CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) infection	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA	
IND Number:	This is a non-IND study	
EudraCT Number:	2015-003001-42	
Clinical Trials.gov Identifier:	Not Available	
Indication:	Hepatitis C Virus Infection	
Protocol ID:	GS-US-342-1522	
Gilead Study Director:	Name: Telephone: Fax: Email:	PPD PPD PPD PPD
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Protocol Version/Date:	Original:	17 July 2015

CONFIDENTIALITY STATEMENT

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

PROTOCOL SYNOPSIS

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Study Title:	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) infection
IND Number:	This is a non-IND study
EudraCT Number:	2015-003001-42
Clinical Trials.gov Identifier:	Not Available
Study Centers Planned:	Approximately 12 sites in the Russian Federation and Sweden
Objectives:	The primary objectives of this study are: • To evaluate the efficacy of treatment with sofosbuvir (SOF)/ velpatasvir (VEL, GS-5816) fixed dose combination (FDC) for 12 weeks in subjects with chronic HCV infection 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 for 12 weeks The secondary objectives of this study are: • To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24) • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment • To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment The exploratory objectives of this study are: PPD [redacted]

Study Design:	Multi-center, open-label study. Approximately 120 subjects with chronic HCV will be enrolled. All subjects will receive SOF/VEL FDC once daily for 12 weeks.
Sub study:	Pharmacogenomics (PG) Substudy In consenting participants, a PG blood sample should be drawn at the Baseline/Day 1 visit. If not obtained at Baseline/Day1 visit, the sample may be drawn at any time during the study.
Number of Subjects Planned:	Approximately 120 subjects
Target Population:	Chronic hepatitis C virus (HCV) infected adults.
Duration of Treatment:	12 Weeks
Diagnosis and Main Eligibility Criteria:	Chronic hepatitis C virus (HCV) infected adults. Up to approximately 20% of subjects may have cirrhosis at baseline and up to approximately 20% may be treatment-experienced. Sections 4.2 and 4.3 of the protocol contain detailed Inclusion and Exclusion criteria.
Study Procedures/ Frequency:	Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. All subjects will complete the following study visits: Screening, Baseline/Day 1, on-treatment visits at the end of Weeks 1, 2, 4, 8, and 12. All subjects will complete the post treatment Week 4 visit. Subjects who achieve SVR4 will complete post treatment Week 12 and Week 24 visits unless confirmed viral relapse occurs. Viral breakthrough or relapse must be confirmed. 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), HCV RNA, HCV genotype, serology (HIV, HCV, HBV), hemoglobin A1c (HbA1c), assessment of the presence or absence of cirrhosis, imaging for HCC, serum β-hCG (females of child bearing potential only), urinalysis and urine drug screen.

	On-treatment assessments include adverse events (AEs), concomitant medications, study medication pill count, physical examination, weight, vital signs, safety laboratory tests, IL28B genotyping (Day 1), HCV RNA, and urine pregnancy tests (females of child bearing potential only). Single 12-lead ECGs will be collected at Baseline/Day 1 (prior to study drug administration) and at Week 1 and Week 12 or End of Treatment. At the time of ECG collection, printed copies (paper) will be reviewed by qualified study staff (as determined by the Investigator) and compared to the subject's Baseline ECG as part of routine safety monitoring. Post-treatment assessments include AEs, concomitant medications, vital signs, safety laboratory tests, HCV RNA, and urine pregnancy tests (females of child bearing potential only). Health Related Quality of Life (HRQoL) survey SF-36 will be completed at Baseline/Day 1, On-treatment Week 4 and Week 12 or Early Termination (if applicable), and post treatment Week 4, and 12 (if applicable). Samples for HCV RNA sequencing/phenotyping will be collected at Day 1 and every visit thereafter. For subjects who provide their additional and specific consent, an optional blood sample will be collected at the Baseline/Day 1 visit for PG (this sample may be drawn after Baseline/Day 1 if necessary). At the following visits an optional plasma sample may be collected and archived for future use: Baseline/Day 1 and Week 12 or ET visit. Subjects may opt out of archive sample collection.
Test Product, Dose, and Mode of Administration:	SOF/VEL fixed dose combination (FDC) is manufactured as a 400 mg/100 mg FDC tablet for oral administration. Subjects will take 1 tablet daily with or without food.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	Adverse events (AEs) and laboratory tests will be collected throughout the study.
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using the COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.

Statistical Methods:	The primary efficacy endpoint for the study is SVR12 in all enrolled and treated subjects. No hypothesis testing will be performed. Secondary efficacy endpoints include SVR4 and SVR24. All continuous endpoints (except for safety endpoints) will be summarized using an 8-number summary (n, mean, standard deviation, and median, Q1, Q3, minimum, maximum) by stratification within group (as appropriate). All categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition. Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data.

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
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APRI	AST: platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BW	body weight
CL_{cr}	creatinine clearance
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)
CRF	case report form(s)
CRO	Contract (or clinical) research organization
DAA	direct acting antiviral
DCV	daclatasvir (HCV NS5A Inhibitor)
DDI	drug-drug interaction
dL	deciliter
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
eCRF	electronic case report form(s)
ESA	erythropoiesis stimulating agent
ET	Early Termination
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination
FSH	follicle stimulating hormone
g	grams
GCP	Good Clinical Practice
GCSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GS-7977	formerly PSI-7977
GSI	Gilead Sciences, Inc.

GT	genotype (viral)
Hb	hemoglobin
HbA1c	hemoglobin A1c
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
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	interferon
IL28B	interleukin-28B gene
IND	Investigational New Drug (Application)
INR	international normalized ratio of prothrombin time
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
kg	kilogram
L	liter
LDL	low-density lipoprotein
LDV	ledipasvir
LH	luteinizing hormone
LLN	lower limit of the normal range
LLOQ	lower limit of quantification
LLT	lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mIU	milli international units
mL	milliliter
mmHg	millimeters mercury
ng	nanogram
ng•h/mL	nanograms times hours per milliliter
NG	norgestrel
NGM	norgestimate
NGM/EE	norgestimate/ethinyl estradiol
NGMN	norelgestromin

NS (3/4A/5A/5B)	Non-structural Protein
OC	oral contraceptive
PCR	Polymerase Chain Reaction
Peg-IFN	pegylated interferon
pg	picogram
pg•h/mL	picograms times hours per milliliter
P-gp	P-glycoprotein
PPI	proton pump inhibitor
PT	preferred term or prothrombin time
QD	once daily (use only in tables)
RBC	red blood cell count
RBV	ribavirin
RNA	ribonucleic acid
Scr	serum creatinine (mg/dL)
SADR	serious adverse drug reaction
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	System Organ Class
SOF	Sovaldi® or sofosbuvir, formerly GS-7977
SOF/VEL	SOF/VEL fixed dose combination
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	sustained virologic response
TPO	thrombopoietin
ULN	upper limit of the normal range
US	United States
VEL	velpatasvir, formerly GS-5816
WBC	white blood cell count

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) infection is a global health challenge with estimates ranging up to 150 million individuals infected worldwide {28346}. In the United States (US), approximately 2.7 million people have chronic HCV infection {28338} and HCV infection causes over 15,000 deaths each year {20446}, 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 {28339}. Successful treatment of chronic HCV infection reduces the need for liver transplant, the incidence of HCC and overall mortality {25891}. Thus, the public health benefit of safe and effective HCV treatment regimens is high.

The development of sofosbuvir (Sovaldi®, SOF), a nucleotide analog HCV NS5B polymerase inhibitor, represents a major advance in the treatment of HCV as SOF-based regimens are shorter in duration, better tolerated, and result in higher SVR rates than prior therapies. SOF is currently approved in the US for the treatment of genotype (GT) 1, 2, 3 and 4 HCV infection and in the European Union for GT1-6 with different regimens and durations dependent on the HCV genotype {27503}.The next wave of therapies for the treatment of HCV includes combinations of direct acting antivirals (DAAs) including SOF that will obviate the need for administration of Peg-IFN and RBV. The first of these treatments, a fixed dose combination (FDC) of SOF and the HCV nonstructural protein 5A (NS5A) inhibitor ledipasvir (LDV), has been approved in the US and Europe. The Phase 3 studies GS-US-337-0102 (ION 1), GS-US-337-0109 (ION 2), and GS-US-337-0108 (ION 3) demonstrated that treatment with LDV/SOF with or without RBV for 8, 12 or 24 weeks resulted in high SVR12 rates in subjects with GT1 HCV infection {28583}, {28585}, {28587}.

Most current HCV drug development effort focuses on GT1 HCV infection as this is the most prevalent HCV genotype in developed countries {32174}. However, over half of all HCV infections are non-GT1: estimates from 2 recent meta-analyses indicate GT3 HCV is the next most common accounting for 22-30% of infections, while GT2 and GT4 each account for approximately 8 to 13%, GT6 for approximately 2 to 5%, and GT5 for approximately 1% of HCV infections worldwide. The availability of a well-tolerated, all oral, short duration therapy that is effective across all HCV genotypes would be a major advance for the treatment of HCV infection globally, particularly in regions where HCV genotyping is not part of routine medical care for HCV infection.

Although some individualization of care will be necessary, particularly for patients with advanced disease, the development of a pangenotypic regimen of short-duration that may not require HCV genotyping, response guided therapy, or intensive safety monitoring due to use of Peg-IFN or RBV will enable more patients to be treated.

1.2. Sofosbuvir/Velpatasvir Fixed Dose Combination

SOF/ velpatasvir (VEL) fixed-dose combination (SOF/VEL FDC) combines two HCV specific direct acting antivirals (DAAs) into a single tablet for the treatment of chronic HCV infection.

SOF is a nucleotide analog HCV NS5B polymerase inhibitor currently approved in the US and other regions for the treatment of HCV infection as a component of an antiviral treatment regimen. VEL (formerly known as GS-5816) is a HCV NS5A inhibitor that has demonstrated activity against HCV genotypes 1, 2, 3 and 4 HCV in a 3-day monotherapy study. Phase 2 studies of SOF +VEL administered as single agents have demonstrated that the combination of SOF 400 mg and VEL100 mg administered for 12 weeks is well tolerated and results in high SVR rates across a broad range of HCV genotypes. The SOF/VEL FDC (400 mg/100 mg) is a co-formulation of SOF 400 mg and VEL 100 mg for Phase 3 evaluation that has demonstrated similar exposure of each component compared to co-administration of the single agents.

The development of SOF/VEL may have a major impact on the global prevalence and burden of HCV as it may represent a simple, well tolerated, highly efficacious pangenotypic treatment for all HCV infected patients.

1.2.1. General Information

Please refer to the SOF/GS-5816 Investigator's Brochure (IB) for additional information on SOF/VEL, and the individual components, including:

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

1.2.2. Additional Clinical Pharmacology Study

1.2.2.1. Study GS-US-281-1058

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

Table 1-1 presents the steady-state PK parameters and statistical comparisons of NGM metabolites norelgestromin (NGMN) and norgestrel (NG) and EE following administration alone or in combination with VEL. Steady-state VEL PK parameters were also assessed. Norgestimate was not quantifiable for all subjects at most time points. Similar systemic exposure of NGMN and NG were achieved following NGM/EE administration with VEL relative to administration of NGM/EE alone. A modest increase in EE C_{max} was observed when administered with VEL with no change in overall exposure (AUC) or C_{tau}. The magnitude of increase in EE C_{max} when administered with VEL is similar to that observed with the concomitant administration of other drugs such as voriconazole and etravirine, which did not warrant dose adjustment {13886}, {24911}. VEL exposures were consistent with historical data (Studies GS-US-281-0115, GS-US-342-0104).

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

PK Parameter	Mean (%CV)		GLSM Ratio (90% CI) NGM/EE + VEL vs. NGM/EE
	NGM/EE Alone (N = 15)	NGM/EE + VEL (N = 13)	
Norelgestromin			
AUC_{tau} (pg•h/mL)	17,700 (16.7)	15,700 (11.2)	0.89 (0.85, 0.94)
C_{max} (pg/mL)	1650 (16.8)	1600 (13.7)	0.97 (0.90, 1.04)
C_{tau} (pg/mL)	454 (18.5)	416 (14.3)	0.92 (0.86, 0.98)
Norgestrel			
AUC_{tau} (pg•h/mL)	47,000 (34.4)	43,000 (32.4)	0.91 (0.73, 1.14)
C_{max} (pg/mL)	2410 (30.6)	2330 (31.5)	0.96 (0.80, 1.17)
C_{tau} (pg/mL)	1760 (34.4)	1640 (35.7)	0.92 (0.74, 1.15)
Ethinyl Estradiol			
AUC_{tau} (pg•h/mL)	666 (30.7)	686 (27.3)[a]	1.06 (0.98, 1.14)
C_{max} (pg/mL)	57.5 (27.3)	80.0 (28.4)[a]	1.42 (1.28, 1.58)
C_{tau} (pg/mL)	14.8 (39.3)	12.4 (43.9)[a]	0.84 (0.77, 0.92)
Velpatasvir			
AUC_{tau} (ng•h/mL)	--	4680 (35.1)	--
C_{max} (ng/mL)	--	626 (22.0)	--
C_{tau} (ng/mL)	--	68.3 (47.6)	--

Note: preliminary data presented to 3 significant figures.

a N = 12

Preliminary luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone concentrations were similar in both treatment cycles, as presented in Table 1-2. Luteinizing hormone and progesterone median values were lower than those expected for ovulatory or luteal

phases, respectively {25217}, {25218}, {25219}. Follicle stimulating hormone was lower or within the expected range for the ovulatory phase {25218}. These results are consistent with a possible decrease in serum LH and FSH by hormonal contraceptives and absence of ovulation, as assessed by very low progesterone values on cycle Day 21.

Table 1-2. Preliminary Summary of LH, FSH, and Progesterone Concentrations Following Administration of NGM/EE alone or with VEL

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

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

1.3. Rationale for This Study

This Phase 3 study has been designed as a multicenter, open-label, non-randomized study evaluating SOF/VEL for 12 weeks. Approximately 120 subjects will be enrolled. The population of the study will be subjects with chronic HCV infection of any genotype, with up to approximately 20% having prior treatment failure with an interferon-based regimen and up to approximately 20% having evidence of compensated cirrhosis at screening.

In Russia, the prevalence of HCV is estimated to be 4.1% {32174}, or approximately 4.9 million adults positive for antibody to-HCV. Although GT1 is the most common genotype in Russia, with a prevalence estimated at 55%, GT3 accounts for approximately 35% and GT2 for approximately 8% of infections {32174}. Anti-HCV prevalence is lower in Sweden (0.7% of adults) and the most common genotypes are similar to Russia: 45% GT1, 34% GT3, 19% GT2, and 2% GT4 {32174}. A single pangenotypic regimen would be of benefit for these diverse HCV populations.

Therapies which are not administered by injection nor associated with IFN-related or RBV-related adverse events are likely to improve patient treatment adherence and support high rates of viral cure. It is also likely that agents with favorable safety profiles which do not require frequent dose modification nor intensive monitoring of clinical adverse events and laboratory abnormalities will facilitate patient management.

Phase 2 evaluation of SOF + VEL demonstrated that co-administration of the single agents for 8 or 12 weeks was well tolerated and resulted in high SVR rates across a broad range of HCV genotypes. In the Phase 2 study GS-US-342-0102, administration of SOF 400mg + VEL 100mg for 12 weeks to treatment-naïve subjects without cirrhosis with genotype 1, 2, 3, 4, or 6 HCV infection resulted in SVR12 rate of 100% (28/28), 100% (10/10), 93% (25/27), 86% (6/7), and 100% (5/5), respectively. In addition, one treatment naïve subject with genotype 5 HCV infection administered SOF +VEL 25mg for 12 weeks achieved SVR12. The GS-US-342-0109 study evaluated SOF + VEL with and without RBV in populations of patients considered more difficult to cure, including subjects who had failed a prior interferon based regimen and those with cirrhosis. Administration of SOF 400mg + VEL 100 mg for 12 weeks resulted in SVR12 rates of 88% (23/26) and 100% (27/27) in treatment experienced subjects with genotype 3 HCV infection with and without cirrhosis, respectively. Administration of SOF 400mg + VEL 100mg for 12 weeks resulted in an SVR4 rates of 100% (27/27) in subjects with genotype 1 HCV infection who had failed prior treatment with a protease inhibitor with Peg-IFN/RBV. Seven of these 27 subjects had cirrhosis.

The Phase 2 data suggest that SOF +VEL 100mg has the potential to cure HCV infected patients across a broad range of HCV genotypes, when administered for 12 weeks without RBV and regardless of prior treatment experience or cirrhosis status. The co-formulation of SOF/VEL (400 mg/100 mg) adds to the simplicity of the regimen in allowing for a once daily pill. Data from this study will support the development of a well-tolerated, short duration, RBV-free regimen for all genotypes of HCV infection that has the potential to make an impact on the global prevalence and burden of HCV infection.

In particular, the availability of a single, pangenotypic regimen is anticipated to be especially beneficial in Russia where genotype diversity is high and genotyping may not be readily available or routinely done. Access to treatment for patients with HCV infection would be expanded as a result.

1.4. Rationale for Dose Selection

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

VEL 100 mg has been administered in combination with SOF 400 mg for 12 weeks to 237 HCV-infected subjects in Phase 2 studies. VEL 100 mg was selected for co-formulation with SOF and evaluation in this study based on the Phase 2 safety, PK and antiviral activity (studies GS-US-342-0102, GS-US-342-0109, and GS-US-337-0122 [Cohort 4]). The Phase 1 study GS-US-281-0102 established the anti-HCV activity of VEL and indicated that the exposures achieved following administration of doses > 25 mg provide at least 80% of maximal antiviral response in all HCV genotypes.

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

1.5. Risk/Benefit Assessment for the Study

This study will provide information of the safety and efficacy of SOF/VEL, a potent HCV nucleotide inhibitor and a potent HCV NS5A inhibitor. This combination has the potential to be a once-daily pangenotypic regimen for the treatment of chronic HCV infection.

The potential benefits of SOF/VEL over the current standard of care for the treatment of chronic HCV are:

- A once-daily, single tablet, single duration, pangenotypic therapy for HCV infection could simplify treatment algorithms and impact worldwide disease prevalence
- A reduction in the AEs currently associated with the use of Peg-IFN and RBV
- A short duration of therapy which should lead to better outcomes through improved adherence

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

The safety profile of SOF/VEL has not been established. The safety profile of SOF + VEL 25mg or VEL 100mg administered for 8 or 12 weeks has been established in over 800 subjects in Phase 2 studies. The safety profile of the proposed therapeutic regimen of SOF 400mg and VEL 100mg administered for 12 weeks has been established in 237 subjects enrolled in Phase 2 studies. No clinical safety issues specifically related to VEL or SOF + VEL have been identified to date. No clinical safety issues specifically related to the NS5A inhibitor class including daclatasvir (DCV) and LDV have been identified to date {28583}, {28585}, {28587}.

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

In summary, if high rates of SVR can be obtained with a short, IFN-free, RBV-free, pangenotypic regimen, the anticipated improvements in safety and tolerability would offer a favourable risk-benefit determination for patients with chronic HCV infection and enhance access to treatment.

1.6. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the efficacy of treatment with SOF/VEL fixed dose combination (FDC) for 12 weeks in subjects with chronic HCV infection 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 for 12 weeks

The secondary objectives of this study are:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

The exploratory objectives of this study are:

PPD

3. STUDY DESIGN

3.1. Endpoints

The primary endpoints of this study are:

- Primary efficacy endpoint is SVR12 in all enrolled subjects after 12 weeks of SOF/VEL treatment
- Primary safety endpoint is Safety and tolerability after 12 weeks of SOF/VEL treatment and AE leading to drug discontinuation

Secondary endpoints of this study are:

- SVR4 and SVR24 in all enrolled subjects after 12 weeks of SOF/VEL treatment
- Kinetics of HCV virus
- Emergence of the viral resistance after 12 weeks of treatment and resistance associated variants

3.2. Study Design

This is a multi-center, open-label study that will evaluate the safety, tolerability and antiviral efficacy of SOF/VEL FDC for 12 weeks in subjects with chronic HCV infection.

3.3. Study Treatments

Approximately 120 subjects will be enrolled to receive: SOF/VEL (400 mg/100 mg) once daily for 12 weeks.

Up to 20% of subjects enrolled in the study may have cirrhosis at baseline and up to approximately 20% may be treatment-experienced.

3.4. Visit Schedule

All subjects will complete the following study visits: Screening, Day 1, On-Treatment visits at the end of Weeks 1, 2, 4, 8, and 12, and Post-Treatment Visits at Weeks 4, 12, and 24 following the last dose of study drug. Subjects who achieve SVR4 will complete post treatment Week 12 and Week 24 visits unless confirmed viral relapse occurs. Viral breakthrough or relapse must be confirmed

Screening assessments will be completed within 28 days of the Day 1 Visit. The screening window can be extended to 42 days prior to Day 1 in extenuating circumstances with sponsor approval.

The assessments performed at each visit are described in Section 6 and Appendix 2**.**

3.5. HCV Virologic Response-Based Treatment Stopping Criteria

The following on-treatment HCV 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 nadir
- HCV RNA ≥ LLOQ through 8 weeks of treatment

Confirmation should be performed as soon as possible and must occur no later than 2 weeks after an initial observation indicating virologic failure.

All subjects will complete the post treatment Week 4 visit. Subjects who achieve SVR4 will complete post treatment Week 12 and Week 24 visits unless confirmed viral relapse occurs.

3.6. Treatment Discontinuation Criteria

When medically feasible, the Medical Monitor must be consulted prior to subject discontinuation.

Study drug must be discontinued in the following instances:

- Unacceptable toxicity, as defined in Section 7.1 of the protocol, 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
- Pregnancy of female subject
- Efficacy failure as defined in Section 3.5
- Significant protocol violation
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason
- Discontinuation of the study at the request of Gilead, regulatory agency, or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

If a subject meets discontinuation criteria during treatment, an Early Termination visit will be required (Section 6.4). Early Termination visits should be scheduled as soon as possible following discontinuation of treatment. All subjects will complete the post treatment Week 4 visit.

3.7. Biomarker Testing

3.7.1. Biomarker Samples for Optional Future Research

PPD

[redacted]

3.7.2. Biomarker Samples for Optional Pharmacogenomic Research

PPD

[redacted]


PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 120 chronic HCV subjects will be enrolled in this study with up to approximately 20% of subjects having cirrhosis at baseline and up to approximately 20% being treatment-experienced.

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 ≥ 10^4 IU/mL at Screening.

4) HCV genotype 1, 2, 3, 4, 5, 6 assessed at Screening by the Central Laboratory.

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

6) Classification as treatment naïve or treatment experienced. Approximately 20% may be treatment-experienced.

   a) Treatment naïve is defined as having never been exposed to approved or experimental HCV-specific direct-acting antiviral agents or prior treatment of HCV with interferon or ribavirin.

   b) Treatment experienced is defined as prior treatment failure to a regimen containing interferon either with or without RBV that was completed at least 8 weeks prior to Day 1. **Subject must not have discontinued the prior regimen that resulted in virologic failure due to an adverse event.**

      The subject's medical records must include sufficient detail of prior virologic failure to allow for categorization of prior response (See Section 6.2.1), as either:

      (1) Non-Responder: Subject did not achieve undetectable HCV RNA levels while on treatment, or

      (2) Relapse/Breakthrough: Subject achieved undetectable HCV RNA levels during treatment or within 4 weeks of the end of treatment but did not achieve SVR.

7) Cirrhosis determination (approximately 20% may have cirrhosis)

   a) Cirrhosis is defined as any one of the following:

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

      ii) FibroTest® score > 0.75 AND an AST:platelet ratio index (APRI) > 2 during Screening

      iii) Fibroscan® with a result of >12.5 kPa

   b) Absence of cirrhosis is defined as any one of the following:

      i) A liver biopsy performed within 2 years of Day 1 showing absence of cirrhosis

      ii) FibroTest score ≤ 0.48 AND APRI ≤ 1 performed during Screening

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

   In the absence of a definitive diagnosis of presence or absence of cirrhosis by FibroTest, APRI using the above criteria, a liver biopsy or Fibroscan is required. Liver biopsy results will supersede FibroTest, APRI or Fibroscan results and be considered definitive.

8) Liver imaging within 6 months of Day 1 is required only in cirrhotic patients to exclude hepatocellular carcinoma (HCC).

9) 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.

10) 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.

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

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

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

4.3. Exclusion Criteria

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

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

   a) Clinically-significant 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) Clinical hepatic decompensation (ie, ascites, encephalopathy or variceal hemorrhage)

   d) Solid organ transplantation

   e) Significant pulmonary disease, significant cardiac disease or porphyria

   f) Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years. Subjects with psychiatric illness (without the prior mentioned conditions) that is well-controlled on a stable treatment regimen for at least 6 months prior to Day 1 or has not required medication in the last 12 months may be included.

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

   h) Significant drug allergy (such as anaphylaxis or hepatotoxicity).

2) Screening ECG with clinically significant abnormalities

3) Any of 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 (CL_{cr}) < 60 mL /min as calculated by the Cockcroft-Gault equation {2202}

g) Hemoglobin < 11 g/dL for female subjects; < 12 g/dL for male subjects.

h) Albumin < 3 g/dL

i) INR > 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR

4) Prior exposure to SOF or other nucleotide analogue HCV NS5B inhibitor or any HCV NS5A inhibitor

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

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

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

8) 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.

9) Use of any prohibited concomitant medications as described in Section 5.3.

10) Chronic use of systemically administered immunosuppressive agents (e.g., prednisone equivalent > 10 mg/day).

11) Known hypersensitivity to VEL, SOF, or formulation excipients.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment and Study Drug supply

An Interactive Web Response System (IWRS) will be employed to manage subject enrollment, and study drug dispensing and re-supply. Eligible subjects will be enrolled and assigned to the open-label treatment. Every subject will receive SOF/VEL tablet for 12 weeks.

5.2. Description and Handling of SOF/VEL FDC

5.2.1. Formulation

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

5.2.2. Packaging and Labeling

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

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

5.2.3. Storage and Handling

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

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

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

5.2.4. Dosage and Administration of SOF/VEL FDC

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

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

5.3. 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 need to be recorded in the source documents and eCRFs.

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

- Hematologic stimulating agents (eg, erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)
- Chronic 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 (such as substrates, inhibitors or inducers of drug transporters or metabolizing enzymes, eg, P-gp or CYP3A) with the study drug may result in pharmacokinetic interactions resulting in increases or decreases in exposure of the study drug or these medications. Table 5-1. below contains medications that are prohibited from **21 days prior to Day 1** through the end of treatment and those medications that may be used with caution. The use of amiodarone is prohibited from **60 days prior to Baseline/Day 1** through the end of treatment.

Table 5-1. List of Disallowed /Use with Caution Medications

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

a The 21 day washout period does not apply to proton pump inhibitors (PPIs), which can be taken up to 7 days before Day 1. H2-receptor antagonists must not exceed a dose of 20 mg famotidine or equivalent and can be taken simultaneously with SOF/VEL and/or staggered by 12 hours. Antacids that directly neutralize stomach acid (i.e. Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/VEL administration.
b May result in a decrease in the concentration of study drugs.
c May result in an increase in the concentration of study drugs and/or concomitant medications
d May result in symptomatic bradycardia. Mechanism is not currently known. The use of amiodarone is prohibited from 60 days prior to Baseline/Day 1 through the end of treatment
e Monitor for signs and symptoms of digoxin toxicity.
f Use with SOF/VEL may result in an increase in the concentration of HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

Medications for disease conditions **excluded** from the protocol (eg, HIV-1 infection, active cancer, 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 excluded concomitant medication, the Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication.

5.4. Accountability for SOF/VEL FDC

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

SOF/VEL FDC accountability records will be captured in IWRS:

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

At the Day 1 visit, subjects will be dispensed 2 bottles of SOF/VEL so that they have sufficient tablets to cover the 3 day time window around the Week 4 and 8 visit. Subjects must be instructed to bring back the study drug in the original container at every post-Day 1 study visit through the end of treatment. The extra bottle dispensed at Day 1 must be brought to each on-treatment visit for accountability purposes and will be re-dispensed to the subject except at the Week 12 or EOT visit.

5.4.1. Investigational Medicinal Product Return or Disposal

Please refer to Section 10.1.7 for Investigational Medicinal Product Accountability and Return.

6. STUDY PROCEDURES

Study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described briefly in the text that follows. All eligible subjects will complete Screening, Day 1, On-Treatment visits at the end of Weeks 1, 2, 4, 8, and 12, and Post Treatment Visits at Weeks 4, 12, and 24, as appropriate. Subjects who achieve SVR4 will complete post treatment Week 12 and Week 24 visits unless confirmed viral relapse occurs. Viral breakthrough or relapse must be confirmed

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

6.1. Subject Enrollment and Treatment Assignment

Eligible subjects will be enrolled on Day 1 and will be assigned to receive SOF/VEL for 12 weeks.

6.2. Pretreatment Assessments

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

Subjects will be screened within 28 days of the Day 1 visit to determine eligibility for participation in the study. The screening window can be extended to 42 days prior to Day 1 for extenuating circumstances with sponsor approval.

The following assessments will be performed and documented at screening:

- Obtain signed informed consent
  - A separate informed consent will be required from subjects participating in the PG sub-study
- Obtain medical history, including information on prior HCV treatment history
  - If treatment experienced, record the duration of the prior treatment and the type of interferon and/or ribavirin or DAA administered
  - Record whether the subject had a Non-response or Relapse/Breakthrough during prior treatment as defined in inclusion criterion #6 (Section 4.2)
- Obtain demographic information
- Perform complete physical examination including vital signs, body weight, and height
- Perform 12-lead ECG

- Obtain details on AEs related to screening procedures (See Section 8 for details)
- Obtain details of concomitant medications
- Obtain blood samples for
  - Hematology and chemistry tests
  - Coagulation tests
  - HCV RNA (quantitative)
  - HCV genotype
  - Fibrotest
  - HCV antibody, HIV 1/2 antibody, and HBV surface antigen (HBsAg)
  - HbA1c
  - Serum β-human chorionic gonadotropin (β-hCG) pregnancy test, for females of childbearing potential only
- Obtain urine sample for
  - Urinalysis
  - Drug screen
- Determine cirrhosis status
  - If the presence of cirrhosis cannot be determined based on medical history or screening lab tests, biopsy or Fibroscan® should be performed
  - If the presence of cirrhosis is determined, appropriate diagnostic imaging (eg, CT or ultrasound) should be performed to exclude the presence of HCC

Retests of Screening labs are permitted only if there is reason to believe the retest value will be within accepted parameters, for example, if the initial exclusionary value was either due to a sample processing error or due to extenuating circumstances such as intercurrent illness.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 28-42 days after screening for enrollment into the study.

From the time of obtaining informed consent through the first administration of investigational medicinal product, all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures will be recorded on the adverse events case report form (eCRF).

All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7, Adverse Events and Toxicity Management for additional details.

6.2.2. Day 1 Assessments

Day 1 tests and procedures must be completed prior to enrollment and dosing/dispensing of study drug (see Appendix 2).

At the Day 1 visit, complete the following:

- Confirm eligibility
- Perform complete physical examination, including vital signs and body weight
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Obtain blood samples for:
  - Hematology and chemistry
  - Coagulation tests
  - HCV RNA(quantitative)
  - Viral RNA sequencing / phenotyping
  - IL28B genotype
  - Biomarker archive sample (for subjects who have not opted out)
  - Pharmacogenomic testing (for subjects who have consented to participate in the PG substudy)
- Obtain urine sample for β-hCG pregnancy test for females of childbearing potential only
- Dispense the study drug as directed by IWRS
- Instruct the subject on the packaging, storage and administration of study drug
- Health Related Quality of life survey, SF-36

6.3. Treatment Assessments (± 3 days)

The following treatment procedures/assessments are to be completed at the end of Weeks 1, 2, 4, and 8, for all subjects (see Appendix 2).

- Obtain vital signs
- Perform 12-lead ECG (at Week 1 only)
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - — Hematology & chemistry
  - — HCV RNA
  - — Viral RNA sequencing / phenotyping sample
- Obtain urine sample for β-hCG pregnancy test for females of childbearing potential only (Weeks 4,and 8)
- Conduct pregnancy prevention counseling at Week 4 only
- Review study drug compliance and drug administration instructions with subject
  - — Reconcile study drug administration using pill counts
- Dispense study drugs as directed by the IWRS (Weeks 4 and 8 only)
- Health Related Quality of life survey, SF-36 (Week 4 only)

6.4. Week 12 (± 3 days) or Early Termination (ET)

If a subject discontinues treatment early for any reason they should complete the Early Termination Visit assessments then the Post-Treatment Week 4 visit (4 weeks following the last dose of the study drug) should be completed (see Appendix 2).

The following procedures/assessments are to be completed at the Week 12 /Early termination Visit as applicable:

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs

- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Obtain blood samples for:
  - Hematology & chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA sequencing / phenotyping sample
  - Biomarker archive sample (for subjects who have not opted out)
- Obtain urine sample for:
  - β -hCG pregnancy test for females of childbearing potential only
- Review study drug compliance
  - Reconcile study drug administration using pill counts
  - Study drug should be returned at this visit
- Health Related Quality of life survey, SF-36

The sponsor (eg, Medical Monitor and Clinical Program Manager)/CRO must be informed as soon as possible when a subject discontinues treatment.

6.5. 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 viral RNA sequencing / phenotyping sample must be collected.

6.6. Post-Treatment Assessments (± 5 days)

All subjects will complete the Post-treatment Week 4 visit. Subjects who achieve SVR4 will complete post treatment Week 12 and Week 24 visits unless confirmed viral relapse occurs. The Post Treatment visits must be scheduled relative to the date of last administration of study drug (see Appendix 2).

6.6.1. Post treatment Week 4 (± 5 days)

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

- Obtain weight and vital signs
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Obtain blood samples for:
  - Hematology &chemistry
  - HCV RNA
  - Viral RNA sequencing / phenotyping sample
- Obtain urine sample for:
  - β -hCG pregnancy test for females of childbearing potential only
- Health-related quality of life questionnaire, SF-36

Subjects with HCV RNA < LLOQ at the post treatment Week 4 visit will return for the post treatment Week 12 visit.

6.6.2. Post treatment Weeks 12 and 24 (± 5 days)

The following procedures/assessments are to be completed for post treatment Weeks 12 and 24:

- Obtain blood samples for:
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample
- Health Related Quality of life survey, SF-36 (post treatment Week 12 only)
- Subjects with HCV RNA < LLOQ at the post treatment Week 12 visit will return for the post treatment Week 24 visit unless confirmed viral relapse occurs.

6.7. End of Study

Discontinuation from study drug dosing and discontinuation from the overall study, including the Post Treatment period, will be collected as two separate events.

Subjects are considered to have completed the study after the completion of Post Treatment Week 24 visit.

6.8. Procedures and Specifications

6.8.1. Clinical Laboratory Analytes

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

Coagulation: international normalized ratio (INR), Prothrombin time (PT), Activated partial thromboplastin time (APTT).

Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatine Kinase , Creatinine, Total Bilirubin (reflex to Direct Bilirubin), Glucose, Lipase, Potassium, Sodium, Fibrotest, APRI calculation and Direct Bilirubin at Screening only.

Urinalysis: Appearance, Blood, Color, Glucose, Leukocyte esterase, pH, Protein, Urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal.

Virological Tests: Serologies for HCV and HBV. 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, v2. 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

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

6.8.2. Medical History

Medical history including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history, including prior HCV treatment history (per Section 6.2.1), will be collected on all subjects during screening.

6.8.3. 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. Assessments by other specialists are not required unless medically indicated.

6.8.4. 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.

6.8.5. Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation {2202} using actual body weight (BW). The calculation will be performed by the central laboratory.

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

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

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

6.8.6. 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. On-treatment ECGs should be compared to the subject's baseline as part of routine safety monitoring.

6.8.7. Viral RNA Sequencing / Phenotyping Sample

Plasma samples will be collected at Day 1 and each subsequent visit for viral sequence analysis. At any unscheduled visit initiated for the purpose of confirming 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.

6.8.8. Health Related Quality of Life Survey (HRQoL)

A HRQoL survey, the short form 36 or SF-36 survey, will be completed by subjects at Day 1, On-Treatment visit at Weeks 4 and 12; Post-Treatment visits at Weeks 4 and 12 (if applicable), and Early Termination (if applicable). The subject should read the questionnaire by himself/herself and write/mark answers directly onto the questionnaire.

6.8.9. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period and 4 weeks after last dose of study drug (post treatment Week 4). Confirmatory serum pregnancy testing should be performed after any positive urine pregnancy test.

7. TOXICITY MANAGEMENT

7.1. Subject Stopping Rules

Administration of all study medication(s) 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 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.

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

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

Refer to Section 3.6 for information regarding discontinuation

8. ADVERSE EVENTS

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

8.1.1. 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, 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 (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 8.5)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

8.1.2. 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.

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

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 8.1.1 and 8.1.2. 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 8.1.3.

8.2. 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.

8.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

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

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

8.2.2. 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.

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

Requirements for collection prior to study drug initiation:

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

Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, pregnancy and other special situation reports, until 4 weeks after last administration of study drug must be collected / reported to the eCRF database as instructed.

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

Serious Adverse Events

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

Any SAEs and deaths that occur after the post treatment follow-up visit and within 30 days of the last dose of study drug, regardless of causality, should also be reported.

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

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

- 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.

8.4. Gilead Reporting Requirements

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

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

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

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

8.5. Special Situations Reports

8.5.1. Definitions of Special Situations

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

Medication error is any unintentional error in the prescribing, dispensing, or administration of a 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.

8.5.2. Instructions for Reporting Special Situations

8.5.2.1. Instructions for Reporting Pregnancies

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

Refer to Section 8.3 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 8.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

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

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com.

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

8.5.2.2. 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 IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications do 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 8.3 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.

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Objectives and Endpoints

9.1.1. Analysis Objectives

The primary objectives of this study are:

- To evaluate the efficacy of treatment with SOF/VEL FDC for 12 weeks in subjects with chronic HCV infection as measured by the proportion of subjects with SVR12
- To evaluate the safety and tolerability of treatment with SOF/VEL for 12 weeks

The secondary objectives of this study are:

- To determine the proportion of subjects who attain SVR4 and SVR24
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

The exploratory objectives of this study are:

9.1.2. Primary Endpoint

The primary efficacy endpoint is SVR12 in the Full Analysis Set (FAS).

9.1.3. Secondary Endpoint

Secondary efficacy endpoints include the proportion of subjects with HCV RNA < LLOQ at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24), the proportion of subjects with HCV RNA < LLOQ on treatment, HCV RNA change from Day 1, and the proportion of subjects with virologic failure.

9.1.4. Safety Endpoints

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

9.1.5. Other Endpoints of Interest

PPD

9.2. Analysis Conventions

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

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

9.2.1. Analysis Sets

9.2.1.1. Efficacy

The analysis set for antiviral activity analyses will be the FAS which include all enrolled subjects who took at least 1 dose of study drug.

9.2.1.2. Safety

The Safety Analysis Set will include all subjects who took at least 1 dose of study drug.

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

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

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

bracketed, the missing data point will also be termed a failure (ie, ≥ LLOQ detected) except for SVR24, which will be imputed according to SVR12 status. Success for SVR12 who have no further HCV RNA measurements collected will be counted as a success for SVR24 due to the high correlation between these 2 endpoints.

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

- If a subject received study medication, the subject will be included in a summary of adverse events according to the treatment received; otherwise, if the subject is not dosed then they will be excluded from the summary.

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

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

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

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

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

9.4. Demographic Data and Baseline Characteristics

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

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

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

9.5. Efficacy Analysis

9.5.1. Primary Analysis

The primary efficacy endpoint is SVR12 in the FAS. The primary analysis will be performed after all enrolled subjects have been followed through 12 weeks post-treatment or discontinued from study.

In the primary efficacy analysis, the SVR12 rate will be calculated along with the two-sided 95% exact confidence interval constructed using the binomial distribution (Clopper-Pearson method) {20839}. No statistical hypothesis testing will be performed.

9.5.2. 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, and other endpoints of interest including PPD .

Exploratory analyses may be performed to assess the relationship between PPD

9.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory, physical examinations, and vital signs measurements at various time points during the study, and by the documentation of AEs. The primary analysis will be the proportion of patients who experienced an AE leading to treatment discontinuation.

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.

9.6.1. Extent of Exposure

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

9.6.2. 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 adverse event will be defined as any adverse event with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug or any adverse event leading to premature discontinuation of study drug.

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

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

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

9.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the laboratory toxicity grading scheme defined in Appendix 3 of this protocol. The incidence of treatment-emergent laboratory abnormalities, defined as values that increase by at least one toxicity grade from Day 1 at any time post-baseline 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 Day 1 result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the Day 1 value will be assumed to be normal (ie, no grade [Grade 0]) for the summary of graded abnormality.

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

9.6.4. Other Safety Evaluations

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

9.7. Sample Size

With a sample size of 120, the 95% exact confidence interval for different observed SVR12 rates are presented in the Table 9-1 below:

Table 9-1. SVR 12 Rates and Associated 95% Confidence Intervals

Observed SVR12 rate	2-sided 95% exact CI
80% (96 out of 120)	72% - 87%
85% (102 out of 120)	77% - 91%
95% (114 out of 120)	89% - 98%

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. 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 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.

10.1.2. 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.

10.1.3. Informed Consent

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

The pharmacogenomics consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

10.1.4. 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 and 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. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

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

10.1.5. 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 and IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

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

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

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

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

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

10.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect

the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 10.1.5.

10.1.7. Investigational Medicinal Product Accountability and Return

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

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

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

10.1.8. Inspections

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

10.1.9. Protocol Compliance

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

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

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

10.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agencies. 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 10.1.4).

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.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. 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.

10.3.2. 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.

10.3.3. 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.

10.3.4. 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.

11. REFERENCES

2202 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

13886 Andrews E, Damle BD, Fang A, Foster G, Crownover P, LaBadie R, et al. Pharmacokinetics and tolerability of voriconazole and a combination oral contraceptive co-administered in healthy female subjects. Br J Clin Pharmacol 2008;65 (4):531-9.

20446 Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med 2012;156 (4):271-8.

20839 Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika 1934 Dec;26 (4):pp. 404-13.

24911 INTELENCE® (etravirine) tablets for oral use. US Prescribing Information. Janssen Pharmaceuticals, Inc. 2008 Titusville NJ. Revised February 2013.

25217 Quest Diagnostics. Progesterone, LC/MS/MS Reference Ranges. 2013:

25218 Quest Diagnostics. FSH and LH Reference Ranges. 2013:

25219 Barditch-Crovo P, Trapnell CB, Ette E, Zacur HA, Coresh J, Rocco LE, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. Clin Pharmacol Ther 1999;65 (4):428-38.

25891 Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9 (6):509-16 e1.

27503 Gilead Sciences Inc. SOVALDI® (sofosbuvir) tablets, for oral use. US Prescribing Information. Foster City, CA. December 2013:

28338 Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic Hepatitis C Virus Infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med 2014;160:293-300.

28339 Mahajan R, Xing J, Liu SJ, Ly KN, Moorman AC, Rupp L, et al. Mortality Among Persons in Care With Hepatitis C Virus Infection: The Chronic Hepatitis Cohort Study (CHeCS), 2006-2010. Clin Infect Dis 2014.

28346 World Health Organization (WHO). Hepatitis C Fact sheet N°164. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/#. Accessed: 20 March 2014.

28583 Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370 (20):1889-98.

28585 Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370 (16):1483-93.

28587 Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370 (20):1879-88.

32174 Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014 ;61:S45-S57.

12. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/ Velpatasvir Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) infection

GS-US-342-1522, Original, 17 July 2015

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

Anu Osinusi
Anu Osinusi, MD (Printed)
Medical Monitor

PPD
Signature

July 20, 2015
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

	Screening (Day -28 to Day 0)	Day 1	On-treatment Study Week (± 3 days)					Post treatment Study Week (± 5 days)		
			1	2	4	8	12/ET	4	12	24
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X	X								
Physical Examination	X	X					X			
Height	X									
Weight	X	X					X	X		
Vital Signs[b]	X	X	X	X	X	X	X	X		
12-Lead ECG[c]	X	X	X				X			
AEs	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling		X			X		X	X		
Health Related Quality of Life Survey, SF-36		X			X		X	X	X	
Review of Study Medication Compliance			X	X	X	X	X			
Study Drug Dispensing[a]		X			X	X				

	Screening (Day -28 to Day 0)	Day 1	On-treatment Study Week (± 3 days)					Post treatment Study Week (± 5 days)		
			1	2	4	8	12/ET	4	12	24
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X		
Coagulation Tests	X	X					X			
HCV RNA	X	X	X	X	X	X	X	X	X	X
Viral Sequencing[H]		X	X	X	X	X	X	X	X	X
Pregnancy Testing[d]	X	X			X	X	X	X		
Urinalysis, Urine Drug Screen	X									
HCV Genotyping,	X									
HCV, HIV, HBV Serology	X									
HbA1c, Cirrhosis assessment (Fibrotest and APRI)	X									
Optional Archive Sample[f]		X					X			
IL28B		X								
Pharmacogenomic Sample[e]		X								
Imaging for Hepatocellular Carcinoma (HCC)[g]	X									

a Day 1 assessments must be performed prior to the first dose of the study drug(s)
b Vital signs include resting blood pressure, pulse, respiratory rate and temperature.
c 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 gross abnormalities.
d For female of child bearing potential only. Serum β-hCG at screening, urine pregnancy test on Day 1 and every 4 weeks on treatment visits.
e For subjects who provide their additional and specific consent, an optional blood sample will be collected at the Baseline/Day 1 visit for PG (this sample may be drawn after Baseline/Day 1 if necessary).
f Subjects may opt out of archive sample collection.
g Imaging for HCC in cirrhotic subjects only.
h Plasma samples will be collected for viral resistance and possible other virology studies

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

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months#**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 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

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

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

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

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

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

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

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

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

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

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

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

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

1) Definitions

a) Definition of Childbearing Potential

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

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

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

b) Definition of Male Fertility

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

2) Study Drug Effects on Pregnancy and Hormonal Contraception

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

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

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

3) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to enrollment. A pregnancy test will be performed at the Post Treatment Week 4 visit. They must also agree to one of the following from Screening until 30 days of the last dose of SOF/VEL.

- 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.
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Tubal sterilization
  - Essure micro-insert system
  - Vasectomy in the male partner
  - Barrier methods (one female barrier and one male barrier must be used in combination)
    - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
    - Male barriers: Male condom (with or without spermicide)
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

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

4) Contraception Requirements for Male Subjects

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

Male subjects must agree to refrain from sperm donation until 30 days after the last dose of SOF/VEL.

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 the last dose of SOF/VEL. Subjects who become pregnant or who suspect that they are pregnant must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 8.5.2.1.