CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic HCV Infection
Sponsor:	Gilead Sciences, Inc.
IND No.:	This is a non-IND study
Clinical Trials.gov Identifier:	Not Applicable
EudraCT No.:	Not Available
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-342-5532
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 25 June 2019 Amendment 1: 04 Oct 2019

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

PROTOCOL SYNOPSIS
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Study Title:	A Phase 3b Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic HCV Infection
IND Number:	This is a non-IND study
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	Not Available
Study Centers Planned:	Approximately 25 Centers in Korea
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 and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) 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 weeks after cessation of treatment (SVR4) • To evaluate the proportion of subjects with virologic failure • To evaluate the emergence of viral resistance to SOF, VEL and VOX 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. Cohort 1: Approximately 50 subjects with chronic HCV infection, genotype 1 or 2, will be enrolled and treated with SOF/VEL FDC for 12 weeks. Subjects may be treatment-naïve or treatment-experienced with Interferon (IFN)-based treatments. Cohort 2: Approximately 30 subjects with chronic HCV infection, genotype 1, will be enrolled and treated with SOF/VEL/VOX FDC for 12 weeks. Subjects will be treatment-experienced with NS5A direct acting antiviral (DAA)-based treatments.
Number of Subjects Planned:	Approximately 80 subjects
Target Population:	Treatment-naïve and Treatment-experienced adults with chronic HCV infection with HCV genotype 1 or 2.
Duration of Treatment:	Subjects in both cohorts 1 and 2 will be treated for 12 weeks
Diagnosis and Main Eligibility Criteria:	Chronic HCV-infected male and non-pregnant/non-lactating female subjects, aged 19 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 and Week 12 visits. Screening assessments will include medical history, physical examination, height, weight, vital signs, 12-lead electrocardiogram (ECG), adverse events (AEs) related to screening procedures, prior and concomitant medications, liver imaging to exclude hepatocellular carcinoma (HCC) within 4 months of Day 1 for subjects with cirrhosis and within 6 months of Day 1 for subjects without cirrhosis, safety laboratory tests (including hematology, chemistry, coagulation, urinalysis), HCV RNA, serum β-hCG (females of childbearing 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 or absence of cirrhosis (including FibroTest®).

	On-treatment assessments include physical examination, weight, vital signs, 12-Lead ECGs, AEs, concomitant medications, pregnancy prevention counseling, review of study drug adherence and drug accountability, study drugs dispensing, safety laboratory tests (including hematology, chemistry, coagulation), HCV RNA, HCV resistance samples, HBV DNA sample (only for HBcAb positive subjects at Screening), pharmacokinetic samples, urine pregnancy tests (females of childbearing potential only), and IL28B genotyping. Posttreatment assessments include weight, vital signs, AEs, concomitant medications, pregnancy prevention counseling, safety laboratory tests (including hematology and chemistry), HCV RNA, HCV resistance samples, HBV DNA sample (only for HBcAb positive subjects at Screening), and urine pregnancy tests (females of childbearing potential only). CCI [redacted]
Test Product, Dose, and Mode of Administration:	Cohort 1: SOF/VEL FDC is manufactured as a 400/100 mg FDC tablet for oral administration. Subjects will take 1 tablet daily with or without food. Cohort 2: SOF/VEL/VOX FDC is manufactured as a 400/100/100 mg FDC tablet for oral administration. Subjects will take 1 tablet daily with 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.
Pharmacokinetics:	A single PK blood sample will be collected at Weeks 2, 4, 8, 12, and Early Termination (if applicable) for all subjects. CCI [redacted]

CCI [redacted]

Statistical Methods:

The primary efficacy endpoint for the study is SVR12 in all enrolled and treated subjects. No hypothesis testing will be performed.

Secondary efficacy endpoints include SVR4.

Continuous endpoints (except for safety endpoints) will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum) by cohort. Categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition by cohort.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) for continuous data by cohort.

For Cohort 1, with approximately 50 subjects enrolled into the study, the 2-sided 95% exact confidence interval (CI) using the binomial distribution (Clopper-Pearson method) of the SVR12 rate will be from 86.3% to 99.5%, assuming the expected SVR12 rate is 95%.

For Cohort 2, with approximately 30 subjects enrolled into the study, the 2-sided 95% exact CI using the binomial distribution (Clopper-Pearson method) of the SVR12 rate will be from 82.8% to 99.9%, assuming the expected SVR12 rate is 95%.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
Ab	antibody
ABW	actual body weight
AE(s)	adverse event(s)
ALT	alanine aminotransferase (also SGPT)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
ASV	asunaprevir
BMI	body mass index
CCDS	Company Core Data Sheet
CFR	Code of Federal Regulations
CI	confidence interval
ClCr	creatinine clearance
CRO	contract research organization
CSR	clinical study report
DAA	direct-acting antiviral
DCV	daclatasvir
Dl	Deciliter
DSV	dasabuvir
EBR	elbasvir
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eg	example given
eSAE	electronic serious adverse event
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
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
i.e.	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
IVDU	Intravenous Drug Use
IWRS	interactive web response system
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
OBV	ombitasvir
OAT	organic anion transporter
PCR	polymerase chain reaction
PI	protease inhibitor
PIB	pibrentasvir
PK	pharmacokinetic
PPIs	proton-pump inhibitors
PT	preferred term or prothrombin time
PTV	paritaprevir
Q1	quartile 1
Q3	quartile 3
RBC	red blood cell count
RBV	ribavirin
RNA	ribonucleic acid
RTV	ritonavir
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	System organ class
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
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
VOX	Voxilaprevir
β-hCG	β-human chorionic gonadotropin
µg	microgram

1. INTRODUCTION

1.1. Background

In Korea, chronic HCV infection is one of the leading causes of chronic liver disease and hepatocellular carcinoma (HCC) {Kwon 2019}. The prevalence of HCV in South Korea has been reported to be 0.78% {Kim 2013}. HCV infection accounts for 10.4% of causative disease of HCC, which makes it the 2nd major cause following Hepatitis B Virus (HBV) infection {Hwang 2010}. The age-standardized prevalence of HCV antibody (HCV Ab) in patients greater than 40 years of age is reported to be on the order of 1.3% which equates to around 193,000 people {Shin 2006}. The prevalence of HCV infection increases with age and peaks in those aged 60 years and older, since the majority of infections occurred via contaminated blood transfusions prior to the introduction of blood-donor HCV Ab screening in 1991 {Lim 2009} {Suh 2006}.

Since the decline of transfusion related hepatitis C, the majority of new infections are behavior-related. Of particular note is the practice of acupuncture for chronic illnesses including joint disease, and pain sequelae of trauma. Shin, et al reported results of a case study in which 34.1% of men and 62.9% of women in rural Korea reported multiple acupuncture procedures with the associated risk of HCV infection being 38% for men and 55% for women {Shin 2006}. Additionally, more recent study reports that history of blood transfusion and intravenous drug use (IVDU) were found in only 14.3% and 5.6% of the cohort, respectively, suggesting that the majority of patients may have been infected through other settings, such as cosmetics or in healthcare {Kwon 2019}. The predominant HCV genotypes (GT) in Korea are GT-1b and GT-2a which are roughly present in equal proportions and combined account for around 80-90% of infections {Kwon 2019}, {Kwon 2019}, {Shin 2006}.

As of today, the direct-acting antivirals (DAAs) sofosbuvir (SOF), ledipasvir/sofosbuvir (LDV/SOF), daclatasvir (DCV), asunaprevir (ASV), ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (RTV), dasabuvir (DSV), elbasvir (EBR)/grazoprevir (GZR), and glecaprevir (GLE)/pibrentasvir (PIB) are approved in Korea for treatment of chronic HCV {The Korean Association for the Study of the Liver (KASL) 2018}. Despite the availability of these highly efficacious DAA regimens with high SVR rates, there is still an unmet medical need for patients with chronic HCV in Korea. First, as stated above, the elderly population represents the majority of the patient pool, and they are faced with increasing number of comorbidities and co-medications which may have significant and complex interactions with currently available DAAs {The Korean Association for the Study of the Liver (KASL) 2018}. Secondly, protease inhibitors (PIs) are contraindicated in patients with decompensated cirrhosis due to toxicity from increased drug concentrations in the liver {The Korean Association for the Study of the Liver (KASL) 2018}. Currently, the only PI-free regimen approved for treating patients with decompensated cirrhosis in Korea is indicated for GT1 patients. Lastly, there is a small, but significant group of patients who were treated with the DAA regimen of daclatasvir and asunaprevir following its early approval in Korea that subsequently failed treatment due to the

low efficacy of the combination. As the treatment regimen included an NS5A inhibitor, these patients currently do not have a suitable treatment option {Kwon 2019}.

These unmet needs can largely be resolved with SOF/VEL FDC, a pangenotypic PI-free regimen and SOF/VEL/VOX FDC, a DAA retreatment regimen that is efficacious in patients that failed an NS5B, NS5A or PI combination.

Therefore, the aim of this study is to examine the safety and efficacy of SOF/VEL FDC and SOF/VEL/VOX FDC in Korean patients.

1.2. Sofosbuvir/Velpatasvir Fixed-Dose Combination (FDC) and Sofosbuvir/Velpatasvir/Voxilaprevir FDC

SOF/VEL FDC is a co-formulation of SOF 400 mg and VEL 100 mg into a single tablet. SOF/VEL/VOX FDC is a co-formulation of SOF 400 mg, VEL 100 mg, and VOX 100 mg into a single tablet.

Sofosbuvir (SOF) is a nucleotide analog HCV NS5B polymerase inhibitor.

Velpatasvir (VEL) is a pangenotypic HCV NS5A inhibitor.

Voxilaprevir (VOX) is a NS3/4A protease inhibitor with potent antiviral activity against genotypes 1 to 6 HCV.

Epclusa® (SOF/VEL FDC) was first approved in the United States on 28 June 2016 and is currently approved in 75 countries as of 10 April 2019. Cumulative patient exposure to Epclusa® since first marketing approval is estimated to be 64,339 patient-years of treatment as of 27 December 2018. This estimate is based on sales data, which generally overestimate patient exposure because stocks of drug are accumulated by distributors and pharmacies.

Vosevi® (SOF/VEL/VOX FDC) was first approved in the United States on 18 July 2017 and is currently approved in 44 countries as of 07 May 2019. Cumulative patient exposure to Vosevi® since first marketing approval is estimated to be 3,677 patient-years of treatment as of 17 January 2019. This estimate is based on sales data, which generally overestimate patient exposure because stocks of drug are accumulated by distributors and pharmacies.

1.2.1. General Information

For further information on SOF/VEL FDC (Epclusa®) and on SOF/VEL/VOX FDC (Vosevi®), refer to the current Investigator's Brochures and the individual components for each, 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 and SOF/VEL/VOX FDC

Two Phase 3 studies, GS-US-342-1138 (ASTRAL-1) and GS-US-342-1139 (ASTRAL-2), evaluated the efficacy and safety of SOF/VEL FDC in subjects with genotype 1a, 1b, 2, 4, 5, 6 HCV infection, without cirrhosis or with compensated cirrhosis.

Refer to the SOF/VEL FDC Investigator's Brochure for additional information.

Two Phase 3 studies, POLARIS-1 (GS-US-367-1171) and POLARIS-4 (GS-US-367-1170) evaluated the efficacy and safety of SOF/VEL/VOX FDC in DAA-experienced subjects with genotypes 1-6 with chronic HCV infection, without cirrhosis or with compensated cirrhosis.

Refer to the SOF/VEL/VOX FDC Investigator's Brochure for additional information.

1.2.3. Clinical Pharmacology

The PK of SOF and VEL in Asian subjects has been extensively studied in dedicated Phase 1 studies (GS-US-334-0111 and GS-US-367-1905), and phase 2 and 3 studies in the SOF/VEL clinical program, as part of Asian subject subpopulations.

These data have indicated that there is no clinically meaningful effect of Asian race on the PK of SOF, its metabolites GS-566500 and GS-331007, or VEL, and supported the approval of Sovaldi® (SOF), Harvoni® (LDV/SOF FDC), and Epclusa (SOF/VEL FDC) in China.

The PK of SOF, its metabolites GS-566500 and GS-331007, VEL, and VOX were assessed in healthy Japanese subjects in the Phase 1 study GS-US-367-1905. The results of this analysis demonstrate that there was no clinically significant impact of Asian race on the PK of SOF, its metabolites, VEL, or VOX.

Additionally, the PK of SOF, GS-331007, VEL, and VOX were analyzed in the SOF/VEL/VOX clinical program, in which a substantial number of Asian subjects were enrolled. The results of these analyses demonstrate no clinically significant impact of Asian race on the population PK model-based exposures of SOF, GS-331007, VEL, or VOX compared with a predominantly Caucasian reference population. Importantly, race was not identified as a clinically meaningful covariate in the population PK models for SOF, GS-331007, VEL, or VOX.

Collectively, these data demonstrate no clinically significant differences in the PK of SOF, its metabolites, VEL, or VOX in healthy and HCV-infected Asian and non-Asian subjects, and they support the use of SOF/VEL FDC, and SOF/VEL/VOX FDC for the treatment of HCV-infected Korean patients.

1.3. Rationale for This Study

The population for Cohort 1 will be subjects with chronic HCV Genotype 1 or 2 who are either treatment-naïve or treatment-experienced with IFN-based treatments. As a large proportion of the Korean HCV population are elderly there is a need for a highly efficacious regimen that is PI-free and has a favorable direct drug interaction (DDI) profile. Therefore, this study aims to examine the safety and efficacy of 12 weeks of SOF/VEL, a PI-free, pangenotypic regimen, in a Korean population.

The population for Cohort 2 will be subjects with chronic HCV infection without cirrhosis or with compensated cirrhosis and who have previously not achieved SVR following treatment with an NS5A DAA agent. With the increasing use of NS5A inhibitors with or without NS5B inhibitors, the unmet medical need for effective retreatment options for the few patients who fail these regimens will increase. This study will examine the safety and efficacy of SOF/VEL/VOX for 12 weeks for these patients in Korea.

1.4. Rationale for Dose Selection

1.4.1. Rationale for Dose Selection for SOF/VEL FDC

Subjects in Cohort 1 of 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 the Phase 3 ASTRAL 1-3 studies (GS-US-342-1138, GS-US-342-1139, GS-US-342-1140), treatment of HCV infected subjects infected without cirrhosis or with compensated cirrhosis for 12 weeks with SOF/VEL FDC was well tolerated and resulted in high SVR12 rates.

Refer to the SOF/VEL FDC Investigator's Brochure for additional information.

1.4.2. Rationale for Dose Selection of SOF/VEL/VOX FDC

Subjects in Cohort 2 of this study will be administered SOF/VEL/VOX FDC, a co-formulation of SOF 400 mg, VEL 100 mg and VOX 100 mg that is approved in the US and other markets as Vosevi® for the treatment of HCV infection in adults.

In the POLARIS-1 study, treatment with SOF/VEL/VOX FDC for 12 weeks in subjects with HCV infected subjects with Genotype 1, NS5A-inhibitor experienced without cirrhosis or with compensated cirrhosis (POLARIS-1) was highly efficacious and well tolerated.

Refer to the SOF/VEL/VOX FDC Investigator's Brochure for additional information.

1.5. Risk/Benefit Assessment for the Study

This study will provide information on the safety and efficacy of the combination of SOF/VEL FDC for 12 weeks in Korean patients that are treatment-naïve or treatment-experienced with IFN-based treatment and SOF/VEL/VOX FDC for 12 weeks in Korean patients that are treatment-experienced with NS5A DAA-based treatments.

The safety profile of SOF/VEL FDC has been established in 3,345 subjects, included in the Phase 3 studies, Phase 2 studies and Phase 1 studies which enrolled subjects with compensated and decompensated cirrhosis. 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.

The safety assessment of SOF/VEL/VOX FDC has been established based on data from Phase 3 clinical studies in which > 1,000 subjects received SOF/VEL/VOX FDC for 12 weeks. There were no patients receiving SOF/VEL/VOX FDC for 12 weeks who permanently discontinued treatment due to adverse reactions. Overall, SOF/VEL/VOX FDC for 12 weeks was safe and well tolerated in patients for the treatment of chronic HCV infection in adults without cirrhosis or with compensated cirrhosis who have failed prior treatment with a HCV DAA.

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

1.6. Compliance

This study will be conducted in compliance with this protocol, GCP, and all applicable regulatory requirements.

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the antiviral efficacy of therapy with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) for 12 weeks and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) 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 weeks after cessation of treatment (SVR4)

- To evaluate the proportion of subjects with virologic failure

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

3. STUDY DESIGN

3.1. Study Design and Study Treatments

This is a multicenter, open-label study in approximately 80 subjects with chronic HCV infection.

Cohort 1: Approximately 50 subjects with chronic HCV infection, genotype 1 or 2, will be enrolled and treated with SOF/VEL FDC for 12 weeks. Subjects may be treatment-naïve or treatment-experienced with IFN-based treatments.

Cohort 2: Approximately 30 subjects with chronic HCV infection, genotype 1, will be enrolled and treated with SOF/VEL/VOX FDC for 12 weeks. Subjects will be treatment-experienced with NS5A DAA-based treatments.

3.2. Duration of Treatment

Subjects in both Cohorts 1 and 2 will be treated for 12 weeks.

The total time to complete all study visits is approximately 28 weeks (30 weeks for those requiring an extension to the Screening period).

- 28 days (4 weeks) screening period [up to 42 days (6 weeks) for extenuating circumstances may be granted]
- 12 weeks study treatment period
- 12 weeks posttreatment period

3.3. 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.

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

Subjects who permanently discontinue SOF/VEL FDC or SOF/VEL/VOX FDC should complete an Early Termination (ET) visit. For subjects who have completed an ET visit, the posttreatment Week 4 and 12 visits will be completed after the last dose of study drug.

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 3.3.2)
- 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)

3.3.1. Toxicity Based Stopping Criteria

The Medical Monitor must be consulted prior to study drug discontinuation of SOF/VEL FDC or SOF/VEL/VOX 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 or SOF/VEL/VOX FDC dose reduction. If either SOF/VEL FDC or SOF/VEL/VOX 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 and Week 12 visits must also be scheduled, 4 and 12 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 (ULN) 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 and SOF/VEL/VOX FDC

3.3.2. 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 as described above 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 80 adults with chronic HCV infection will be enrolled in this study, including approximately 50 subjects in Cohort 1 and approximately 30 subjects in Cohort 2.

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

4.2. Inclusion Criteria

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

1) Willing and able to provide written informed consent

2) Male or female, age ≥ 19 years at Screening

3) Body mass index (BMI) ≥ 18 kg/m^2

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) Cohort 1 only: HCV genotype 1 or 2 assessed at Screening by the Central Laboratory, and HCV treatment status defined as one of the following, with medical records that include sufficient detail to allow for categorization as follows:

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

    b) HCV treatment-experienced defined as prior treatment failure to a regimen containing interferon either with or without RBV that was completed at least 8 weeks prior to Day 1. Subject must not have discontinued the prior regimen that resulted in virologic failure due to an adverse event. *Note: See Exclusion Criterion #6: prior exposure to any direct acting antiviral agent targeting the HCV NS5A or NS5B is prohibited.*

7) Cohort 2 only: HCV genotype 1, assessed at Screening by the Central Laboratory, and treatment experienced with a NS5A inhibitor-containing regimen of at least a 4-week duration

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

b) Subjects must not have discontinued the most recent regimen due to either an adverse event or virologic failure due to noncompliance

c) The subject's medical records must include sufficient detail of prior treatment(s) to confirm eligibility

8) Cirrhosis Determination:

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

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

ii) Fibroscan within 4 months of Day 1, showing cirrhosis as reflected by a result > 12.5 kPa

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

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

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

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

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

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

a) Within 4 months for subjects with cirrhosis

b) Within 6 months for subjects without cirrhosis

10) Females of childbearing potential (as defined in Appendix 4) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to 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 until at least 30 days after the last dose SOF/VEL FDC or SOF/VEL/VOX FDC.

13) Lactating females must agree to discontinue nursing before study drug is administered.

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 drugs

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

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

   e) Solid organ transplantation

   f) Significant pulmonary disease

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

   h) Porphyria

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

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

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

   l) Prior or current hepatocellular carcinoma (HCC)

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

2) Infection with human immunodeficiency virus (HIV) at Screening

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

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

5) Screening ECG with clinically significant abnormalities

6) Cohort 1 only: Prior exposure to any HCV NS5A or NS5B inhibitor

7) 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)

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

9) 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 or SOF/VEL/VOX FDC

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

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

    b) AST > 10 x ULN

    c) Direct bilirubin > 1.5 × ULN

    d) Platelets < 50,000/μL

    e) HbA1c > 8.5%

    f) 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

11) Use of any prohibited concomitant medications as described in Section 5.4

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

13) Known hypersensitivity or contraindication to sofosbuvir, velpatasvir, voxilaprevir 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 two different subject cohorts with chronic HCV infection. No blinding is required.

All subjects will be enrolled to receive SOF/VEL FDC (Cohort 1) or SOF/VEL/VOX FDC (Cohort 2) for 12 weeks.

5.2. Description and Handling of SOF/VEL FDC and SOF/VEL/VOX FDC

5.2.1. Formulation

5.2.1.1. Formulation SOF/VEL FDC

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.

5.2.1.2. Formulation SOF/VEL/VOX FDC

The SOF/VEL/VOX FDC (400/100/100 mg) tablets are beige, capsule-shaped film-coated tablets debossed with "GSI" on one side and a "3" on the other side. In addition to the active ingredients, SOF/VEL/VOX FDC tablets also contain copovidone, microcrystalline cellulose, lactose monohydrate, silicon dioxide, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol 3350, talc, iron oxide yellow, iron oxide red, and ferrosoferric oxide.

5.2.2. Packaging and Labeling

5.2.2.1. Packaging and Labeling SOF/VEL FDC

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 study centers in Korea shall be labeled to meet all applicable requirements of the Ministry of Food and Drug Safety (MFDS) guideline to Good Manufacturing Practice Annex 11 (Investigational Medicinal Products) and/or local regulations as applicable.

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

5.2.2.2. Packaging and Labeling SOF/VEL/VOX FDC

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

SOF/VEL/VOX FDC bottles to be distributed to study centers in Korea shall be labeled to meet all applicable requirements of the Ministry of Food and Drug Safety (MFDS) guideline to Good Manufacturing Practice Annex 11 (Investigational Medicinal Products) and/or local regulations as applicable.

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

5.2.3. Storage and Handling

Both study drugs, SOF/VEL FDC and SOF/VEL/VOX FDC tablets, should be stored below 30 °C(86 °F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs 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, study drugs should not be stored in a container other than the container in which they are supplied. Keep the bottle tightly closed to protect from moisture.

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 and SOF/VEL/VOX FDC tablets.

5.3. Dosage and Administration of SOF/VEL FDC and SOF/VEL/VOX FDC

5.3.1. Dosing and Administration of SOF/VEL FDC (Cohort 1)

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.

5.3.2. Dosing and Administration of SOF/VEL/VOX FDC (Cohort 2)

SOF/VEL/VOX FDC tablet is to be administered once daily with 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/VOX 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/VOX 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 eCRF (including all blood products).

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

a) Hematologic stimulating agents (eg, erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)

b) Chronic use of systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (eg, infliximab)

c) Investigational agents or devices for any indication

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

Table 5-1 below contains examples of medications that are prohibited from **28 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 (SOF/VEL FDC and SOF/VEL/VOX FDC, unless specified)	Use with Caution Cohort 1 (SOF/VEL FDC)	Use with Caution Cohort 2 (SOF/VEL/VOX FDC)
Acid Reducing Agents		Proton- Pump Inhibitors[a], H2-Receptor Antagonists[b], Antacids[c]	Proton- Pump Inhibitors[a], H2-Receptor Antagonists[b], Antacids[c]
Anticoagulants			Dabigatran Etexilate[d]
Anticonvulsants[e]	Phenytoin, Carbamazepine, Phenobarbital		
Antimycobacterials[e]	Rifampicin, Rifabutin, Rifapentine[g]		
Cardiac Medications[f]	Amiodarone[g]	Digoxin[h]	Digoxin[h]
Herbal/Natural Supplements[e]	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)		
HMG-CoA Reductase Inhibitors[i]	Pitavastatin or Rosuvastatin (Disallowed with SOF/VEL/VOX FDC)	Atorvastatin[j], Rosuvastatin (≤10 mg/day)[j]	Atorvastatin[k], Fluvastatin[k], Lovastatin[k], Pravastatin (<40 mg/day)[j], Simvastatin[k]
Immunosuppressants	Cyclosporine (Disallowed with SOF/VEL/VOX FDC)[f]		
Other	Bosentan[b], Modafinil[b], Sulfasalazine[c], Methotrexate[c]		

a Proton pump inhibitors (PPIs) doses comparable with omeprazole 20mg can be administered with SOF/VEL FDC (when SOF/VEL FDC is administered with food) or with SOF/VEL/VOX FDC. The 28 day washout period does not apply to PPIs, which can be taken up to 7 days before Day 1

b H2 receptor antagonists (H2RAs) must not exceed a dose of 40 mg famotidine or equivalent and can be taken simultaneously with SOF/VEL FDC or SOF/VEL/VOX FDC and/or staggered by 12 hours. The 28 day washout period does not apply to H2RAs, which can be taken up to 7 days before Day 1.

c Antacids that directly neutralize stomach acid may not be taken within 4 hours (before or after) of SOF/VEL FDC or SOF/VEL/VOX FDC administration.

d Administration of SOF/VEL/VOX FDC with dabigatran etexilate results in increased concentrations of dabigatran. Clinical monitoring of dabigatran is recommended when coadministered with SOF/VEL/VOX FDC. Refer to dabigatran etexilate prescribing information for dose modification recommendations in the setting of moderate renal impairment.

e May result in a decrease in the concentration of study drugs.

f May result in an increase in the concentration of study drugs and/or concomitant medications

g 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

h Monitor for signs and symptoms of digoxin toxicity.

i Use with SOF/VEL FDC of SOF/VEL/VOX FDC may result in increased concentrations of HMG CoA Reductase Inhibitors. The 28 day washout period does not apply to HMG CoA Reductase Inhibitors, which can be taken up to the day before Day 1.

j Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

k Coadministration with SOF/VEL/VOX FDC may increase the concentrations of atorvastatin, fluvastatin, lovastatin, and simvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Use the lowest approved statin dose. If higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment.

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 and SOF/VEL/VOX FDC

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

SOF/VEL FDC and SOF/VEL/VOX 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 IMP kits.
- Record the date, subject number and the IMP kit number dispensed.
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

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 the Day 1 visit to determine eligibility for participation in the study. The Screening window can be extended up to 42 days 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:

[redacted]

- Determine inclusion and exclusion eligibility
- Obtain medical history (refer to Section 6.7.3), including:

  Hepatitis C treatment history, if applicable

  - Regimen(s)
  - Dates of previous treatment(s)
  - Response to previous treatment
    - Nonresponder: Subject did not achieve undetectable HCV RNA while on treatment.

  - Relapse/Breakthrough: Subject achieved undetectable HCV RNA during treatment or within 4 weeks of the end of treatment, but did not achieve SVR
  - Discontinuation for any reason

- Obtain details of prior and concomitant medications
- Complete physical examination (refer to Section 6.7.4)
- Obtain height and weight
- Obtain vital signs (refer to Section 6.7.5)
- Perform 12-Lead ECG (refer to Section 6.7.6)
- 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 for subjects with cirrhosis and within 6 months of Day 1 for subjects without cirrhosis.
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.
- Obtain blood samples for test:

  Hematology

  Chemistry

  Coagulation tests

  HCV RNA

  HCV Genotype

  HCV antibody, HIV antibody, HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), HBV core antibody (HBcAb)

  HbA1c

  Serum β-hCG pregnancy test for females of childbearing potential (refer to Section 6.7.10)

  Serum FSH (only for women of any age with amenorrhea of ≥ 12 months (refer to Appendix 4)

  Fibrotest®

- Obtain a Urine sample for:

  Urinalysis

  Urine drug screen

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 28 Days after screening for enrollment into the study. The Screening window can be extended up to 42 days in extenuating circumstances with sponsor approval.

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 6.7.4)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.5)
- Perform 12-Lead ECG (refer to Section 6.7.6)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Obtain blood samples for tests:

  Hematology

  Chemistry

  Coagulation tests

HCV RNA

HCV resistance samples (refer to Section 6.7.8)

IL28B Genotype (refer to Section 6.7.11)

- Obtain urine sample for:

  Pregnancy test for females of childbearing potential only (refer to Section 6.7.10)

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
- Observe the subject taking the first dose of study drug

  Note: SOF/VEL/VOX FDC to be taken with food.

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, or qualified designee, 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 6.7.5)
- Perform 12 Lead ECG (refer to section 6.7.6)
- Assessment of AEs and concomitant medications
- Review of study drug adherence and 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 6.7.5)
- Assessment of AEs and concomitant medications
- Review of study drug adherence and dosing regimen including pill count

- Obtain blood sample for tests:

  Hematology

  Chemistry

  Coagulation tests

  HCV RNA

  HCV resistance samples

  HBV DNA Sample (only for HBcAb positive subjects at Screening)

  Single PK (refer to Section 6.7.2.1)

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6.2.3. Weeks 4 and 8 (± 3 Days)

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

- Obtain vital signs (refer to Section 6.7.5)
- Assessment of AEs and concomitant medications
- Review of study drug adherence and dosing regimen including pill count
- Dispense study drug as directed by the IWRS (Week 4 only)
- Obtain blood sample for tests:

  Hematology

  Chemistry

  Coagulation tests

  HCV RNA

  HCV resistance samples

  HBV DNA Sample (only for HBcAb positive subjects at Screening)

  Single PK (refer to Section 6.7.2.1)

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- Obtain urine sample for:

  Pregnancy test for females of childbearing potential only (refer to Section 6.7.10)

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 (see Section 6.7.4)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.5)
- Perform 12-Lead ECG (refer to section 6.7.6)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Review of study drug adherence and dosing regimen including pill count
- Collect any remaining study drug from the subject
- Obtain blood sample for tests:

  Hematology

  Chemistry

  Coagulation tests

  HCV RNA

  HCV resistance samples

  HBV DNA Sample (only for HBcAb positive subjects at Screening)

  Single PK (refer to Section 6.7.2.1)

- Obtain urine sample for:

  Pregnancy test for females of childbearing potential only (refer to Section 6.7.10)

6.3. Posttreatment Assessments

The posttreatment Weeks 4 and 12 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 6.7.5)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Obtain blood samples for tests:

  Hematology

  Chemistry

  HCV RNA

  HCV resistance samples

  HBV DNA Sample (only for HBcAb positive subjects at Screening)
- Obtain urine sample for:

  Pregnancy test for females of childbearing potential only (refer to Section 6.7.10)

6.3.2. Posttreatment Week 12 (± 5 Days)

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

- Obtain weight
- Obtain vital signs (refer to Section 6.7.5)
- Obtain blood samples for tests:

  Chemistry

  HCV RNA

HCV resistance samples

HBV DNA Sample (only for HBcAb positive subjects at Screening)

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 3.3, 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

For subjects who have completed an ET visit, the posttreatment Week 4 and 12 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:

- Complete physical examination (refer to Section 6.7.4)
- Obtain weight
- Obtain vital signs (refer to Section 6.7.5)
- Perform 12-Lead ECG (refer to Section 6.7.6)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Review of study drug adherence and 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 (only for HBcAb positive subjects at Screening)

Single PK (refer to Section 6.7.2.1)

- 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: International Normalized Ratio (INR), Prothrombin time (PT), Activated partial thromboplastin time (aPTT)

Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatine Kinase, Creatinine, Direct Bilirubin, 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 including HBsAb, HBsAg, or HBcAb. HBV DNA (reflex testing done when ALT > ULN or > Day 1 value in subjects who are 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. Pharmacokinetic (PK) Sampling

6.7.2.1. Single PK Samples

Single PK blood samples will be collected for all subjects at Weeks 2, 4, 8, 12, and Early Termination (if applicable) and archived for PK analysis of SOF (and its metabolites GS-566500 and GS-331007), VEL, and VOX (as appropriate). The exact time the study drug was taken and whether or not the study drug was taken with food on PK assessment days will be recorded in the source documents and eCRF.

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[redacted]

6.7.3. 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.

6.7.4. 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.

6.7.5. Vital Signs

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

Blood pressure will be measured using the following standardized process:

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

6.7.6. 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.

6.7.7. Creatinine Clearance

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

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

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

S_{cr} serum creatinine (mg/dL)

6.7.8. 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. CCI [redacted]

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

6.7.9. HBV DNA Sample

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

6.7.10. Pregnancy Testing

All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks through posttreatment Week 4 and at Early Termination, if applicable. 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.

6.7.11. 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 12 visit, regardless of treatment duration or early termination of study drug.

6.9. Poststudy Care

No poststudy ongoing care will be provided.

7. ADVERSE EVENTS

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 (i.e., 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 or CRO:

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

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study IMP, and they 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 (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead 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 authorization 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, i.e., 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 (CFR), 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 (SSR) 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 medication and throughout the study, including the post study drug follow-up period, to the or Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

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

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

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

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

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to or 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 drugs 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, i.e., 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 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are as follows:

- To evaluate the antiviral efficacy of therapy with SOF/VEL FDC for 12 weeks and SOF/VEL/VOX FDC for 12 weeks as measured by the proportion of subjects with 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 weeks after cessation of treatment (SVR4)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the emergence of viral resistance to SOF, VEL and VOX during treatment and after cessation of treatment

8.1.2. Primary Endpoint

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

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

8.1.3. Secondary Endpoint

Secondary endpoints include the following:

- The proportion of subjects with SVR4 (HCV RNA < LLOQ 4 weeks after discontinuation of study treatment)
- The proportion of subjects with virologic failure
- The proportion of subjects with HCV RNA < LLOQ on treatment
- HCV RNA change from baseline
- ALT normalization

8.2. Analysis Conventions

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

The study drugs in this study include SOF/VEL FDC and SOF/VEL/VOX FDC. Last dose of study drug refers to the last dose of SOF/VEL FDC (Cohort 1) or SOF/VEL/VOX FDC (Cohort 2) and will be used in the definition of treatment-emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various post treatment time points.

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis will be the FAS, which includes all enrolled subjects who took at least 1 dose of study drug.

8.2.1.2. Safety

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

8.2.1.3. Pharmacokinetics

The PK Analysis Set will include all subjects who received at least 1 dose of study drug, and have at least 1 nonmissing postdose concentration value for the corresponding analyte in plasma. The analytes of interest may include SOF (and its metabolites GS-566500 and GS-331007), VEL or VOX where applicable.

CCI [redacted]

8.2.2. Data Handling Conventions

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

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

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

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

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

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

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

CCI [redacted]

CCI [redacted]

8.3. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods by cohort.

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

Baseline characteristics data will include BMI, HCV RNA level (log_{10} IU/mL), genotype of HCV infection, IL28B genotype, and additional endpoints as necessary

8.4. Efficacy Analysis

8.4.1. Primary Analysis

The primary efficacy endpoint for this study will be the proportion of subjects with SVR12 in all enrolled and treated subjects. The primary analysis will be performed after all enrolled subjects have been followed through 12 weeks posttreatment or discontinued from study. The point estimate with a 2-sided 95% exact confidence interval (CI) using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate by cohort. No hypothesis testing will be performed.

8.4.2. Secondary Analyses

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

Descriptive summaries and listings will be provided for additional efficacy evaluations of the proportion of subjects who experience virologic failure, ALT normalization, serum HCV RNA actual values and change from baseline. Continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum) by cohort. Categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition by cohort.

CCI [redacted]

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

8.5. Safety Analysis

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

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

8.5.1. Extent of Exposure

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

8.5.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) coding 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 AE will be defined as any AE with an onset date on or after the date of first dose of study drug and no later than 30 days after permanent discontinuation of the study drug; or any AE leading to premature discontinuation of study drug.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by SOC and PT) will be provided by cohort:

- 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 study drug
- AEs leading to interruption of study drug

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

8.5.3. Laboratory Evaluations

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

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

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

8.5.4. Other Safety Evaluations

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

8.6. Pharmacokinetic Analysis

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

CCI [redacted]

8.7. Sample Size

For Cohort 1, with approximately 50 subjects enrolled into the study, the 2-sided 95% exact CI using the binomial distribution (Clopper-Pearson method) of the SVR12 rate will be from 86.3% to 99.5%, assuming the expected SVR12 rate is 95%.

For Cohort 2, with approximately 30 subjects enrolled into the study, the 2-sided 95% exact CI using the binomial distribution (Clopper-Pearson method) of the SVR12 rate will be from 82.8% to 99.9%, assuming the expected SVR12 rate is 95%.

8.8. Data Monitoring Committee

No data monitoring committee will be used in this study.

8.9. Endpoint Adjudication Committee

No Adjudication committee will be used in this study.

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.

9.1.2. Financial Disclosure

The investigator and sub-investigators 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 sub-investigator's) participation in the study. The investigator and sub-investigator 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 (ICF), 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 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/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, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled;
- Participation in study (including study number);
- Study discussed and date of informed consent;

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

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e., 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 captures the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the

investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g., data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

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 QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator 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 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, e.g., attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

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

10. REFERENCES

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Lim YS. Current status of liver disease in Korea: hepatitis C. The Korean journal of hepatology 2009;15 Suppl 6:S25-8.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

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

GS-US-342-5532, Original Protocol, 04 October 2019

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

PPD

PPD

8 Oct 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. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) | Signature

Date | Site Number

Appendix 2. Study Procedures Table

	Screening	Day 1[a]	Treatment Week (±3 days)					Posttreatment Week (±5 days)	
			1	2	4	8	12/ET[b]	4	12
Clinical Assessments									
Informed Consent	X								
Determine Eligibility	X	X							
Medical History	X								
Physical Examination	X	X					X		
Height	X								
Weight	X	X					X		X
Vital Signs[c]	X	X	X	X	X	X	X	X	X
12 Lead ECG[d]	X	X	X				X		
Adverse Events and Concomitant Medications[e]	X	X	X	X	X	X	X	X	
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	X	X		X	X	X	X	X	
Chemistry	X	X		X	X	X	X	X	X
Coagulation (PT, aPTT and INR)	X	X		X	X	X	X		
Urinalysis, Urine drug screen	X								
HCV RNA	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
HCV resistance samples		X		X	X	X	X	X	X
HBV DNA Sample[i]				X	X	X	X	X	X
Single PK				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								
CCI [redacted]									

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 drugs.
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) within 4 months of Day 1 for subjects with cirrhosis, and within 6 months of Day 1 for subjects without cirrhosis.
g Study drugs will be reconciled at every post Day 1 visit by the investigator in order to monitor the subject's adherence with the study drugs. Subjects must be instructed to bring back all bottles of study drugs in the original container at every post Day 1 visit through the end of treatment.
h The IWRS will provide direction on the specifics of each subject's study drug dispensing.
i Sample only to be collected for HBcAb positive subjects at Screening. Reflex testing done only when ALT > ULN or > Day 1 value in these subjects.
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 and at ET if applicable. 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).
[redacted]

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months#**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infant <1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L

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

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

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

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

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

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

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

Notes:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential 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 of 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.

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

However, the risks of treatment with SOF/VEL FDC or SOF/VEL/VOX FDC during pregnancy in humans have not been evaluated. Please refer to the latest version of the Investigator's Brochures 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 pregnancy test on the Day 1 visit prior to first dose of drug. Pregnancy tests will be performed every 4 weeks throughout duration of trial up until and including the 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 or SOF/VEL/VOX 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 or SOF/VEL/VOX 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)

  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

  Hormonal methods

  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Implants of levonorgestrel
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

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

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they 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.