)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single PK			X	X	X	X	X	X	X	X	X	X	X	X	X			
Intensive PK Substudy Collection[k]				X	X	X												
Serum or Urine Pregnancy Test[l]	X	X				X			X		X	X	X	X	X	X	X	X
Urinalysis	X																	
HCV Genotype, IL28B Genotype	X																	
HCV Ab, HIV Ab, HBsAg, HBsAb, HBcAb	X																	
HbA1c	X																	
FibroTest®	X																	
Archive plasma sample[m]		X									X			X	X			
Single Genomic Sample[n]		X																

a Day 1 assessments must be performed prior to dosing.
b Only to be completed for subjects on the 24 week treatment regimen
c ET = Early Termination.
d Vital signs include resting blood pressure, pulse, respiratory rate and temperature.
e 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.
f Adverse events and Concomitant Medications will be collected up to 30 days after the last dose of all study drugs.
g Health Related Quality of Life (HRQoL) Surveys (eg, SF-36, CLDQ-HCV, FACIT-F and WPAI) will be conducted for all subjects where the surveys are available at Day 1, Week 12, Week 24 (if applicable), and posttreatment Week 12.
h Liver imaging (eg, ultrasound or CT scan, at the discretion of the investigator) should be performed to exclude the presence of hepatocellular carcinoma (HCC) in all subjects. For subjects without cirrhosis, imaging must have been performed within 6 months prior to Day 1. For subjects with cirrhosis, imaging must have been performed within 4 months of Day 1.
i Study drugs will be reconciled at every post- Day 1 visit by the investigator in order to monitor the subject's adherence with the study drugs. Subjects must be instructed to bring back all bottles of study drugs in the original container at every post- Day 1 visit through the end of treatment.
j Dispense study drugs as directed by the IWRS

k Subjects that consent to the optional PPD .

l All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period. Females of childbearing potential will have additional urine pregnancy testing every 4 weeks for a minimum of 6 months following last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. In the event of a positive urine pregnancy result, subjects will be instructed to return to the clinic as soon as possible for a serum pregnancy test. Pregnancy test kits will be dispensed to female subjects of childbearing potential after the posttreatment Week 4 visit. The subject will be contacted by telephone monthly to confirm that urine pregnancy testing has been performed posttreatment and to record the outcome. Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine pregnancy tests.

m Only for subjects who have provided separate consent for this sample and testing

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

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

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months#**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
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 mmolL	2.0 to < 2.5 mEq/L 2.0 to <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L

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

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

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

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

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

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

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

Notes:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1) 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. Please refer to the latest version of the product insert for additional information.

2) Definitions

a. Definition of Childbearing Potential

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

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

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

b. Definition of Male Fertility

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

3) Study Drug Effect 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.

4) 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 first dose of study drug. Pregnancy testing will occur at regular intervals throughout the duration of the trial. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from Screening until 30 days after 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 used 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 (unapproved in Japan)
  - — Vasectomy in the male partner
  - — Barrier methods
    - ■ Female barriers: Diaphragm with spermicide or Cervical cap with spermicide (unapproved in Japan)
  - — Hormonal methods
    - ■ Oral contraceptives (either combined or progesterone only)
    - ■ Injectable progesterone (unapproved in Japan)
    - ■ Implants of levonorgestrel or etonorgestrel (unapproved in Japan)
    - ■ Transdermal contraceptive patch (unapproved in Japan)
    - ■ Contraceptive vaginal ring (unapproved in Japan)

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

5) 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 treatment or 6 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 6 months after last dose of RBV, whichever comes last.

Male subjects must also refrain from sperm donation during treatment and until at least 30 days after the last dose of SOF/VEL or 6 months after the last dose of RBV, whichever comes last.

6) Unacceptable Birth Control Methods

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

7) 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, if they become pregnant within 30 days of last dose of SOF/VEL, or if they become pregnant within 6 months of the last dose of RBV. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant within 30 days of the last dose of SOF/VEL or 6 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.