CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic HCV Infection and Compensated Cirrhosis	
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-342-5531	
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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Study Title:	A Phase 3 Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic HCV Infection and Compensated Cirrhosis
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 as follows: • To evaluate the antiviral efficacy of therapy with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) for 12 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 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 emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment
Study Design:	This is a multicenter, open-label study in subjects with chronic hepatitis C virus (HCV) infection and compensated cirrhosis. Approximately 36 subjects will be enrolled and treated with SOF/VEL FDC for 12 weeks. Subjects may have HCV of any genotype; based on the HCV genotype (GT) distribution in Japan, it is expected that approximately 70% of subjects will be GT1, and approximately 30% of subjects will be non-GT1. Subjects may be either treatment-naive or treatment-experienced with IFN-based

	treatments.
Number of Subjects Planned:	Approximately 36 subjects
Target Population:	Patients with chronic HCV infection and compensated cirrhosis.
Duration of Treatment:	Subjects will be treated for 12 weeks
Diagnosis and Main Eligibility Criteria:	Chronic HCV-infected male and non-pregnant/non-lactating female subjects, aged 18 years or older.
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. Study visits will occur at Screening, Day 1, and on-treatment at the end of Weeks 1, 2, 4, 8, and 12. Following the last dose of study drug, all subjects will complete posttreatment Week 4, 12 and 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 4 months of Day 1, safety laboratory tests (including hematology, chemistry, coagulation, urinalysis), HCV RNA, serum β-hCG (females of child bearing potential only), serum FSH (only for women of any age with amenorrhea of ≥ 12 months, [refer to Appendix 4]), HCV genotype, serology (HIV, HCV, HBV), hemoglobin A1c (HbA1c), and assessment of the presence of cirrhosis (including FibroTest®). On-treatment assessments include physical examination, weight, vital signs, 12-lead ECG, AEs, concomitant medications, pregnancy prevention counseling, review of study drug adherence and drug accountability, study drug dispensing, safety laboratory tests (including hematology, chemistry, coagulation), HCV RNA, HCV resistance samples, HBV DNA sample, urine pregnancy tests (females of child bearing potential only), and IL28B genotyping. Posttreatment assessments include weight, vital signs, AEs and concomitant medications, pregnancy prevention counseling, safety laboratory tests (including hematology and chemistry), HCV RNA, HCV resistance samples, HBV DNA, and urine pregnancy tests (females of childbearing potential only).

Test Product, Dose, and Mode of Administration:	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.
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.
Statistical Methods:	The primary efficacy endpoint for the study is SVR12 in all enrolled and treated subjects. In the primary efficacy analysis, the SVR12 rate in the Full Analysis Set (FAS) will be compared to a performance threshold rate of 78% using the two-sided exact one-sample binomial test at significance level of 0.05. In addition, 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. Secondary efficacy endpoints include SVR4, SVR24, and the proportion of subjects with virologic failure. All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum). All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition. Safety endpoints will be analyzed by the number and percentage of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data. Different studies have reported SVR12 rates for compensated cirrhotic subjects infected with HCV in Japanese populations. The SVR12 performance threshold of 78% for this study is determined as clinically relevant by referring to results in the confirmatory studies of approved DAA products in Japan. Among these studies, the average lower bound of the exact 95% confidence interval is 78%.

Based on this, a performance threshold of 78% was established for the primary efficacy endpoint. A success for the primary endpoint will be claimed if the following criterion is met: point estimate of SVR12 is statistically significantly higher than 78% by a two-sided exact one-sample binomial test at significance level 0.05, ie, p-value for the hypothesis testing for superiority is ≤ 0.05.

This study intends to enroll patients who have compensated cirrhosis. A sample size of approximately 36 compensated cirrhotic Japanese subjects in the study will provide > 80% power to demonstrate superiority to a performance threshold of 78%, assuming an expected SVR12 rate of 96% with 12 weeks of SOF/VEL therapy (based on a two-sided exact one-sample binomial test of superiority at a significance level of 0.05). This expected 96% SVR12 rate represents a clinically relevant response for compensated cirrhotic patients, who are at risk of PI-based liver toxicity and currently have no highly-effective PI-free pan-genotypic treatment options.

This study will be conducted in accordance with the guidelines of 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
AE(s)	adverse event(s)
ALT	alanine aminotransferase (also SGPT)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
ASV	asunaprevir
BMI	body mass index
BCV	beclabuvir
CFR	Code of Federal Regulations
CI	confidence interval
ClCr	creatinine clearance
CPT	Child-Pugh-Turcotte
CRO	contract (or clinical) research organization
CSR	clinical study report
DAA	direct-acting antiviral
DCV	daclatasvir
dL	Deciliter
DNA	deoxyribonucleic acid
EBR	elbasvir
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eg	example given
eSAE	electronic serious adverse event
ESLD	end stage liver disease
Et al	(Latin) and others
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed-dose combination
FSH	Follicle-stimulating hormone
g	grams
GCP	Good Clinical Practice

GLE	glecaprevir
GS-7977	sofosbuvir, formerly PSI-7977
GSI	Gilead Sciences, Inc.
GT	Genotype
GZR	grazoprevir
h	hour
H2	histamine
Hb	hemoglobin
HbA1c	hemoglobin A1c
HBcAb	HBV core antibody
HBsAb	HBV surface antibody
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
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IFN	interferon
ie	in essence
IL28B	interleukin-28B gene
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
INR	international normalized ratio of prothrombin time
IRB	institutional review board
IU	International Units
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
J-GCP	Ministerial Ordinance on Good Clinical Practice for Drugs
JSH	Japan Society of Hepatology
kg	kilogram
kPA	kilopascal
L	liter

LAM	lactational amenorrhea method
LDV	ledipasvir
LLOQ	lower limit of quantification
LLT	lower-level term
MCV	mean corpuscular volume or mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MGB	minor groove binder
MHLW	Ministry of Health, Labour and Welfare
mL	milliliter
mm^3	cubic millimeter
mmHg	millimeters mercury
n	number
NS (3/4A/5A/5B)	non-structural protein
PCR	polymerase chain reaction
PI	protease inhibitor
PIB	pibrentasvir
PK	pharmacokinetic
PPIs	proton-pump inhibitors
PT	preferred term or prothrombin time
Q1	quartile 1
Q3	quartile 3
RAS	resistance associated substitutions
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
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SNP	single nucleotide polymorphism
SOC	standard of care
SOF	sofosbuvir, formerly GS-7977
SOP	standard operating procedure
SSR	special situation report
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
TND	target not detected
ULN	upper limit of normal
US	United States
WBC	white blood cell
VEL	velpatasvir
β-hCG	β-human chorionic gonadotropin
µg	microgram

1. INTRODUCTION

1.1. Background

With published HCV prevalence estimates from blood-donor and subgroup-based studies on the order of 1-1.9% in Japan {Sievert 2011}, it is estimated that there are approximately 1.3-2.4 million people chronically infected with HCV. An estimated 70% of HCV patients in Japan are infected with genotype (GT) 1b, and 25% to 30% with GT 2a or 2b {Sievert 2011}. 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 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 also common in this population. and 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 2008}.

In Japan, ledipasvir/sofosbuvir (LDV/SOF), SOF + ribavirin (RBV), elbasvir (EBR) + grazoprevir (GZR), glecaprevir/pibrentasvir (GLE/PIB), and beclabuvir/daclatasvir/asunaprevir (BCV/DCV/ASV) are currently approved and recommended as the first-line standard of care (SOC) for the treatment of HCV. Per the Japan Society of Hepatology (JSH) guidelines, the choice of HCV treatment regimen is to be based on the patient's HCV genotype, prior treatment history and cirrhosis status.

Patients that are treatment naïve with compensated cirrhosis are recommended to be treated with 12 weeks of LDV/SOF, EBR + GZR or GLE/PIB for GT1 or with 12 weeks of SOF+RBV, GLE/PIB or LDV/SOF for GT2. These have been recommended as the first-line SOC in the JSH treatment guidelines as they are highly efficacious and well-tolerated (GT1: 100%, GT2: 93% to 100%) {Akuta 2012, Kawaoka 2011, Sakamoto 2011}.

Although recent treatment advances have begun to address several of the unmet needs in the treatment of HCV infection in Japan, resulting in a 20% reduction in chronic hepatitis C infection rate over a 3 year period, the number of HCV patients with compensated cirrhosis (estimated to be 40,000) over the same period remained unchanged suggesting that despite the availability of highly efficacious treatment, there is a high rate of progression to cirrhosis in the Japanese population {Ito 2016}.

1.2. Sofosbuvir/Velpatasvir Fixed-Dose Combination

Sofosbuvir (SOF) is a nucleotide analog HCV NS5B polymerase inhibitor. Velpatasvir (VEL) is a pangenotypic HCV NS5A inhibitor.

1.2.1. General Information

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

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

1.2.2. Clinical Trials of SOF/VEL FDC

1.2.2.1. GS-US-342-4019 SOF/VEL+/-RBV for 12 Weeks in Japanese subjects with Chronic HCV Infection and Decompensated Cirrhosis

This Phase 3 study included 102 subjects with chronic HCV and decompensated cirrhosis who were randomized to be treated with SOF/VEL with or without RBV for 12 weeks. All subjects completed the full 12 weeks of treatment with SOF/VEL+/-RBV. 57% were treatment naive, 78% and 20% had genotype 1 and 2 HCV infection, respectively, and 77% and 20% had Child-Pugh-Turcotte (CPT) class B and C cirrhosis, respectively, at baseline. Overall, 61% of patients were female and the mean age was 66 years (range 41–83). Rates of SVR12 were 92% (47/51) in each group. Among patients who achieved SVR12, 26% had improved CPT class from baseline to posttreatment week 12. Most adverse events (AEs) were consistent with clinical sequelae of advanced liver disease or known toxicities of ribavirin. Four patients (8%) who received SOF/VEL and seven (14%) who received SOF/VEL plus ribavirin experienced a serious AE. The results from this study formed the basis for registration of SOF/VEL (Epclusa®) in Japan for the treatment of chronic HCV infection with decompensated cirrhosis {Takehara 2019}.

1.2.2.2. GS-US-342-3921 SOF/VEL+ RBV for 12 or 24 Weeks in Japanese subjects with Chronic Genotype 1 or 2 HCV Infection Who Have Previously Failed a Direct-Acting Antiviral-Containing Regimen

This Phase 3 study included 117 subjects with chronic HCV who failed a direct-acting antiviral (DAA) based regimen who were treated with SOF/VEL with RBV for 12 or 24 weeks. All but one subject completed the full treatment duration with SOF/VEL+RBV. 81% had HCV genotype 1 infection, 33% had cirrhosis, and 95% had NS5A resistance associated substitutions (RAS) at baseline. Overall, SVR12 rates were 97% (58/60; 95% CI 88–100%) with 24 weeks of treatment and 82% (47/57; 95% CI 70–91%) with 12 weeks. For HCV genotype 1 and 2 infected patients, the SVR12 rates with 24 weeks of treatment were 98% and 92%, respectively. For patients with NS5A RASs at baseline, 85% (46/54) in the 12-week group and 96% (54/56) in the 24-week group achieved SVR12. The most common adverse events were upper respiratory tract viral infection, anemia, and headache. Three (2.6%) patients discontinued treatment because of adverse events. The results from this study formed the basis for registration of SOF/VEL (Epclusa®) + RBV in Japan for the treatment of chronic HCV infection who failed a direct-acting antiviral (DAA) based regimen {Izumi 2018}.

1.3. Rationale for This Study

As patients with asymptomatic compensated cirrhosis are at high risk of developing clinical signs of decompensation such as portal hypertension and variceal bleeds {D'Amico 2006}, there remains a need in Japan for a protease inhibitor (PI)-free HCV treatment regimen that is safe and effective for both compensated and decompensated HCV patients.

SOF/VEL FDC is already approved for use in decompensated patients and DAA failure patients with or without compensated cirrhosis in Japan, and the aim of this study is to examine the safety and efficacy of SOF/VEL FDC in Japan for DAA naïve compensated cirrhotic patients. This has the potential to offer a simplified, safe, and effective PI-free HCV treatment option without the need to distinguish between compensated and decompensated cirrhosis.

1.4. Rationale for Dose Selection of SOF/VEL FDC

Subjects in this study will be administered SOF/VEL FDC, a co-formulation of SOF 400 mg and VEL 100 mg that is approved in the US, EU and other regions as Epclusa® for the treatment of HCV infection in adults. In addition, this co-formulation is already approved in Japan for HCV infected subjects with decompensated cirrhosis or those who are DAA failures with or without compensated cirrhosis.

In the Phase 3 ASTRAL 1-3 studies (GS-US-342-1138, GS-US-342-1139, GS-US-342-1140), treatment of HCV infected subjects without cirrhosis or with compensated cirrhosis for 12 weeks with SOF/VEL FDC 400/100 mg was well tolerated and resulted in high SVR12 rates. In the global ASTRAL-4 (GS-US-342-1137) study and in the identical Phase 3 Japanese study (GS-US-342-4019), treatment of HCV-infected subjects with decompensated CPT class B and C cirrhosis with SOF/VEL FDC 400/100 mg for 12 weeks was well tolerated and resulted in high SVR12 rates across all HCV genotypes.

These data support evaluation of SOF/VEL FDC 400/100 mg in this phase 3 study in Japanese patients with compensated cirrhosis. Refer to the SOF/VEL FDC Investigator's Brochure for additional information.

1.5. Risk/Benefit Assessment for the Study

This study will provide information of the safety and efficacy of the combination of SOF/VEL FDC for 12 weeks in Japanese patients with compensated cirrhosis.

The safety profile of SOF/VEL FDC has been established in 3,345 subjects, including the Phase 3 studies, Phase 2 studies and Phase 1 studies in subjects with compensated and decompensated cirrhosis. The safety of SOF/VEL FDC has also been established in 219 Japanese patients. No clinical safety issues specifically related to the combination of SOF/VEL FDC have been identified to date. Overall, SOF/VEL FDC for 12 weeks was safe and well tolerated in patients with or without cirrhosis.

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

In summary, safety and efficacy of SOF/VEL FDC for 12 weeks has been evaluated in subjects with compensated and decompensated cirrhosis and without cirrhosis.

1.6. Compliance

This study will be conducted in accordance with the guidelines of 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.

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the antiviral efficacy of therapy with SOF/VEL fixed-dose combination (FDC) for 12 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 by review of the accumulated safety data

The secondary objectives of this study are:

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

3. STUDY DESIGN

3.1. Study Design

This is a multicenter, open-label study evaluating efficacy and safety of SOF/VEL FDC in subjects with chronic HCV and compensated cirrhosis.

Subjects may have HCV of any genotype, and based on the HCV genotype (GT) distribution in Japan, it is expected that approximately 70% of subjects will be GT1, and approximately 30% of subjects will be non-GT1. Subjects may be either treatment-naïve or treatment-experienced with IFN-based treatments.

3.2. Study Treatments

Approximately 36 subjects will be enrolled to be treated with SOF/VEL FDC.

3.3. Duration of Treatment

Subjects will be treated for 12 weeks.

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

- 28 days (4 weeks) screening period
- 12 weeks study treatment period
- 24 weeks posttreatment period

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

There is no option for SOF/VEL FDC dose reduction.

Subjects who permanently discontinue SOF/VEL FDC should complete an Early Termination (ET) visit. For subjects who have completed an ET visit, the posttreatment Weeks 4, 12, and 24 visits will be completed after the last dose of the study drug. When medically feasible, the medical monitor must be consulted prior to subject discontinuation.

Study drug must be discontinued in the following instances:

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

- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Virologic failure (as defined in Section 3.4.2)
- 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. Toxicity-Based Stopping Criteria

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

Due to a clinical or laboratory event, administration of study drug may be discontinued. There is no option for SOF/VEL FDC dose reduction. If SOF/VEL FDC is stopped due to toxicity, it must not be restarted. In these cases that study drug is discontinued permanently, the subject must complete an ET visit. Posttreatment Week 4, 12, and 24 visits must also be scheduled, 4, 12, and 24 weeks from the last dose of study drug.

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

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

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

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

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 36 chronic HCV infected male and non-pregnant female subjects, ages 18 or older, with compensated cirrhosis at Screening will be enrolled in this study.

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

4.2. Inclusion Criteria

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

1) Willing and able to give informed consent prior to any study specific procedures being performed. If subject is a minor, legal representative will provide consent.

2) Male or female, age ≥ 18 years at Screening

3) Body weight ≥ 40 kg at Screening

4) Quantifiable HCV RNA (≥ lower limit of quantitation [LLOQ]) at Screening

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

6) Confirmation of cirrhosis by any one of the following methods:

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

    b) Fibroscan within 4 months of Day 1 showing cirrhosis or results > 12.5 kPa

    c) FibroTest® score of > 0.75 at Screening (only in the absence of liver biopsy or availability of Fibroscan)

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

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

    b) HCV treatment-experienced: Subject has had prior treatment with an approved or experimental IFN-containing regimen with or without NS3/4A protease inhibitors. Note: *See Exclusion Criterion #5: if treatment-experienced, prior exposure to any direct-acting antiviral agent targeting the HCV NS5A or NS5B is prohibited.*

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

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

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 enrollment.

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 during treatment and until at least 30 days after the last dose SOF/VEL FDC. Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the last dose of SOF/VEL FDC.

13) Lactating females must agree to discontinue nursing before the study drug is administered and through at least 30 days 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 drug administration and able to complete the study schedule of assessments, including all required posttreatment visits.

4.3. Exclusion Criteria

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

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

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

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

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

   d) Any current or past clinical evidence of decompensated liver disease (eg, ascites, hepatic encephalopathy, or variceal bleeding).

   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 human immunodeficiency virus (HIV) at Screening

3) Hepatitis B virus (HBV) surface antigen positive at Screening

4) Screening ECG with clinically significant abnormalities

5) Prior exposure to any HCV NS5A or NS5B inhibitor

6) 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)

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

8) Women who wish to become pregnant or males with female partners who wish to become pregnant during study treatment and through 30 days after the last dose SOF/VEL FDC

9) Subjects with any of the following laboratory parameters at Screening:

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

b) AST > 10 × ULN

c) Direct bilirubin > 1.5 × ULN

d) Platelets < 50,000/μL

e) HbA1c > 8.5%

f) Hemoglobin < 10 g/dL

g) Albumin < 3 g/dL

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

i) Neutrophil count < 500/μL

10) Use of any prohibited concomitant medications as described in Section 5.4 of the Protocol

11) Chronic use of systemically administered immunosuppressive agents (eg, prednisone equivalent > 10 mg/day)

12) Known hypersensitivity or contraindication to SOF, VEL, or the metabolites or formulation excipients

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

This is a multicenter, open-label study in subjects with chronic HCV infection with compensated cirrhosis. No blinding is required.

All subjects will be enrolled to receive SOF/VEL FDC for 12 weeks.

5.2. Description and Handling of SOF/VEL FDC

5.2.1. Formulation

The SOF/VEL FDC (400/100 mg) tablets are pink, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side. In addition to the active ingredients, the SOF/VEL FDC 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 FDC (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 polypropylene screw cap with an induction-sealed, aluminum-faced liner.

SOF/VEL FDC 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 below 30 °C (86 °F).

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

5.3. Dosage and Administration of SOF/VEL FDC

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

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

5.4. Prior and Concomitant Medications

All concomitant medications taken within 30 days prior to Screening, up to and including 30 days after the last dose of study drug, need to be recorded in the source documents and electronic case report form (eCRF) (including all blood products).

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

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

Investigators should refer to the product/package inserts of other medications for recommendations or contraindications related to their use.

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

Table 5-1. Disallowed and Concomitant Medications to be Used with Caution

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing Agents[a]		Proton- Pump Inhibitors, H2-Receptor Antagonists, Antacids
Anticonvulsants[b]	Phenytoin, Carbamazepine, Phenobarbital	
Antimycobacterials[b]	Rifampicin	Rifabutin
Cardiac Medications[c]	Amiodarone[d]	Digoxin[e]
Herbal/Natural Supplements[b]	St. John's Wort	
HMG-CoA Reductase Inhibitors[f]		Rosuvastatin (≤10 mg/day), Atorvastatin
Other	Bosentan[b], Modafinil[b], Sulfasalazine[c], Methotrexate[c]	Dabigatran etexilate[g]

a Proton pump inhibitor (PPI) doses comparable with omeprazole 20mg can be administered with SOF/VEL FDC when SOF/VEL FDC is administered with food and taken 4 hours before the PPI. H2-receptor antagonists must not exceed a dose of 40 mg famotidine or equivalent and can be taken simultaneously with SOF/VEL FDC 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 FDC administration.

b May result in a decrease in the concentration of study drug.
c May result in an increase in the concentration of study drug 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 FDC may result in an increase in the concentration of HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis. Rosuvastatin may be coadministered at a dose that does not exceed 10 mg.
g As dabigatran exposure may increase when coadministered with SOF/VEL FDC, clinical monitoring for signs of bleeding and anemia is recommended, in addition to monitoring patients using coagulation testing.

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.

5.5. Study Drug Adherence and Accountability for SOF/VEL FDC

The investigator or designee (ie pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.
SOF/VEL FDC 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 drug kits
- Record the date, subject number and the study drug kit number dispensed
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

Refer to Section 9.1.8 for information on return and disposal of study drug.

6. STUDY PROCEDURES

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

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

6.1. Subject Enrollment

Entry into screening does not guarantee enrollment into the study. In order to manage the total trial enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or trial-wide at any time.

6.1.1. Screening Visit

Subjects will be screened within 28 days before Day 1 visit to determine eligibility for participation in the study. The screening window can be extended up to 42 days for subjects in 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 due to a sample processing error or due to an extenuating circumstance such as an intercurrent infection.

The following will be performed and documented at screening:

- Obtain written informed consent
- Determine inclusion and exclusion eligibility
- Obtain medical history (refer to Section 6.7.2), including:
  - Hepatitis C treatment history, if applicable
    - Regimen (s)
    - Dates of previous treatment(s)
    - Response to previous treatment (i.e. nonresponder, relapse, discontinuation including reason)
- 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 prior and concomitant medications
- Liver biopsy and/or Fibroscan results (if available)
- Diagnostic imaging (eg, ultrasound or CT scan, at the discretion of the Investigator) should be performed to exclude the presence of hepatocellular carcinoma (HCC). Imaging must be performed within 4 months of Day 1.
- Obtain blood samples for tests:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Serum β-hCG pregnancy test for females of childbearing potential only
  - Serum follicle stimulating hormone (FSH) (only for women of any age with amenorrhea of ≥ 12 months [refer to Appendix 4])
  - HCV 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 enrollment into the study.

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

6.1.2. Day 1 Assessments

An Interactive Web Response System (IWRS) will be employed to manage subject enrollment.

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

- Determine inclusion and exclusion eligibility (refer to Sections 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)
- Perform 12-Lead ECG (refer to Section 6.7.5)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Obtain blood samples for tests:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - IL28B Genotype
  - HCV resistance samples
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

When ready to administer study drug to the subject:

- Dispense study drug as directed by the IWRS
- Instruct the subject on the packaging, storage, and administration of study drug
- Instruct the subject on how to complete the subject diary
- Observe the subject taking the first dose of study drug.

6.2. Treatment Assessments (± 3 days)

On-treatment visits will be performed at the end of Weeks 1, 2, 4, 8, and 12 for all subjects.

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

6.2.1. Week 1 (± 3 days)

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

- 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

6.2.2. Week 2 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 2:

- 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:
  - Hematology
  - Chemistry
  - HCV RNA
  - HCV resistance samples
  - HBV DNA Sample

6.2.3. Weeks 4 and 8 (± 3 days)

The following procedures/assessments are to be completed at the end of Weeks 4 and 8:

- 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 drug as directed by the IWRS (Week 4 only)
- Obtain blood samples for tests:
  - Hematology
  - Chemistry
  - HCV RNA
  - HCV resistance samples
  - HBV DNA Sample
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

6.2.4. 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
- Perform 12-Lead ECG (refer to Section 6.7.5)
- Conduct pregnancy prevention counseling
- Assess adherence with study drug dosing regimen including pill count
- Collect any remaining study drug from the subject

- Obtain blood samples for tests:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - HCV resistance samples
  - HBV DNA Sample
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only

6.3. Posttreatment Assessments (± 5 days)

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

6.3.1. 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:

- Obtain vital signs (refer to Section 6.7.4)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Obtain blood samples for tests:
  - Hematology
  - Chemistry
  - HCV RNA
  - HCV resistance sample
  - HBV DNA Sample
- Obtain urine sample for:
  - Pregnancy test for females of childbearing potential only (refer to Section 6.7.9)

6.3.2. Posttreatment Weeks 12 and 24 (± 5 days)

The following procedures/assessments are to be completed for all subjects, 12 and 24 weeks after taking the last dose of study drug:

- Obtain weight
- Obtain vital signs (refer to Section 6.7.4)
- Obtain blood samples for tests:
  - HCV RNA
  - HCV resistance sample

6.4. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 3.4, Stopping Rules and Discontinuation Criteria). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.5. Early Termination (ET)

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

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
- Perform 12-Lead ECG (refer to Section 6.7.5)
- Conduct pregnancy prevention counseling
- Assess adherence with study drug dosing regimen including pill count
- Collect any remaining study drug from the subject

- Obtain blood samples for tests:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - HCV resistance samples
  - HBV DNA Sample
- 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 HCV resistance sample 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, Reticulocyte count and mean corpuscular volume (MCV).

Coagulation: INR, Prothrombin Activation %, 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, Total Bilirubin, Glucose, Lipase, Potassium, Sodium, phosphate, uric acid, 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), and serum FSH.

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.

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. Creatinine Clearance

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

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

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

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

6.7.7. HCV Resistance Sample

Plasma samples will be collected at Day 1 and at on-treatment visits at Weeks 2, 4, 8, and 12, early termination (if applicable), and all posttreatment visits 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. HBV DNA Sample

A sample for HBV DNA testing will be collected at on-treatment visits at Weeks 2, 4, 8, and 12 or early termination (if applicable) and posttreatment week 4. HBV DNA will only be tested when ALT > 2x Day 1 value in subjects who are HBsAb or HBcAb positive at Screening.

6.7.9. 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 through posttreatment 4. 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.

6.7.10. IL28B Testing

A blood sample will be obtained at Day 1 for specific genetic analysis of the rs12979860 (IL28B) genetic variant.

6.8. End of Study

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

6.9. Post Study Care

No poststudy ongoing care will be provided.

7. ADVERSE EVENTS

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 post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.5.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

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

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

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drug and Procedures

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

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

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

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

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

7.2.2. Assessment of Severity

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

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

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

Adverse Events

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

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

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required posttreatment follow-up period, must be reported to the eCRF database and Gilead Pharmacovigilance & Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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

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 PVE 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 PVE: Fax: PPD *E-mail:* PPD

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

7.4. Gilead Reporting Requirements

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

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

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

7.5. Special Situations Reports

7.5.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs associated with product complaints, occupational exposure with an AE, pregnancy reports regardless of an associated AE, and an AE in an infant following exposure from breastfeeding.

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

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

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

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

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

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

7.5.2. Instructions for Reporting Special Situations

7.5.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study drug(s) and throughout the study, including the post study drug(s) follow-up period, to Gilead PVE 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 PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE 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 PVE. Gilead PVE contact information is as follows:

Email: PPD

Fax: PPD

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

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

7.5.2.2. Reporting Other Special Situations

All other special situation reports must be reported on electronic special situations report form and transmitted to Gilead PVE within 24 hours of the investigator becoming aware of the situation. If for any reason it is not possible to record the special situation report (SSR) information electronically, ie, the eCRF database is not functioning, record the SSR on the paper special situation reporting form and submit within 24 hours to:

Gilead PVE: Fax: PPD

Email: PPD

As soon as it is possible to do so, any SSR reported via paper must be transcribed into the eCRF.

Database according to instructions in the eCRF completion guidelines. These reports must consist of situations that involve study drug(s) and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To evaluate the antiviral efficacy of therapy with SOF/VEL FDC for 12 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 by review of the accumulated safety data

The secondary objectives of this study are:

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

8.1.2. Primary Endpoint

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

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

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)
- The proportion of subjects with virologic failure

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CCI [redacted]

[redacted]

[redacted]

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 drug in this study includes SOF/VEL FDC. Last dose of study drug refers to the last dose of SOF/VEL FDC and will be used in the definition of treatment-emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various posttreatment time points.

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

8.2.1.2. Safety

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

8.3. Data Handling Conventions

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

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

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

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

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

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

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

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

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

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

8.4. Demographic Data and Baseline Characteristics

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

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

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

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 enrolled subjects have been followed through 12 weeks posttreatment or discontinued from study.

In the primary efficacy analysis, the SVR12 rate in FAS will be compared to the efficacy threshold rate of 78% (described in Section 8.7.1) using a two-sided exact one-sample binomial test at significance level of 0.05: ie, the hypothesis for superiority is as follows:

H0: SVR12 rate = 78%,

H1: SVR12 rate $\neq$ 78%

In addition, 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.

A success for the primary endpoint will be claimed if the following criterion is met: point estimate of SVR12 is statistically significantly higher than 78% by a two-sided exact one-sample binomial test at significance level 0.05, ie, p-value for above hypothesis testing for superiority is ≤ 0.05.

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 efficacy evaluation of the proportion of subjects who experience virologic failure and additional efficacy evaluations including HCV RNA values and change from baseline through end of treatment.

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

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, 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 the study drug administration up to 30 days after the last dose of the study drug will be summarized.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

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

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

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

- 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 (including death)
- All treatment-related SAEs
- AEs leading to premature discontinuation of the study drug

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

8.6.3. Laboratory Evaluations

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

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

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

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

8.6.4. Other Safety Evaluations

Individual data for vital sign measurements will be listed by subject and summarized descriptively by descriptive statistical summaries (n, mean, SD, median, Q1, Q3, minimum, and maximum), as appropriate.

8.7. Sample Size

8.7.1. Justification for Performance Threshold

Different studies have reported SVR rates for compensated cirrhotic subjects infected with HCV in Japanese populations {Asahina 2018, Krishnan 2018, Kumada 2015, Kumada 2016, Kumada 2017, Mizokami 2015, Omata 2014, Toyota 2017}. The SVR12 performance threshold of 78% for this study is determined as clinically relevant by referring to results in the confirmatory studies of approved DAA products in Japan.

The calculated average of the SVR12 rates for the studies is 96.2% (95% CI: 93.2%-98.2%). The point estimates of the SVR12 rates for compensated cirrhotic subjects ranged from 88.9% to 100% across the eight studies conducted in Japan. Among these studies, the average lower bound of the exact 95% confidence interval is 78%. Based on these considerations, a performance threshold of 78% was established for the primary efficacy endpoint. A success for the primary endpoint will be claimed if the following criterion is met: point estimate of SVR12 is statistically significantly higher than 78% by a two-sided exact one-sample binomial test at significance level 0.05, ie, p-value for the hypothesis testing for superiority is ≤ 0.05.

8.7.2. Determination of Sample Size on Basis of Threshold

This study intends to enroll patients who have compensated cirrhosis. A sample size of approximately 36 compensated cirrhotic Japanese subjects in the study will provide > 80% power to demonstrate superiority to a performance threshold of 78%, assuming an expected SVR12 rate of 96% with 12 weeks of SOF/VEL therapy (based on a two-sided exact one-sample binomial test of superiority at a significance level of 0.05). This expected 96% SVR12 rate, based on the observed SVR12 rate in ASTRAL-1 (GS-US-342-1138) for GT1b compensated cirrhotic subjects, represents a clinically relevant response for compensated cirrhotic patients,

who are at risk of PI-based liver toxicity and currently have no highly-effective PI-free pan-genotypic treatment options.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) Good Clinical Practices and applicable laws and regulations.

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}.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide 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.

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

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

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

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person

conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

9.1.5. Confidentiality

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

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

9.1.6. Study Files and Retention of Records

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

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

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

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

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

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

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

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

9.1.7. 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 9.1.6.

9.1.8. Investigational Medicinal Product Accountability and Return

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

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

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

9.1.9. Inspections

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

9.1.10. 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 IRB or IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. 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 9.1.5).

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

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

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3 Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic HCV Infection and Compensated Cirrhosis

GS-US-342-5531, Original, 03 July 2019

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

PPD

PPD (Printed)

PPD

Signature PPD

8 July 2019

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 drug and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

	Screening	Day 1[a]	Treatment Week (± 3 days)					Posttreatment Week (± 5 days)		
			1	2	4	8	12/ET[b]	4	12	24
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X					X			
Height	X									
Weight	X	X					X		X	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[d]	X	X					X			
Adverse Events and Concomitant Medications[e]	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling		X					X	X		
Imaging for HCC[f]	X									
Review of Study Drug Adherence and Drug Accountability[g]			X	X	X	X	X			
Study Drug Dispensing[h]		X			X					
Laboratory Assessments										
Hematology, Chemistry	X	X		X	X	X	X	X		
Coagulation (Prothrombin activation %, PT, aPTT and INR)	X	X					X			
Urinalysis	X									
HCV RNA	X	X		X	X	X	X	X	X	X
HCV resistance samples		X		X	X	X	X	X	X	X

	Screening	Day 1[a]	Treatment Week (± 3 days)					Posttreatment Week (± 5 days)		
			1	2	4	8	12/ET[b]	4	12	24
HBV DNA sample[i]				X	X	X	X	X		
Serum or Urine Pregnancy Test[j]	X	X			X	X	X	X		
Serum FSH[k]	X									
HCV Genotyping	X									
IL28B Genotype		X								
HCV Ab, HIV Ab, HBsAg, HBsAb, HBcAb	X									
HbA1c	X									
FibroTest®	X									

a Day 1 assessments must be performed prior to dosing.
b ET = early termination.
c Vital signs include resting blood pressure, pulse, respiratory rate and temperature.
d Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording. The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities.
e Adverse events and concomitant medications will be collected up to 30 days after the last dose of all study drug.
f 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 within 4 months of Day 1.
g Study drug will be reconciled at every post- Day 1 visit by the investigator in order to monitor the subject's adherence with the study drug. Subjects must be instructed to bring back all bottles of study drug in the original container at every post- Day 1 visit through the end of treatment.
h The interactive web response system (IWRS) will provide direction on the specifics of each subject's study drug dispensing.
i Reflex testing done only when ALT > 2x Day 1 value in subjects who are HBsAb or HBcAb positive at Screening.
j All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks through posttreatment Week 4. 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.
k Women of any age with amenorrhea of ≥ 12 months (see Appendix 4).

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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Infant <1 Year	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 to <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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 .51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated 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
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

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 weakness 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
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)

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

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

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

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

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

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

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

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

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

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

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) 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. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

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

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

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 FDC during pregnancy in humans have not been evaluated. Please refer to the latest version of the Investigator's Brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Day 1 visit prior to enrollment. Pregnancy tests will be performed every 4 weeks throughout duration of trial including posttreatment Week 4 visit. 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 FDC.

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom from the date of Screening until 30 days after the last dose of SOF/VEL FDC.
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure) (unapproved in Japan)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)
  - Barrier methods (one female barrier and one male barrier must be used in combination)
    - 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 (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 treatment and until at least 30 days after the last dose of SOF/VEL FDC.

3) 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 FDC 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 FDC.

Male subjects must also refrain from sperm donation during treatment and until at least 30 days after the last dose of SOF/VEL FDC.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. 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 during the study or within 30 days of last study drug dose must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.5.2.