CLINICAL STUDY PROTOCOL

Study Title:	An Open-Label Study to Evaluate the Safety And Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination for 12 Weeks in Subjects who Participated in a Prior Gilead-Sponsored HCV Treatment Study
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	125751
EudraCT Number:	2017-000179-98
Clinical Trials.gov Identifier:	Not Available
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-367-4181
Gilead Study Director:	Name: PPD Telephone: PPD Cell: PPD Email: PPD
Protocol Version/Date:	Original 19 January 2017

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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IND Number:	125751
EudraCT Number:	2017-000179-98
Clinical Trials.gov Identifier:	Not Available
Study Centers Planned:	Approximately 40 centers in the United States, Canada, New Zealand, Australia, France, Germany, and the United Kingdom.
Objectives:	The primary objective of this study is as follows: • To determine the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL)/voxilaprevir (VOX) fixed-dose combination (FDC) for 12 weeks as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12) • To evaluate the safety and tolerability of treatment with SOF/VEL/VOX FDC 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 kinetics of circulating HCV RNA during treatment and after cessation of treatment • To evaluate the emergence of viral resistance to SOF, VEL, and VOX during treatment and after cessation of treatment

Study Design:	Approximately 50 subjects with chronic HCV infection who did not achieve an SVR in a prior Gilead-sponsored HCV treatment study will be enrolled. Subjects will receive SOF/VEL/VOX FDC (400/100/100 mg) once daily with food for 12 weeks.
Number of Subjects Planned:	Approximately 50 subjects.
Target Population:	Adults with chronic hepatitis C virus (HCV) infection who participated in a prior Gilead-sponsored HCV treatment study and did not achieve SVR
Duration of Treatment:	Subjects will be treated for 12 weeks.
Diagnosis and Main Eligibility Criteria:	Chronically HCV-infected male and non-pregnant/non-lactating female subjects aged 18 years or older who did not achieve SVR in a prior Gilead-sponsored HCV treatment study. Refer to Section 4.2 and 4.3 for detailed Inclusion and Exclusion Criteria.
Study Procedures/ Frequency:	All subjects will complete the following study visits: Screening, Day 1, and on-treatment visits at the end of Weeks 2, 4, 8, and 12. Posttreatment visits will occur at Weeks 4 and 12 after last dose of study drug. Screening assessments will include physical examination, medical history, height, weight, vital signs, 12-lead electrocardiogram (ECG), adverse events related to Screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), HCV RNA, HCV genotyping, serology (HCV, HBV, HIV), hemoglobin A1c (HbA1c), assessment of the presence or absence of cirrhosis (including Fibrotest®), screening for hepatocellular carcinoma (HCC) for subjects with cirrhosis, serum β-human chorionic gonadotropin (β-hCG) (females of child-bearing potential only), IL28B genotyping, urinalysis, and urine drug screen. On-treatment assessments include adverse events (AEs), concomitant medications, study drug dispensation and pill count, physical examination, weight, vital signs, safety laboratory tests, HCV RNA, pharmacokinetic samples (after Day 1), and urine pregnancy tests (females of childbearing potential only). Samples for the viral RNA sequencing/phenotyping will be collected at Day 1 and every visit thereafter. Single 12-lead ECGs will be collected at Early Termination (ET), if applicable.

	Posttreatment assessments include AEs, concomitant medications, vital signs, safety laboratory tests (including hematology, chemistry, and coagulation), HCV RNA, and urine pregnancy tests (females of child-bearing potential only). For subjects who are Hepatitis B core antibody positive (HBcAb+), HBV DNA will be measured at Day 1, on-treatment Weeks 4, 8, and 12 or ET, and posttreatment Weeks 4 and 12. PPD
Test Product, Dose, and Mode of Administration:	SOF/VEL/VOX (SOF/VEL/GS-9857) FDC is manufactured as a 400/100/100 mg 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 laboratory tests will be collected throughout the study.
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0.
Statistical Methods:	The primary efficacy endpoint is SVR12 in all enrolled and treated subjects; a point estimate with a two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate in the FAS. Secondary endpoints include SVR4, the proportion of subjects with virologic failure, and change in HCV RNA from baseline. All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum). All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition.

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

Approximately 50 subjects will be enrolled in this study. The sample size is based on practical considerations.

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
β-hCG	β-human chorionic gonadotropin
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
APRI	AST:platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BMI	body mass index
BW	body weight
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
Cr_{cl}	creatinine clearance
CLDQ-HCV	Chronic Liver Disease Questionnaire
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CRO	contract (or clinical) research organization
CSR	Clinical study report
CYP2C8	Cytochrome P450 2C8
CYP3A	Cytochrome P450 3A
DAA	Direct-acting antiviral
DDI	drug-drug interaction
dL	deciliter
DMC	Data Monitoring Committee
DSPH	Gilead Drug Safety and Public Health
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
EE	Ethinyl Estradiol
eCRF	electronic case report form(s)
ESA	erythropoiesis stimulating agent
EoT	End of Treatment
ET	Early Termination

EU	European Union
FACIT-F	Fatigue Index
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 (Guidelines)
GCSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GS-331007	formerly PSI-6206
GS-566500	formerly PSI-352707
GS-7977	formerly PSI-7977
GSI	Gilead Sciences, Inc.
H2	Histamine
Hb	Hemoglobin
HbA_{1c}	Hemoglobin A_{1c}
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
HRQoLs	Health Related Quality of Life
IB	Investigator Brochure
ICH	International Conference on Harmonization
IDSA	Infectious Disease Society of America
IEC	independent ethics committee
IFN	Interferon
IL28B	IL28B gene
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio of prothrombin time
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
IWRS	interactive web response system
kg	Kilogram

L	Liter
LDL	low-density lipoprotein
LDV	ledipasvir
LLN	lower limit of the normal range
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalents
mg	Milligram
MH	Mantel-Haenszel
mL	Milliliter
Min	Minute
mmHg	millimeters mercury
Mmol	millimole
MRP2	Multidrug resistance protein 2
NI	Noninferiority
NGM	Norgestimate
nM	nanometer
NS (3/4A/5A/5B)	Non-structural Protein
OATP	organic anion-transporting polypeptide
PCR	Polymerase Chain Reaction
Peg-IFN	pegylated interferon
PI	Protease Inhibitor
P-gp	P-glycoprotein
PG	Pharmacogenomic
PK	Pharmacokinetic
PPI	Proton-pump inhibitor
PT	prothrombin time or preferred term
Q1	Quartile 1
Q3	Quartile 3
QA	Quality assurance
RAV	Resistance-associated variants
RBC	Red blood cell count
RBV	ribavirin
RNA	ribonucleic acid
SADR	Serious adverse drug reaction
S_{cr}	serum creatinine (mg/dL)
SAE	serious adverse event
SD	Standard deviation

SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SNP	Single nucleotide polymorphism
SOC	System Organ Class
SOF	Sofosbuvir (GS-7977)
SOP	Standard operating procedure
SSR	Special Situations Report
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
T_{max}	The time (observed time point) of Cmax
TND	Target not detected
TPO	Thrombopoietin
$T_{½}$	An estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
ULN	Upper limit of normal
US	United States
VEL	velpatasvir (GS-5816)
VOX	voxilaprevir (GS-9857)
WBC	White blood cell
WPAI	Work Productivity and Activity Impairment

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) infection is a global health challenge with an estimated 150 million individuals infected worldwide {World Health Organization (WHO) 2014}. In the United States (US), approximately 2.7 million people have chronic HCV infection {Denniston 2014} and HCV infection causes over 15,000 deaths each year {Ly 2012}, although under-reporting of HCV infection on death certificates may contribute to as much as a 5-fold underestimation of the actual number of deaths {Mahajan 2014}. Direct-acting antivirals (DAAs) have provided a major advance in the treatment of HCV. The drugs have increased efficacy and safety compared to historical pegylated interferon (Peg-IFN) and ribavirin (RBV)-based therapy. However, despite high sustained virologic response (SVR) rates following DAA treatment in both clinical trials and "real world" cohorts, there is a growing population of patients who fail DAA-based therapies {Nelson 2015}, {Welzel 2015}, {Dieterich 2016}, {Dieterich 2015a}, {Younossi 2015}, {Dieterich 2015b}.

In the last 5 years, HCV treatment has been transformed by the development and approval of direct-acting antiviral (DAA) agents that target viral proteins and cellular processes essential to HCV replication, such as those that contain sofosbuvir (SOF), a HCV nonstructural protein (NS)5B-directed inhibitor with potent, broad genotypic activity {Gilead Sciences Inc 2016a}, {Gilead Sciences Inc 2016b}, {Gilead Sciences Inc 2015}. The recently developed fixed-dose combination (FDC) Epclusa® tablet combines SOF and velpatasvir (VEL), a potent, pangenotypic, next-generation HCV NS5A inhibitor, to provide a 12-week treatment option for nearly all HCV-infected patients, regardless of HCV genotype, demographics, and other disease characteristics {Gilead Sciences International Ltd 2016}, {Gilead Sciences Inc 2016a}. This and other recently approved DAA–based treatment regimens are well tolerated and highly effective, resulting in the cure of HCV infection in ≥ 95% of treated patients {Feld 2015}, {Zeuzem 2014a}, {Zeuzem 2014b}, {Kowdley 2014}, {Foster 2015}.

Retreatment options are available for patients who have failed pegylated interferon (Peg-IFN) and ribavirin (RBV) with or without an NS3/4A PI (eg, telaprevir, boceprevir, simeprevir). Large, registrational, clinical studies have demonstrated that subjects previously treated with Peg-IFN and RBV and who fail treatment can be retreated in a manner similar to the initial treatment of naive subjects, thus currently approved DAA regimens are recommended for use in patients who fail treatment with Peg-IFN and RBV {European Association For The Study of the Liver 2016}, {AASLD-IDSA 2016}. Additionally, there are approved regimens, including Harvoni® (a FDC of ledipasvir [LDV; an NS5A inhibitor] and SOF) and Epclusa®, which are indicated for treatment in patients who previously failed treatment with an NS3/4A PI with Peg-IFN and RBV. However, retreatment options are limited for patients who fail DAA-only treatment, particularly regimens that include an NS5A inhibitor and/or NS5B inhibitor. The current HCV treatment guidelines from the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) and European Association for the Study of the Liver (EASL) acknowledge the limited clinical data to support retreatment

recommendations for these DAA-experienced patients and suggest deferral of treatment for all patients without an urgent need for retreatment until more data and/or additional options become available {European Association For The Study of the Liver 2016}, {AASLD-IDSA 2016}. Development of highly potent DAA regimens that combine 3 drug classes may offer improved, broad efficacy as a salvage therapy for DAA-experienced patients.

1.2. SOF/VEL/VOX FDC (SOF/VEL/GS-9857)

SOF/VEL/VOX FDC is a coformulation of SOF 400 mg, VEL 100 mg, and VOX 100 mg into a single tablet for the treatment of chronic HCV infection. This fixed-dose combination combines three unique mechanisms of action into a single tablet:

- Sofosbuvir, a nucleotide analog HCV NS5B polymerase inhibitor, which is currently approved in the US and other regions for the treatment of HCV infection as a component of an antiviral treatment regimen.
- Velpatasvir, an HCV NS5A inhibitor that has potent in vitro anti-HCV activity across all genotypes, which is currently approved in the US and other regions for the treatment of HCV infection in combination with SOF.
- Voxilaprevir, a macrocyclic HCV NS3/4A protease inhibitor (PI) with potent in vitro antiviral activity against genotypes 1 to 6 HCV, and an improved resistance profile compared with previously developed PIs.

There are currently 4 ongoing Phase 3 studies of the combination of SOF/VEL/VOX in subjects with chronic HCV infection (GS-US-367-1171 [POLARIS-1], GS-US-367-1170 [POLARIS-4], GS-US-367-1172 [POLARIS-2] and GS-US-367-1173 [POLARIS-3]). In these studies, 1056 subjects have received SOF/VEL/VOX (400/100/100 mg). Data from these trials have been submitted to support marketing authorization of SOF/VEL/VOX for the treatment of chronic HCV infection in the USA and elsewhere. The preliminary results from these studies are described in Section 1.2.2. below.

1.2.1. General Information

Please refer to the SOF/VEL/VOX FDC IB for additional information on SOF/VEL/VOX FDC, VOX and SOF/VEL (the VOX IB and SOF/VEL Core Company Data Sheet are appended to the SOF/VEL/VOX IB). Information in the IB includes:

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

1.2.2. Additional Clinical Trials of SOF/VEL/VOX

In addition to studies detailed in the IB, information from the following clinical studies with SOF/VEL/VOX are provided herein and include two completed Phase 1 clinical studies (GS-US-367-1726 and, GS-US-367-1909), one completed Phase 2 clinical study (GS-US-367-1871 [TRILOGY-3]) and four ongoing Phase 3 clinical studies (GS-US-367-1171 [POLARIS-1], GS-US-367-1170 [POLARIS-4], GS-US-367-1172 [POLARIS-2] and GS-US-367-1173 [POLARIS-3]).

1.2.2.1. GS-US-367-1726

This completed Phase 1, randomized, open-label, single-center, 5-cohort, single- and multiple-dose study evaluated the PK of SOF/VEL/VOX upon coadministration with a representative histamine H2 receptor antagonist (H2RA) (famotidine) or proton-pump inhibitor (PPI) (omeprazole) in healthy subjects. The study was planned to include up to 5 cohorts (Cohorts 1 to 5); Cohorts 1, 2, and 3 were conducted and are described below. Cohorts 4 and 5 were not conducted.

In Cohort 1, subjects were randomized to 1 of 3 study treatments, according to their assigned treatment sequences (ABC, BCA, CAB, CBA, ACB, or BAC):

- **Reference (Treatment A):** A single dose of SOF/VEL/VOX 400/100/100 mg administered in the morning with food.
- **Simultaneous H2RA Administration (Treatment B):** A single dose of SOF/VEL/VOX 400/100/100 mg administered simultaneously with single dose of famotidine 40 mg in the morning with food.
- **12-Hour H2RA Stagger (Treatment C):** A single dose of famotidine 40 mg administered in the evening with a standardized meal, 12 hours before single dose of SOF/VEL/VOX 400/100/100 mg administered in the morning with food.

In Cohort 2, subjects were randomized to 1 of 2 following treatments, according to their assigned treatment sequences (DE or ED):

- **Reference (Treatment D):** A single dose of SOF/VEL/VOX 400/100/100 mg administered in the morning with food.
- **2-Hour PPI Stagger (Treatment E):** Omeprazole 20 mg administered once daily in the morning for 6 days under fasted conditions followed by a single dose of SOF/VEL/VOX 400/100/100 mg administered with food 2 hours after omeprazole administration on the sixth day of omeprazole dosing.

In Cohort 3, subjects were randomized to 1 of 2 following treatments, according to their assigned treatment sequences (GH or HG):

- **Reference (Treatment F):** A single dose of SOF/VEL/VOX FDC 400/100/100 mg administered in the morning with food.
- **4-Hour PPI Stagger (Treatment G):** Omeprazole 20 mg administered once daily 1 hour before lunch for 6 days; on the sixth day, a single dose of SOF/VEL/VOX 400/100/100 mg was administered with food 4 hours before the omeprazole dose.

Of the 147 subjects screened, 104 subjects were randomized (36 subjects in Cohort 1 and 34 subjects each in Cohorts 2 and 3). All 104 randomized subjects received study drug and were included in the Safety Analysis Set. Overall, 1 of 104 subjects (1.0%) prematurely discontinued study drug and from the study due to an AE (tooth infection). All other subjects completed study drug and the study.

Pharmacokinetics Results

The table below summarizes the changes in PK parameters of SOF, the SOF metabolite GS-331007, VEL, and VOX following single-dose administration of SOF/VEL/VOX alone and either simultaneously with or 12 hours after administration of a single dose of famotidine 40 mg (Cohort 1), 2 hours after administration of omeprazole 20 mg once daily (Cohort 2), or 4 hours before administration of omeprazole 20 mg once daily (Cohort 3).

PK Parameter		SOF/VEL/VOX + Simultaneous Famotidine 40 mg (Cohort 1)	SOF/VEL/VOX 12 Hours After Famotidine 40 mg (Cohort 1)	SOF/VEL/VOX 2 Hours After OME 20 mg (Cohort 2)	SOF/VEL/VOX 4 Hours Before OME 20 mg (Cohort 3)
SOF	AUC_{last}	↔	↔	↓ 27%	↔
	AUC_{inf}	↔	↔	↓ 27%	↔
	C_{max}	↔	↔	↓ 23%	↔
GS-331007	AUC_{last}	↔	↔	↔	↔
	AUC_{inf}	↔	↔	↔	↔
	C_{max}	↔	↔	↔	↔
VEL	AUC_{last}	↔	↔	↓ 54%	↓ 51%
	AUC_{inf}	↔	↔	↓ 54%	↓ 51%
	C_{max}	↔	↔	↓ 57%	↓ 51%
VOX	AUC_{last}	↔	↔	↔	↔
	AUC_{inf}	↔	↔	↔	↔
	C_{max}	↔	↔	↓ 24%	↔

GLSM = geometric least squares mean; OME = omeprazole
The lower bound of the 90% CIs of the %GLSM ratios were within (↔) or extended below (↓) the predetermined equivalence boundary of 70%.

No alteration in the AUC (AUC_{inf} or AUC_{last}) or C_{max} of SOF, GS-331007, VEL, or VOX was observed following administration of SOF/VEL/VOX with famotidine 40 mg, simultaneously or staggered by 12 hours, relative to SOF/VEL/VOX alone.

Sofosbuvir AUC and C_{max} were 27% and 23% lower, respectively, with no alteration in GS-331007 PK, following administration of SOF/VEL/VOX 2 hours after administration of omeprazole 20 mg, relative to SOF/VEL/VOX alone. Velpatasvir AUC and C_{max} were 54% and 57% lower, respectively, following administration of SOF/VEL/VOX 2 hours after administration of omeprazole 20 mg, relative to SOF/VEL/VOX alone. Overall VOX exposure (AUC) was unchanged, while C_{max} was lower (24%) following the administration of SOF/VEL/VOX 2 hours after administration of omeprazole 20 mg, relative to SOF/VEL/VOX alone.

No alteration in SOF, GS-331007, or VOX AUC or C_{max} was observed following administration of SOF/VEL/VOX 4 hours before the administration of omeprazole 20 mg, relative to SOF/VEL/VOX alone. Velpatasvir AUC and C_{max} were both approximately 51% lower following administration of SOF/VEL/VOX 4 hours before administration of omeprazole 20 mg, relative to SOF/VEL/VOX alone.

Pharmacokinetics Conclusions

- Famotidine 40 mg did not impact SOF/VEL/VOX PK.
- Administration of SOF/VEL/VOX with omeprazole 20 mg resulted in ~50% lower VEL exposure. Changes in the PK of SOF and VOX were minor and likely secondary to effects on VEL.

1.2.2.2. GS-US-367-1909

This Phase 1, open-label, single-center, fixed-sequence, multiple-dose study evaluated the PK, safety, and tolerability of SOF/VEL/VOX+VOX when administered with a representative hormonal contraceptive medication, Norgestimate/ Ethinyl Estradiol (NGM/EE), in healthy females of childbearing potential. Following screening procedures, eligible subjects were either enrolled in a 28-day lead-in period (Part A), during which they completed dosing with NGM/EE prior to initiation of Study Day 1 in Cycle 1 (Part B), or for subjects with a documented history of taking NGM/EE for at least 1 menstrual cycle, directly enrolled into Part B of the study within 28 days of screening.

If enrolled in the lead-in period, subjects were admitted to the study center on Day L –1 and confined until completion of NGM/EE dosing on Day L 1. Daily dosing with NGM/EE continued for 28 days. For Part B, all subjects returned to the study center on Study Day –1, where they remained until completion of NGM/EE dosing on Study Day 1. Subjects continued daily dosing with NGM/EE through Study Day 56 (2 full 28-day menstrual cycles). Subjects were administered SOF/VEL/VOX+VOX during Cycle 2 on Study Days 36 to 42. Subjects received a follow-up telephone call 7 to 10 days after the last dose of NGM/EE to monitor any adverse events (AEs) and concomitant medications.

A total of 15 subjects were enrolled in the lead-in period (Part A) of the study. All 15 subjects continued to Part B, received study drug in Part B, were included in each PK and PD analysis set, and completed study drug and the study.

Pharmacokinetic/Pharmacodynamic Results

Similar systemic exposures (AUC_{tau}, C_{max}, and C_{tau}) of NGMN and NG (active metabolites of NGM) and EE were observed following administration of NGM/EE alone or in combination with SOF/VEL/VOX+VOX. All 90% CIs of the GLSM ratios for AUC_{tau}, C_{max}, and C_{tau} were within the lack of PK alteration boundaries of 70% to 143%.

Systemic exposures of VOX, VEL, SOF, and GS-331007 were within the ranges of exposures observed in historical data (reference treatments for healthy subjects receiving multiple-dose SOF/VEL/VOX+VOX in Studies GS-US-380-1999 and GS-US-367-1905).

Luteinizing hormone, FSH, and progesterone serum concentrations were similar across both treatments. Median concentrations of LH and FSH were lower than those expected for the ovulatory phase, consistent with decreased LH and FSH serum concentrations caused by oral hormonal contraceptives. Progesterone median values were substantially lower than those expected for the luteal phase, consistent with absence of ovulation.

Pharmacokinetic/Pharmacodynamic Conclusions

- No PK interaction was observed following administration of SOF/VEL/VOX+VOX with NGM/EE.
- The exposures of VOX, VEL, SOF, and GS-331007 were within the ranges of exposures observed in historical data.
- No loss of contraceptive efficacy is expected upon coadministration of SOF/VEL/VOX with oral contraceptives.

1.2.2.3. GS-US-367-1871 (TRILOGY-3)

This single-center, open-label study evaluated the safety and efficacy of SOF/VEL/VOX FDC with or without RBV in subjects with chronic genotype 1 HCV infection previously treated with a DAA regimen.

Study Design and Subject Population

A total of 49 DAA-experienced subjects with genotype 1 HCV infection (25 with compensated cirrhosis and 24 without cirrhosis) were randomized in a 1:1 ratio to receive SOF/VEL/VOX (400/100/100 mg) once daily with food for 12 weeks (Group 1) or SOF/VEL/VOX (400/100/100 mg) once daily with food plus RBV (1000 or 1200 mg/day divided twice daily) with food for 12 weeks. Randomization was stratified by the presence of an NS5A inhibitor in the prior DAA regimens and the presence of cirrhosis. All subjects were DAA experienced:

40.8% had previously been treated with an NS5A inhibitor-containing regimen, 30.6% had previously been treated with an NS3/4A PI alone, and 28.6% had previously been treated with an NS5B inhibitor alone or with an NS3/4a PI. Most subjects (87.8%) had received only 1 prior treatment for HCV infection. A total of 24 subjects (49.0%) received SOF/VEL/VOX and 25 subjects (51.0%) received SOF/VEL/VOX+RBV. All subjects completed study treatment.

Conclusions

- SOF/VEL/VOX administered daily with food for 12 weeks to DAA-experienced subjects with genotype 1 HCV infection was highly effective and the addition of RBV did not improve efficacy.
  - SVR12 rate was 100% in DAA-experienced subjects with or without cirrhosis treated with SOF/VEL/VOX for 12 weeks.
  - SVR12 rate was 96.0% in DAA-experienced subjects with or without cirrhosis treated with SOF/VEL/VOX+RBV for 12 weeks.
- Presence of baseline RAVs had no impact on SVR12 rates.
- SOF/VEL/VOX and SOF/VEL/VOX+RBV administered daily for 12 weeks were generally safe and well tolerated with few SAEs, Grade 3 AEs, discontinuations due to AEs, and Grade 3 laboratory abnormalities reported in the study overall. There were no Grade 4 AEs or laboratory abnormalities. Subjects receiving treatment with SOF/VEL/VOX+RBV reported more AEs and graded laboratory abnormalities than those receiving treatment with SOF/VEL/VOX alone.

1.2.2.4. SOF/VEL/VOX Phase 3 Studies

The SOF/VEL/VOX Phase 3 program consists of 4 registrational studies, 2 studies evaluating 12 weeks of SOF/VEL/VOX in DAA-experienced subjects (GS-US-367-1171 [POLARIS-1], GS-US-367-1170 [POLARIS-4]), and 2 studies evaluating 8-weeks of SOF/VEL/VOX in DAA-naïve subjects (GS-US-367-1172 [POLARIS-2] and GS-US-367-1173 [POLARIS-3]).

1.2.2.4.1. DAA-Experienced Subjects

1.2.2.4.1.1. GS-US-367-1171 (POLARIS-1)

This ongoing, Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study assessed the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL/VOX treatment compared with 12 weeks of placebo treatment in DAA-experienced subjects with chronic HCV infection who have previously been treated with a nonstructural protein 5A inhibitor.

Study Design and Subject Population

A total of 416 DAA experienced subjects with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who had previously received an NS5A inhibitor were enrolled or randomized into 1 of 2 treatment groups to receive either SOF/VEL/VOX once daily with food for 12 weeks (SOF/VEL/VOX 12 Week group) or placebo once daily with food for 12 weeks (Placebo 12 Week group). Subjects with genotype 1 HCV infection were planned to be randomized 1:1 to each group. Randomization was stratified by the presence or absence of cirrhosis at screening. Subjects with other HCV genotypes were planned to be enrolled in the SOF/VEL/VOX 12 Week group.

A total of 415 subjects received at least 1 dose of study drug and were included in the Safety Analysis and Full Analysis Sets (263 subjects in the SOF/VEL/VOX 12 Week group and 152 subjects in the Placebo 12 Week group). Overall, demographics and baseline characteristics were generally balanced between the 2 treatment groups. In the SOF/VEL/VOX 12 Week group, the majority of subjects had genotype 1 HCV infection (57.0%) or genotype 3 HCV infection (29.7%), 46.0% had cirrhosis and 99.6% of subjects had been previously treated with an NS5A inhibitor; 1 subject had failed prior treatment with only an NS5B inhibitor (SOF). The majority of subjects (98.8%, 410 of 415 subjects) completed study treatment. Five subjects prematurely discontinued study treatment: 1 subject was lost to follow up and 4 subjects discontinued due to AEs.

Conclusions from Interim Analysis

- The study met its predefined primary efficacy endpoint: SOF/VEL/VOX for 12 weeks resulted in an SVR12 rate of 96.2%, which was statistically superior relative to the prespecified performance goal of 85% ($p < 0.001$).

- The presence of baseline RAVs did not impact the treatment outcome in the SOF/VEL/VOX 12 Week group; no subject who relapsed with data available developed treatment-emergent RAVs.

- The steady-state PK of SOF, GS-566500, GS-331007, VEL, and VOX for subjects receiving SOF/VEL/VOX were similar to that observed in SOF/VEL+VOX Phase 2 studies.

- Treatment with SOF/VEL/VOX for 12 weeks was generally well tolerated with a safety profile generally similar to placebo. There was a low incidence of Grade 3 or 4 AEs, SAEs, and discontinuations due to AEs, and no clinically meaningful laboratory abnormalities.

1.2.2.4.1.2. GS-US-367-1170 (POLARIS-4)

This ongoing Phase 3, randomized, open-label, multicenter, international study evaluated the safety and efficacy of SOF/VEL/VOX treatment for 12 weeks and SOF/VEL treatment for 12 weeks in DAA-experienced subjects with chronic HCV infection who have not previously been treated with a nonstructural protein (NS) 5A inhibitor. Subjects who had DAA exposure to a NS3/4A PI only were excluded.

Study Design and Subject Population

A total of 333 DAA-experienced subjects with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who had not previously received an NS5A inhibitor were enrolled or randomized into 1 of 2 treatment groups to receive either SOF/VEL/VOX once daily with food for 12 weeks (SOF/VEL/VOX 12 Week group) or SOF/VEL once daily with or without food for 12 weeks (SOF/VEL 12 Week group). Subjects with genotype 1, 2, or 3 HCV infection were randomized 1:1 to each group. Randomization was stratified by HCV genotype (1, 2, or 3), and by the presence or absence of cirrhosis at screening. Subjects with genotype 4 and other HCV genotypes were enrolled in the SOF/VEL/VOX 12 Week group per the clinical study protocol design.

All enrolled/randomized subjects received at least 1 dose of study drug and were included in the Safety Analysis and Full Analysis Sets (182 subjects in the SOF/VEL/VOX 12 Week group and 151 subjects in the SOF/VEL 12 Week group). Overall, demographics and baseline characteristics were generally balanced across both treatment groups. Most subjects had genotype 1 (43.2%) or genotype 3 (31.8%) HCV infection. Overall, 45.9% of subjects had cirrhosis. Most subjects (73.0%) had been previously treated with an NS5B inhibitor only; 25.2% of subjects had been previously treated with a combination of an NS5B inhibitor and NS3 inhibitor. The majority of subjects (99.4%, 331 of 333 subjects) completed study treatment. Two subjects prematurely discontinued study treatment: 1 subject due to lack of efficacy and 1 subject due to an AE.

Conclusions from the Interim Analysis

- Treatment with SOF/VEL/VOX resulted in an SVR12 rate of 97.3%, which was statistically superior to the performance goal of 85% at the pre-specified 0.025 significance level ($p < 0.001$), meeting the primary efficacy endpoint.

- Treatment with SOF/VEL for 12 weeks resulted in an SVR12 rate of 90.1%, which was not statistically superior to the performance goal of 85% at the pre-specified 0.025 significance level.

- The presence of NS3, NS5A, and NS5B NI RAVs at baseline did not impact the treatment outcome; no treatment-emergent RAVs were detected in the subject who relapsed in the SOF/VEL/VOX 12 Week group.

- Treatment with SOF/VEL/VOX or SOF/VEL for 12 weeks was generally well tolerated with similar incidence and severity of AEs. Few Grade 3 or 4 AEs, SAEs, deaths, or discontinuations due to AEs were reported, and no clinically meaningful laboratory abnormalities were observed.

1.2.2.4.2. DAA-Naive Subjects

1.2.2.4.2.1. GS-US-367-1172 (POLARIS-2)

This ongoing, Phase 3, randomized, open-label, multicenter study is assessing the antiviral efficacy, safety, and tolerability of SOF/VEL/VOX for 8 weeks compared with SOF/VEL for 12 weeks in subjects with chronic HCV infection who are naive to direct-acting antiviral (DAA) treatment (i.e., DAA naive).

Study Design and Subject Population

A total of 943 DAA-naive subjects with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis were enrolled or randomized into 1 of 2 treatment groups to receive either SOF/VEL/VOX once daily with food for 8 weeks (SOF/VEL/VOX 8 Week group) or SOF/VEL once daily with or without food for 12 weeks (SOF/VEL 12 Week group). Subjects with genotype 3 HCV infection and cirrhosis were excluded from enrollment in this study; they were enrolled in Study GS US-367-1173 (POLARIS-3). Subjects with genotype 1, 2, 3, or 4 HCV infection were randomized 1:1 to each group. Randomization was stratified by HCV genotype (1, 2, 3, or 4), by treatment history (treatment naive or treatment experienced with an IFN based regimen), and by the presence or absence of cirrhosis at screening. Subjects with other HCV genotypes were enrolled in the SOF/VEL/VOX 8 Week group.

A total of 941 subjects received at least 1 dose of study drug and were included in the Safety Analysis and Full Analysis Sets (501 subjects in the SOF/VEL/VOX 8 Week group and 440 subjects in the SOF/VEL 12 Week group). Overall, demographics and baseline characteristics were generally balanced between the 2 treatment groups. The majority of subjects had genotype 1 (49.4%) or genotype 3 (19.2%) HCV infection; 12.3% of subjects had genotype 2, 12.8% had genotype 4, 1.9% had genotype 5, and 4.1% had genotype 6. Most subjects (81.5%, 767 subjects) did not have cirrhosis and were treatment naive (76.8%, 723 subjects). Of the treatment experienced subjects, most had failed prior treatment with Peg IFN+RBV (79.8%, 174 of 218 subjects). The majority of subjects (99.6%, 937 of 941 subjects) completed study treatment. Four subjects prematurely discontinued study treatment: 2 subjects due to AEs, 1 subject was lost to follow up, and 1 subject became pregnant.

Conclusions from the Interim Analysis

- The SVR12 rate for SOF/VEL/VOX for 8 weeks was 95.0% and the SVR12 rate for SOF/VEL for 12 weeks was 98.2%.

- The SVR12 rate for the SOF/VEL/VOX 8 Week group did not demonstrate noninferiority to the SVR12 rate for the SOF/VEL 12 Week group (proportional difference [95% CI]: −3.4% [−6.2% to −0.6%]).

- Among subjects with virologic failure following treatment with SOF/VEL/VOX, treatment emergent RAVs were uncommon, observed in only 1 of the 20 subjects with available data (5.0%).

- Treatment with SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks was generally well tolerated with similar incidence and severity of AEs. There was a low incidence of SAEs and discontinuations due to AEs, and no clinically meaningful laboratory abnormalities.

1.2.2.4.2.2. GS-US-367-1173 (POLARIS-3)

This ongoing, Phase 3, randomized, open-label, multicenter study evaluated the antiviral efficacy, safety, and tolerability of SOF/VEL/VOX for 8 weeks and SOF/VEL for 12 weeks in subjects with chronic genotype 3 HCV infection and cirrhosis who are naive to DAA treatment (ie, DAA naive).

Study Design and Subject Population

A total of 220 DAA-naive subjects with genotype 3 HCV infection with compensated cirrhosis were randomized into 1 of 2 treatment groups to receive either SOF/VEL/VOX once daily with food for 8 weeks (SOF/VEL/VOX 8 Week group) or SOF/VEL once daily with or without food for 12 weeks (SOF/VEL 12 Week group). Randomization was stratified by treatment history (treatment naive or treatment experienced with an IFN-based regimen).

A total of 219 subjects received at least 1 dose of study drug and were included in the Safety Analysis and Full Analysis Sets (110 subjects in the SOF/VEL/VOX 8 Week group and 109 subjects in the SOF/VEL 12 Week group). Demographics and baseline characteristics were generally balanced across both treatment groups. The majority of subjects were treatment naive (69.4%, 152 subjects). Of the treatment-experienced subjects, the majority had failed prior treatment with Peg-IFN+RBV (91.0%, 61 of 67 subjects). The majority of subjects (99.1%, 217 of 219 subjects) completed study treatment. Two subjects prematurely discontinued study treatment: 1 subject due to an SAE and 1 subject due to lack of efficacy.

Conclusions from the Interim Analysis

- Both treatment groups met their primary efficacy endpoints, demonstrating statistically superior SVR12 rates to the pre-specified 83% rate:
  - 8 weeks of treatment with SOF/VEL/VOX resulted in an SVR12 rate of 96.4% in DAA-naive subjects with genotype 3 HCV infection and cirrhosis
  - 12 weeks of treatment with SOF/VEL resulted in an SVR12 rate of 96.3% in DAA-naive subjects with genotype 3 HCV infection and cirrhosis
  - Baseline RAVs had no impact on virologic outcome in either treatment group; all subjects with baseline NS3 and/or NS5A RAVs achieved SVR12
- Treatment with SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks was generally well tolerated with similar incidence and severity of AEs. There were few Grade 3 or 4 AEs, SAEs, or discontinuations due to AEs; there were no treatment-emergent deaths and no clinically meaningful laboratory abnormalities.

1.2.2.4.3. Overall Safety of SOF/VEL/VOX

The overall safety of SOF/VEL/VOX is based on pooled Phase 3 clinical trial data from DAA-experienced subjects (POLARIS-1 and POLARIS-4) and DAA-naïve subjects (POLARIS-2 and POLARIS-3) with HCV infection (without cirrhosis or with compensated cirrhosis) including:

- 445 subjects who received SOF/VEL/VOX for 12 weeks
- 611 subjects who received SOF/VEL/VOX for 8 weeks
- 700 subjects who received SOF/VEL for 12 weeks
- 152 subjects who received placebo for 12 weeks

The proportion of subjects who permanently discontinued treatment due to AEs was 0.2% for subjects receiving SOF/VEL/VOX for 12 weeks. There were no subjects receiving SOF/VEL/VOX for 8 weeks who permanently discontinued treatment due to AEs.

The most frequent AEs occurring in subjects receiving SOF/VEL/VOX for 12 weeks were headache (26%), fatigue (22%), diarrhea (19%), and nausea (13%). The rates of AEs, except diarrhea and nausea, were similar in all groups in the pooled Phase 3 clinical trial data. Diarrhea and nausea occurred most frequently in subjects received SOF/VEL/VOX.

In the Phase 3 trials, Grade 1 increases in total bilirubin were observed in 4% of subjects without cirrhosis and 10% of subjects with compensated cirrhosis, due to inhibition of OATP1B1 and OATP1B3 by voxilaprevir. Total bilirubin levels decreased after completing SOF/VEL/VOX treatment. No subjects experienced jaundice.

1.3. Rationale for This Study

The population of this study will be subjects with chronic HCV infection who have previously not achieved SVR following treatment in a Gilead-sponsored trial. The majority of subjects will have received SOF/VEL for 12 weeks, or SOF/VEL/VOX FDC for less than 12 weeks. At this time there are no approved retreatment options for these patients. 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 help inform the role of SOF/VEL/VOX FDC for 12 weeks for these patients.

1.3.1. Rationale for the Study Design

This Phase 3 study has been designed as a multicenter, single arm open-label study evaluating the safety and efficacy of SOF/VEL/VOX FDC for 12 weeks in subjects with chronic HCV infection who had previously received active treatment in a Gilead-sponsored study. Approximately 50 subjects will be included.

Data from the Phase 3 studies POLARIS-1 and POLARIS-4 demonstrate that SOF/VEL/VOX FDC for 12 weeks is a potent combination regimen which provides effective retreatment for subjects who have previously failed treatment with multiple DAAs. In POLARIS-1, subjects who had previously been treated with an NS5A inhibitor-containing regimen demonstrated high SVR12 rates regardless of the presence of preexisting baseline RAVs or prior treatment regimen. Retreatment of subjects previously treated with SOF/VEL/VOX for 8 weeks with a12-week duration of the same regimen is supported by the rarity of treatment emergent resistance among subjects who relapsed following SOF/VEL/VOX for 8 weeks in POLARIS-2 and POLARIS-3. In the Phase 3 program, treatment with SOF/VEL/VOX was safe and generally well tolerated.

A single arm study will allow for the most precise estimate of the efficacy of the regimen among the small number of subjects eligible for this retreatment study.

1.3.2. Rationale for the Dose of SOF/VEL/VOX FDC

Sofosbuvir 400 mg and VEL 100 mg are the approved marketed doses in the SOF/VEL FDC for the treatment of HCV infection. The favorable safety and efficacy profile of this combination support selection of SOF 400 mg and VEL 100 mg for co-formulation into an FDC with VOX.

The VOX 100 mg dose was selected for co-formulation with SOF 400 mg and VEL 100 mg based on the anti-HCV activity of VOX established in the phase 1 study GS-US-338-1121 (50 - 300 mg VOX dose evaluated), which indicated that VOX exposures achieved in Phase 2 studies after administration of VOX 100 mg + SOF/VEL 400/100 mg with food are associated with >90% of the maximum antiviral response across all HCV genotypes. Results from the relative bioavailability study GS-US-367-1176 show that the SOF/VEL/ VOX FDC formulation achieves similar exposures of the relevant analytes to those observed with SOF/VEL+VOX.

The combination of SOF 400 mg, VEL 100 mg and VOX 100 mg has been administered in Phase 2 and ongoing Phase 3 studies to over 1900 subjects. The favorable safety and efficacy profiles support evaluation of this combination and doses in clinical development.

1.4. Risk/Benefit Assessment for the Study

This study will provide information on the safety and efficacy of SOF/VEL/VOX FDC in subjects who have been treated with a DAA regimen. The potential benefits of SOF/VEL/VOX FDC for the treatment of chronic HCV for patients included in the current study population are:

- Addressing the unmet medical need of the growing population of patients who have failed prior therapies.
- Provision of a once-daily, single tablet, pangenotypic therapy for patients who have failed prior therapies and have limited or no current treatment options.

The safety profile of SOF/VEL has been established in 3126 subjects, including 1558 subjects in the Phase 3 studies, 802 in the Phase 2 studies, 499 in the Phase 1 studies, and 267 subjects with decompensated cirrhosis in the Phase 3 Study GS-US-342-1137 (ASTRAL-4). No clinical safety issues specifically related to the combination of SOF/VEL have been identified to date.

The SOF/VEL/VOX clinical development program has allowed extensive characterization of the safety of the regimen. In particular, the high number of subjects with cirrhosis enrolled in the Integrated Phase 3 Safety Population provides reassurance regarding the safety and tolerability of the regimen in this population. Compared with SOF/VEL and placebo, there are similar rates of AEs overall, with the only notable difference being increased rates of mild (Grade 1) nausea and diarrhea. There is no pattern of VOX-associated ALT elevation; of the 1056 subjects receiving SOF/VEL/VOX in the Integrated Phase 3 Safety Population, 1 subject had a Grade 3 elevation in ALT (0.1%) and none had a Grade 4 elevation in ALT.

There is a potential risk for subjects to develop multiclass resistance if treatment in this study is unsuccessful. However, based on the virology analysis of subjects who relapsed and failed treatment with SOF/VEL/VOX in the Phase 2 and Phase 3 clinical studies, the risk of generation of treatment-emergent resistance is low.

In summary, there is no approved treatment available for HCV-infected patients who are eligible for the current study. If high rates of SVR can be obtained with a 12-week pangenotypic regimen, the anticipated value of achieving an SVR for patients with limited or no current therapeutic options, with a safe and tolerable regimen, offers a favorable risk-benefit determination.

1.5. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To determine the efficacy of treatment with SOF/VEL/VOX FDC for 12 weeks as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12)

- To evaluate the safety and tolerability of treatment with SOF/VEL/VOX FDC

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 kinetics of circulating HCV RNA during treatment and after cessation of treatment

- 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

This is a multicenter, open-label Phase 3 study that will evaluate the safety and efficacy of SOF/VEL/VOX FDC for 12 weeks in subjects with chronic HCV infection with or without cirrhosis, who have received prior treatment in a Gilead-sponsored HCV treatment study of DAA-containing regimens.

3.2. Study Treatments

There will be one treatment group of approximately 50 subjects:

- SOF/VEL/VOX FDC (400/100/100 mg) once daily with food

3.3. Duration of Treatment

Subjects will be treated for 12 weeks.

3.4. Discontinuation Criteria

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 procedures (see Section 6.5). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

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

Study drug must be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator
- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Virologic failure (as defined in Section 3.5)
- 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)

All subjects who terminate early will complete the ET visit and posttreatment Week 4 and 12 visits.

3.5. Virologic Response Based Stopping Criteria

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

- Confirmed HCV RNA ≥ LLOQ after 2 consecutive HCV RNA < LLOQ
- Confirmed > 1 $\log_{10}$ increase from on-treatment nadir

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

All subjects who terminate treatment early will complete the ET visit and posttreatment Week 4 and 12 visits.

3.6. Optional Archival Sample

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 50 subjects will be enrolled. In order to manage the total study enrollment, Gilead Sciences, Inc., at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

4.2. Inclusion Criteria

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

1) Willing and able to provide written informed consent

2) Male or female, age ≥18 years

3) HCV RNA ≥ LLOQ at Screening

4) Received SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks in GS-US-367-1172 (POLARIS-2), GS-US-367-1173 (POLARIS-3), or GS-US-367-1170 (POLARIS-4), or received HCV treatment with a DAA-based regimen in another Gilead-sponsored study, with approval from Gilead Sciences prior to Screening

   The subject must have completed the protocol-mandated treatment and posttreatment assessments in the prior Gilead-sponsored study.

5) Cirrhosis Determination

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

      i) FibroTest® score > 0.75 and AST:platelet ratio index (APRI) > 2 during Screening

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

      iii) Transient elastography (FibroScan®) with a result of > 12.5 kPa

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

      i) FibroTest® score ≤ 0.48 and APRI ≤ 1 performed during Screening

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

      iii) Transient elastography (FibroScan®) with a result of ≤ 12.5 kPa within 6 months of Day 1

6) Liver imaging within 6 months prior to Day 1 is required in cirrhotic subjects to exclude hepatocellular carcinoma (HCC)

7) 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

8) 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

9) Lactating females must agree to discontinue nursing before starting study drug.

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

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

4.3. Exclusion Criteria

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

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

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

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

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

    d) Hepatic decompensation (e.g., clinical ascites, encephalopathy, and/or variceal hemorrhage)

    e) Solid organ transplantation

    f) Significant cardiac disease

    g) Unstable psychiatric condition including hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within 2 years prior to Screening

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

i) Significant drug allergy (e.g., hepatotoxicity)

13) Screening ECG with clinically significant abnormalities

14) Subject has the following laboratory parameters at Screening:

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

b) AST > 10 × ULN

c) Direct bilirubin > 1.5 × ULN

d) Platelets < 50,000/μL

e) HbA1c > 8.5%

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

g) Hemoglobin < 10 g/dL

h) Albumin < 3 g/dL

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

15) Prior treatment with SOF/VEL/VOX±RBV for ≥12 weeks

16) Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency, cholangitis)

17) Infection with human immunodeficiency virus (HIV)

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

19) 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

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

21) Known hypersensitivity to the study drug, the metabolites, or formulation excipient

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

This is an open-label study. There will be one treatment group:

- SOF/VEL/VOX FDC (400/100/100 mg) once daily with food for 12 weeks

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

5.2.1. Formulation

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) tablets, 400/100/100 mg, are available as 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 tablets also contain copovidone, microcrystalline cellulose, lactose monohydrate, silicon dioxide, croscarmellose sodium and magnesium stearate. The active tablet film coating material contains polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol 3350, talc, iron oxide yellow, iron oxide red, and ferrosoferric oxide.

5.2.2. Packaging and Labeling

SOF/VEL/VOX (SOF/VEL/GS-9857) 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 the US and other participating countries shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (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

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

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Keep the container 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/VOX FDC.

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

Subjects will take one tablet of SOF/VEL/VOX FDC once daily with food. For a missed dose of study drug, subjects will be instructed to take the missed dose of study drug as soon as possible during the same day. Subjects will be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

5.4. Study Drug Adherence and Drug Accountability

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

Study drug will be reconciled using a drug pill count at every study visit after Day 1 by the investigator or designee (i.e. pharmacist), in order to monitor the subject's adherence with the medication regimen.

5.5. Prior and Concomitant Medications

Concomitant medications taken within 30 days prior to Screening, up to, and including 30 days after the last dose of study drug need to be recorded in the source documents and electronic case report form(s) (eCRFs). The following medications are prohibited during the screening period and for a minimum of 28 days prior to the Day 1 visit through the end of treatment:

- Hematologic stimulating agents (eg, erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)
- 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)
- Investigational agents or devices for any indication

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters, i.e., OATP and P-gp) with study drug(s) may result in PK interactions resulting in increases or decreases in exposure of study drug(s). The use of amiodarone is prohibited from **60 days prior to Day 1** through the end of treatment; other examples of representative medications that are prohibited or are to be used with caution from 21 days prior to Day 1 through the end of treatment are listed below:

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

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

a Proton-pump inhibitors (PPIs) comparable to omeprazole 20 mg once-daily may be taken. H2 receptor antagonists must not exceed the equivalent of 40 mg of famotidine twice daily. Antacids that directly neutralize stomach pH (i.e. Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/VEL/VOX FDC administration.
b May result in a decrease in the concentrations of study drugs.
c May result in symptomatic bradycardia. Mechanism is not currently known. The use of amiodarone is prohibited from **60 days prior toDay-1** through the end of treatment.
d May result in an increase in the concentration of study drugs and/or concomitant medications
e Use with study drugs may result in an increase in the concentration of the HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis. Pravastatin may be administered with SOF/VEL/VOX FDC at a dose that does not exceed pravastatin 40 mg.

Medications for disease conditions **excluded** from the protocol (eg, transplantation) are not listed under this Concomitant Medication section and are disallowed in the study.

Should subjects have a need to initiate treatment with any disallowed concomitant medication, the medical monitor must be consulted prior to initiation of the new medication. In instances where disallowed 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 medication.

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. Additional information is provided in the study procedures manual.

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

6.1. Screening Visit

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

Screening assessments will include physical examination, medical history, height, weight, vital signs, 12-lead ECG, adverse events related to Screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), creatinine clearance calculation, HCV RNA, HCV genotyping, serology (HCV, HBV, HIV), hemoglobin A1c (HbA1c), assessment of the presence or absence of cirrhosis (including Fibrotest®), screening for hepatocellular carcinoma (HCC) for subjects with cirrhosis, serum β-hCG (females of child-bearing potential only), IL28B genotyping, urinalysis, and urine drug screen.

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

6.1.1. Day 1 Assessments

All Day 1 assessments must be performed prior to study drug dosing.

6.2. Enrollment

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

6.3. On Treatment Assessments (± 3 days)

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

6.4. Post-treatment Assessments (± 5 days)

The posttreatment Week 4 and 12 visits should be timed from the date of last dose of study drug. All subjects will complete the posttreatment Week 4 and 12 visits.

6.5. Early Termination (ET)

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

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

6.6. Unscheduled Visit

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

6.7. Procedures and Specifications

6.7.1. Clinical Laboratory Analytes

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

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

Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatine Kinase, Creatinine, Direct Bilirubin Total Bilirubin, Glucose, Lipase, Potassium, Sodium; Fibrotest®/APRI calculation 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 HBcAb, HBsAg, and HBsAb); HBV DNA (only in subjects who are HBcAb+ at Screening);serology and/or antigen testing for HIV, including reflex testing as necessary. HCV RNA will be measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV genotype should the above assays become unavailable.

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

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

Additional Tests: Urine Drug screen (for Amphetamines, Cocaine, Methadone, Opiates), and Hemoglobin A1c (HbA1c).

6.7.2. Medical History

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

6.7.3. Complete Physical Examination

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

6.7.4. Vital Signs

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

Blood pressure will be measured using the following standardized process:

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

6.7.5. Creatinine Clearance

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

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

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

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

6.7.6. Body Mass Index (BMI)

BMI is calculated by the following equation.

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

6.7.7. 12-Lead ECGs

Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording. The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities.

6.7.8. Viral RNA Sequencing / Phenotyping Sample

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

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

6.7.9. Single Pharmacokinetic (PK) Sample

Single PK blood samples will be collected for all subjects at each on-treatment visit and archived for PK analysis of SOF (and its metabolites GS-566500 and GS-331007), VEL, and VOX. 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.

6.7.10. HBV DNA sample

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

6.7.11. Optional Archive Sample

PPD

6.7.12. Pregnancy Testing

All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period and for 30 days following the last dose of study drug. If required by local regulations, additional pregnancy tests beyond 4 weeks may be added. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drug immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

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 AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or 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 7.6.1.)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

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

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

- A congenital anomaly/birth defect.

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

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

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

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

7.2.2. Assessment of Severity

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

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

Requirements for collection prior to study drug initiation:

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

A subject's treatment history is a pre-requisite for entry into the study (eg, lack of effect of a prior Gilead product for the treatment of HCV); this will not be recorded on a Special Situations Report (SSR).

Adverse Events:

Following initiation of study drug, collect all AEs, regardless of cause or relationship, special situation reports, and pregnancy reports until 30 days after last dose of study drug.

All AEs should be followed up until resolution or until the AE 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 posttreatment follow-up period, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

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

Medical monitor contact information is as follows:

Gilead Medical Monitor:	Luisa M. Stamm, MD, PhD
Telephone:	PPD
Cell:	PPD
Fax:	PPD
Email:	PPD

7.4. Gilead Reporting Requirements

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

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

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

7.5. Toxicity Management

7.5.1. Subject Stopping Rules

Administration of study drug may be discontinued in the event of a clinical or laboratory event. The Gilead Medical Monitor must be consulted prior to dose discontinuation of SOF/VEL/VOX FDC unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject.

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

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

- Elevation of ALT and/or AST above the upper limit of normal and > 5x Day 1 or nadir, confirmed by immediate repeat testing.
- 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/VOX FDC.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

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

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

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

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

Refer to Section 7.3 and the 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 Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

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

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

7.6.2.2. Reporting Other Special Situations

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

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

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

Refer to Section 7.3 and the 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 determine the efficacy of treatment with SOF/VEL/VOX FDC for 12 weeks as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of treatment with SOF/VEL/VOX FDC

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 kinetics of circulating HCV RNA during treatment and after cessation of treatment
- 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 is SVR12 in the Full Analysis Set (FAS) population.

8.1.3. Secondary Endpoint

Secondary endpoints include the following:

- SVR4
- The proportion of subjects with HCV RNA < LLOQ on treatment
- The proportion of subjects with virologic failure
- HCV RNA change from Baseline/Day 1

8.1.4. Safety Endpoint

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

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).

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum). All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition.

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

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

8.2.1.2. Safety

The analysis set for safety analyses will include subjects who received at least one 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 last dose date of the study drug plus 30 days.

8.3. Data Handling Conventions

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

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

If a data point is missing and is preceded and followed in time by values that are "< LLOQ target not detected (TND)," then the missing data point will be set to "< LLOQ TND." If a data point is missing and preceded and followed by values that are "< LLOQ detected," or preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected," then the missing value will be set to "< LLOQ detected." In these situations the data point will be termed a bracketed success; otherwise, the data point will be termed a bracketed failure (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 the summary statistics for that time point. If the subject is missing a predose value, then the subject will be excluded from the calculation of the summary statistics for the predose value and the change from predose values.

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

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

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

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

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods

Demographic data will include sex, self-identified race/ethnicity, and age. Baseline characteristic data will include body mass index, HCV RNA level ($\log_{10}$ IU/mL), genotype of HCV infection, IL28B genotype, and additional endpoints as necessary.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is SVR12 (HCV RNA < LLOQ 12 weeks after cessation of treatment) in the FAS population. The primary analysis will be performed after all enrolled subjects have been followed through 12 weeks posttreatment or discontinued from study.

A point estimate with a two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) {Clopper 1934} will be constructed for the SVR12 for the FAS.

8.5.2. Secondary Analyses

The proportion of subjects with HCV RNA below the 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, HCV RNA actual values and change from baseline.

8.5.3. Exploratory Analysis

8.6. Safety Analysis

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

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

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

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

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

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

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

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

8.6.3. Laboratory Evaluations

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

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

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

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

8.6.4. Other Safety Evaluations

Individual data for 12-lead ECG, vital sign measurements will be listed by subject and incidence of events/abnormalities will be summarized descriptively by study visit as appropriate.

8.7. Sample Size

Approximately 50 subjects will be enrolled in this study. The sample size is based on the number of subjects who failed to achieve SVR12 in prior Gilead-sponsored HCV treatment studies and are eligible to be enrolled into 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 the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

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

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

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

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

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

9.1.3. Informed Consent

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

must use the most current IRB/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 local IRB/IEC requirements.

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria 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 study drug, including dates of dispensing and return
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity)
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (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.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRFs should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields

will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

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

The study monitor will provide instructions for return.

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

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

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met: the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, 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 eCRF.

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

An Open-Label Study to Evaluate The Efficacy And Safety Of Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination For 12 Weeks In Subjects Who Participated In A Prior Gilead-Sponsored HCV Treatment Study

GS-US-367-4181, Original, 19 January 2017

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

Luisa M. Stamm
Luisa M. Stamm MD, PhD (Printed)

PPD
Signature

20 Jan 2017
Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

			On-Treatment Study Week (±3 Days)					Posttreatment Study Week (±5 Days)	
	Screen[a]	Day 1[b]	2	4	8	12/EoT	ET	4	12
Informed Consent	X								
Determine Eligibility	X	X							
Medical History	X								
Physical Examination	X	X				X	X		
Height	X								
Weight	X	X							
Vital Signs	X	X	X	X	X	X	X	X	
12-Lead ECG	X						X		
Imaging for HCC[c]	X								
AEs/ SAEs	X	X	X	X	X	X	X	X	X[d]
Concomitant Medications	X	X	X	X	X	X	X	X	
Review of Study Drug Compliance (Pill Count)			X	X	X	X	X		
Study Drug Dispensing		X		X	X				
Hematology, Chemistry	X	X	X	X	X	X	X	X	
Coagulation Tests	X	X				X	X		
HCV RNA	X	X	X	X	X	X	X	X	X
HBV DNA[e]				X	X	X	X	X	X
Viral Sequencing/phenotyping[f]		X	X	X	X	X	X	X	X
Pregnancy Testing[g]	X	X		X	X	X	X	X	

	Screen[a]	Day 1[b]	On-Treatment Study Week (±3 Days)					Posttreatment Study Week (±5 Days)	
			2	4	8	12/EoT	ET	4	12
Urinalysis, Urine Drug Screen	X								
HCV Genotyping[h], IL28B	X								
HCV, HIV, HBV Serology	X								
HbA1c, Fibrotest®	X								
PPD									
Single PK Sample			X	X	X	X	X		

a Screening assessments to be completed within 28 days of the Day 1 visit. The screening window can be extended to 42 days for subjects requiring a liver biopsy, or for extenuating circumstances with sponsor approval.
b Day 1 assessments must be performed prior to dosing.
c Cirrhotic subjects will have liver imaging within 6 months of Day 1 to exclude HCC.
d Only SAEs will be collected at the posttreatment week 12 visit.
e Only for subjects who are HBcAb+ at Screening.
f Plasma will be collected for possible viral resistance or other virology studies.
g For females of childbearing potential only: serum β-hCG at Screening, urine pregnancy testing will occur every 4 weeks during the dosing period and for 30 days following the last dose of study drug.
h HCV genotyping to be performed by the central laboratory utilizing the LiPa assay.
PPD

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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

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

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric** **> 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric** **> 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine[**]	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

*Calcium should be corrected for albumin if albumin is < 4.0 g/dL
** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

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

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

Notes:

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

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

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

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

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

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

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

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

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

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

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

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

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Data on the effects of SOF/VEL/VOX on pregnant women is not available.

From nonclinical studies, there is no evidence that SOF, VEL, or VOX is genotoxic. Relevant nonclinical reproductive studies have demonstrated no adverse effect on fertility or embryo-fetal development for SOF, VEL and VOX as individual agents.

Data from clinical pharmacokinetic interaction studies of SOF/VEL/VOX have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using acceptable effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Day 1 visit prior to enrollment. A pregnancy test will be performed at the week 4, 8, 12, and the posttreatment week 4 visits. Female subjects must agree to one of the following from Screening until 30 days after the last dose of study drug.

- 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:
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Tubal sterilization
  - Bilateral tubal occlusion
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and has received medical assessment of the surgical success)
  - Female barrier method (diaphragm or cervical cap) with spermicide (where locally available)
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel or etonorgestrel
    - 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 end of relevant systemic exposure.

3) Contraception Requirements for Male Subjects

All male study participants must agree to consistently and correctly use a condom during treatment until 30 days after the last dose of study drug. 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 study drug.

Male subjects must also refrain from sperm donation during treatment and for at least 30 days after the last dose of study drug.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.6.2.1