CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir Fixed Dose Combination Administered for Four Weeks in Patients Infected with Chronic HCV in the Peri-Operative Liver Transplantation Setting	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA	
IND Number:	This is a non-IND study	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	Not Available	
Indication:	Hepatitis C Virus Infection	
Protocol ID:	GS-US-342-2083	
Gilead Study Director:	Name: Telephone: Email:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Email:	Benedetta Massetto, MD PPD PPD
Protocol Version/Date:	Original	26 February 2016

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

Study Title:	A Phase 2, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir Fixed Dose Combination Administered for Four Weeks in Patients Infected with Chronic HCV in the Peri-Operative Liver Transplantation Setting
IND Number:	This is a non-IND study
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	Not Available
Study Centers Planned:	Approximately one center in New Zealand
Objectives:	The primary objectives of this study are as follows: • To explore the antiviral efficacy of treatment with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) therapy administered for four weeks following liver transplantation as measured by sustained virologic response (SVR) 12 weeks after cessation of treatment(SVR12) • To evaluate the safety and tolerability of SOF/VEL in HCV-infected subjects in the peri-operative and post-transplant period The secondary objectives of this study are as follows: • To determine the percentage of subjects who attain SVR at 4 weeks after cessation of treatment (SVR4) • To evaluate the proportion of subjects with virologic failure • To assess rates of graft survival, graft function, acute rejection and immunosuppressive therapy during treatment with SOF/VEL • To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment • To characterize pharmacokinetics of SOF/VEL

	The exploratory objectives of this study are as follows: PPD
Study Design:	This is an open-label study that will evaluate the safety, tolerability and antiviral efficacy of SOF/VEL administered for 4 weeks in HCV-infected adult male and female subjects who are undergoing liver transplantation. For all subjects SOF/VEL tablet (400/100 mg) once daily will be started the day of the subject's liver transplant if the transplant is completed before noon and the following day if it is completed after noon and will continue for 4 weeks. Treatment initiation may be delayed for up to 1 day if warranted by the subject's medical condition post-surgery. HCV RNA will be assessed at each visit.
Sub-Study:	**Pharmacogenomics (PG) Sub-study** PPD **Pharmacokinetic (PK) Sub-study (Required)** All subjects will participate in a PK sub-study in which intensive serial PK sample collection (samples obtained over 24 hours) will be performed on Day 1 to determine pharmacokinetics of SOF, its metabolites GS-566500 and GS-331007, and VEL.
Number of Subjects Planned:	Approximately 10
Target Population:	HCV infected adults who are undergoing primary liver transplantation
Duration of Treatment:	Subjects will be treated for 4 Weeks
Diagnosis and Main Eligibility Criteria:	HCV infected, male and non-pregnant/non-lactating female subjects, ages 18 years or older, who are undergoing liver transplantation, may be eligible for the study. Reference Section 4.2 and 4.3 of the protocol for detailed Inclusion and Exclusion criteria.

Study Procedures/ Frequency:	Screening assessments will be completed at the time a subject is identified as a potential study participant to give sufficient time for the subject to provide informed consent and perform screening assessments. Subject's screening data will be confirmed in the pre-operative period (within 48 hours of the planned transplant) at the Pre-surgery visit if the screening visit occurs more than 48 hours before the liver transplant surgery is started. All subjects will complete the following study visits: Screening; Pre-surgery (if needed); On-Treatment visits Days 1, 3, 5, 7, 14, 21, and 28; and Post-treatment Visits at Weeks 1, 2, 4, and 12 following the last dose of study drug. After consent is obtained, initial screening assessments will include physical examination, medical history, height (initial screening only), weight, vital signs, resting 12-lead electrocardiogram (ECG), screening procedure-related adverse events (AEs), concomitant medications (CMs), CPT and MELD score, safety laboratory tests (including hematology, chemistry, and coagulation), estimated creatinine clearance (Cl_{cr}), HCV RNA, HCV genotype, serology (HIV, HCV, HBV), serum β-hCG (females of child bearing potential only), and urinalysis. If the screening visit occurs more than 48 hours before the liver transplant surgery is started, the subject will also be reassessed within 48 hours of transplantation to determine their continued eligibility at the pre-surgery visit. The assessments will include physical examination, re-review of the medical history, weight, vital signs, resting ECG, AEs, CMs, CPT and MELD score, safety laboratory tests, estimated Cl_{cr}, HCV RNA, urine pregnancy tests (females of childbearing potential only) and pregnancy prevention counseling. If a separate informed consent is signed, samples of the explanted liver will be taken during surgery. If the transplant is completed before noon, the subject will take their first dose that day after the transplant which will be considered Day 1. If the transplant is completed after noon, the subject will take their first dose the following morning which will be considered Day 1. The planned first dose may be delayed for up to 1 day if, in the investigators opinion, delay is in the subject's medical interest. The subject will receive 4 weeks of study drug. On-treatment assessments starting at Day 1 will include vital signs, ECG (only at Day 28), AEs, CMs (including immunosuppressive therapy), safety laboratory tests, estimated Cl_{cr}, HCV RNA, study drug dosing adherence and urine pregnancy tests (females of childbearing potential only).

	Post-treatment assessments through Post-treatment week 4 only include AEs and CMs. Weight, vital signs, and urine pregnancy tests (females of child bearing potential only) will only be done at Post-treatment week 4. Pregnancy prevention counseling will be done at Post-treatment week 1 only. Safety laboratory tests, HCV RNA and viral sequencing samples will be collected through all Post-treatment visits. Samples for viral RNA sequencing/phenotyping will be collected starting at Day 1 and every visit thereafter. PPD
Test Product, Dose, and Mode of Administration:	SOF/VEL is manufactured as a FDC tablet, consisting of 400 mg SOF and 100 mg of VEL, for oral administration. Subjects will take 1 tablet daily with or without food.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	AEs and safety laboratory tests will be collected throughout the study (through the Post-treatment week 4 visit).
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v. 2.0.
Pharmacokinetics:	A single PK blood sample will be collected at each on-treatment visit for all subjects except on Days 1, 3 and 5. All subjects will be required to participate in an intensive serial PK sub-study to be performed on Day 1. The PK of SOF (and its metabolites GS-566500 and GS-331007), and VEL will be assessed. Serial PK samples will be collected at the following time points: 0 (pre-dose), 0.5, 1, 2, 4, 8, 12 and 24 hours post-dose.

Statistical Methods:

The primary efficacy endpoint is the percentage of subjects who achieve SVR12 (HCV RNA < lower limit of quantitation [LLOQ] 12 weeks after stopping study drug) for subjects in the Full Analysis Set (FAS).

Secondary efficacy endpoints include the percentage of subjects who attain SVR at 4 weeks after cessation of treatment (SVR4); the percentage of subjects who have HCV RNA <LLOQ at each on-treatment visit; and the percentage of subjects with virologic failure (VF, defined as HCV RNA ≥ LLOQ at end of treatment or relapse during the Post-treatment follow-up period).

The primary safety endpoint is the percentage of subjects who discontinue from study drug due to an adverse event. Deaths, graft loss, and rejection episodes will also be listed or summarized, as appropriate.

Other endpoints of interest include changes to immunosuppressive therapy and the emergence of viral resistance to SOF or VEL during and after cessation of treatment, and HCV RNA levels (IU/mL) at each on-treatment visit, if relevant.

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
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
BMI	body mass index
BW	body weight
CI	confidence interval
CrCL	creatinine clearance
CM	concomitant medication
CP	Child-Pugh
CPK	creatinine phosphokinase
CPT	Child-Pugh-Turcotte
CRF	case report form(s)
CRO	Contract (or clinical) research organization
CSA	colony stimulating agents
DAA	Direct acting antiviral
dL	Deciliter
DMC	Data Monitoring Committee
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
EOT	End of Treatment
ET	Early Termination
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	Fixed-dose combination
FEV_1	forced expiratory volume in one second
G	Gram
GCP	Good Clinical Practice (Guidelines)
GCSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
GT	Genotype (viral)

Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	Interferon
IL28B	IL28B gene
IMP	Investigational Medical Product
INR	International Normalized Ratio of prothrombin time
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
Kg	Kilogram
L	Liter
LDL	low-density lipoprotein
LDV	Ledipasvir
LLN	lower limit of the normal range
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
MCV	mean corpuscular volume or mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MGB	minor groove binder
mL	Milliliter
Min	Minute
mmHg	millimeters mercury
NS (3/4A/5A/5B)	non-structural protein
PCR	polymerase chain reaction
PEG	pegylated interferon
PG	Pharmacogenomics
PO	per os, by mouth or orally
PT	preferred term or prothrombin time

QD	once daily (use only in tables)
RBC	red blood cell count
RBV	Ribavirin
RNA	ribonucleic acid
SADR	serious adverse drug reaction
Scr	serum creatinine
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SOF	Sofosbuvir
Sofosbuvir	Formerly GS-7977
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
ULN	upper limit of the normal range
US	United States
VEL	Velpatasvir
VF	Virologic failure
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 {World Health Organization (WHO) 2014}. In the United States (US), approximately 2.7 million people have chronic HCV infection {Denniston et al 2014} and HCV infection causes over 15,000 deaths each year {Ly et al 2012}, although under-reporting of HCV infection on death certificates may contribute to as much as a 5-fold underestimation of the actual number of deaths {Mahajan et al 2014}. Successful treatment of chronic HCV infection reduces the need for liver transplant, the incidence of HCC and overall mortality {Backus et al 2011}. 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 {Gilead Sciences Inc 2015b} and in the European Union for GT1-6 with different regimens and durations dependent on the HCV genotype {Gilead Sciences Limited 2015}. SOF is also approved in both the US and Europe to be used in combination with ribavirin in patients awaiting liver transplantation in order to prevent HCV reoccurrence, and in Europe in patients who have already received liver transplants {Gilead Sciences Inc 2015b}, {Gilead Sciences Limited 2015}.

The next wave of therapies for the treatment of HCV includes combinations of direct acting antivirals (DAAs) including SOF that offer even higher response rates without the need for pegylated interferon (PEG-IFN), and often without the need for ribavirin, depending on patient characteristics and HCV genotype. 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 for genotypes 1, 4, 5, and 6 {Gilead Sciences Inc 2016}and Europe for genotypes 1, 3, and 4, 5, and 6 infections {Gilead Sciences Inc 2015a}. Currently, LDV/SOF in combination with ribavirin is approved in Europe for the treatment of genotypes 1, 4, 5, and 6 HCV in patients after liver transplantation. There are no currently approved ribavirin-free regimens for treatment of HCV in patients with who have had a liver transplant.

Most current HCV drug development effort focuses on GT1 HCV infection as this is the most prevalent HCV genotype in developed countries {Gower et al 2014}. 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, ribavirin-free, short duration therapy such as SOF/VEL that is effective across all HCV genotypes would be a major advance for the treatment

of HCV infection globally. This is particularly true for patients with who also have liver transplants who often have reduced blood cell counts or GFRs at baseline, making them susceptible to ribavirin-associated toxicities.

1.2. Investigational Medicinal Product Name

Sofosbuvir/velpatasvir 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.

Sofosbuvir 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 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 of 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 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. Pharmacology Studies

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 {Andrews et al 2008, Janssen Pharmaceuticals Inc. 2013}. VEL exposures were consistent with historical data (Studies GS-US-281-0115, GS-US-342-0104).

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

PK Parameter	Mean (%CV)		GLSM Ratio (90% CI) NGM/EE + VEL vs. NGM/EE
	NGM/EE Alone (N = 15)	NGM/EE + VEL (N = 13)	
Norelgestromin			
AUC_{tau} (pg•h/mL)	17,700 (16.7)	15,700 (11.2)	0.90 (0.82, 0.98)
C_{max} (pg/mL)	1650 (16.8)	1600 (13.7)	0.97 (0.88, 1.07)
C_{tau} (pg/mL)	454 (18.5)	416 (14.3)	0.92 (0.83, 1.03)
Norgestrel			
AUC_{tau} (pg•h/mL)	47,000 (34.4)	43,000 (32.4)	0.91 (0.73, 1.15)
C_{max} (pg/mL)	2410 (30.6)	2330 (31.5)	0.96 (0.78, 1.19)
C_{tau} (pg/mL)	1760 (34.4)	1640 (35.7)	0.92 (0.73, 1.18)
Ethinyl Estradiol			
AUC_{tau} (pg•h/mL)	666 (30.7)	686 (27.3)[a]	1.04 (0.87, 1.24)
C_{max} (pg/mL)	57.5 (27.3)	80.0 (28.4)[a]	1.39 (1.17, 1.66)
C_{tau} (pg/mL)	14.8 (39.3)	12.4 (43.9)[a]	0.83 (0.65, 1.06)
Velpatasvir			
AUC_{tau} (ng•h/mL)	--	4680 (35.1)	--
C_{max} (ng/mL)	--	626 (22.0)	--
C_{tau} (ng/mL)	--	68.3 (47.6)	--

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

Luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone concentrations were similar in both treatment cycles, as presented in Table 1-2. Luteinizing hormone and progesterone median values were lower than those expected for ovulatory or luteal phases, respectively {Quest Diagnostics 2013b}, {Quest Diagnostics 2013a}, {Barditch-Crovo et al 1999}. Follicle stimulating hormone was lower or within the expected range for the ovulatory phase {Quest Diagnostics 2013a}. These results are consistent with a possible decrease in serum LH and FSH by hormonal contraceptives and absence of ovulation, as assessed by very low progesterone values on cycle Day 21.

Table 1-2. 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 (eg, norgestimate/ethinyl estradiol) is permitted. Accordingly, the use of hormonal contraceptives with VEL as a single agent or as part of SOF/VEL FDC is permitted.

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

GS-US-342-1346 and GS-US-342-1709 were open-label, Phase 1, single-dose drug-drug interaction studies in healthy volunteers evaluating the effect of gastric acid suppressants (H2RAs and PPIs) on the PK of SOF/VEL. These studies were conducted because VEL has demonstrated pH-dependent solubility in vitro. A summary of results from these studies is presented in the table below.

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

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

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

Study GS-US-342-1709 also demonstrates that the nature of VEL exposure decrease was not uniform across the study population. The largest decreases were observed in subjects with the highest exposure at the reference condition of dosing, with SOF/VEL fasted without an acid reducing agent, and those with low exposure at the reference condition were generally unaffected by administration with a PPI. These data suggests that gastric pH is a contributor to the natural variability of VEL, and the range of exposure for HCV-infected subjects on PPIs is expected to be within that observed in Phase 3 ASTRAL studies. Accordingly, PPI doses comparable with omeprazole 20 mg can be administered with SOF/VEL when SOF/VEL is administered with food.

Table 1-3. Summary of Changes in SOF/VEL PK following administration with Representative H2RAs and PPIs

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

Study	Dosing Scheme	SOF PK Parameters			GS-331007 PK Parameters			VEL PK Parameters		
		AUC_{last}	AUC_{inf}	C_{max}	AUC_{last}	AUC_{inf}	C_{max}	AUC_{last}	AUC_{inf}	C_{max}
	SOF/VEL (fed) 4 hours Before OME 40 mg	↔	↔	↓30%	↔	↔	↔	↓53%	↓53%	↓56%

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

1.2.3. Clinical Trials of SOF/VEL

1.3. Additional Clinical Studies

Four Phase 3 studies are ongoing evaluating the efficacy and safety of SOF/VEL in subjects with genotype 1-6 HCV infection. Three studies enrolled subjects without cirrhosis or with compensated cirrhosis, GS-US-342-1138 (ASTRAL-1), GS-US-342-1139 (ASTRAL-2) and GS-US-342-1140 (ASTRAL-3); and one study enrolled subjects with decompensated cirrhosis GS-US-342-1137 (ASTRAL-4). Summaries of interim results from the individual Phase 3 studies are presented below.

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

Design

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

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

Disposition

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

The majority of subjects (99.3%) completed study treatment. Five subjects (0.7%) prematurely discontinued study treatment; 2 subjects in the SOF/VEL group and 3 subjects in the placebo group. The reasons for premature discontinuation of study drug for subjects in the SOF/VEL 12 Week group were an AE (1 subject) and lost to follow-up (1 subject) and for subjects in the Placebo 12 Week group were AEs (2 subjects) and investigator discretion (1 subject).

Demographics and Baseline Characteristics

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

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

Efficacy Results

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

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

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

Table 1-4. GS-US-342-1138: SVR12 Overall and by HCV Genotypes

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

GT = genotype

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

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

Virologic Resistance

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

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

Safety Results

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

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

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

Most laboratory abnormalities were Grade 1 or 2 in severity. Subjects in the SOF/VEL 12 Week group had Grade 3 or 4 chemistry abnormalities of elevated AST (Grade 3; 1 subject [0.2%]), elevated creatine kinase (Grade 3; 2 subjects [0.3%], Grade 4; 2 subjects [0.3%]), hyperglycemia (Grade 3, 15 subjects [2.4%]), and elevated lipase (Grade 3; 14 subjects [2.2%], Grade 4, 2 subjects [0.3%]). Among subjects in the SOF/VEL 12 Week, all Grade 3 or 4 creatinine kinase

elevations were transient, all Grade 3 or 4 lipase elevations were asymptomatic and generally transient, and Grade 3 or 4 hyperglycemia occurred in subjects with a medical history of diabetes. The most frequently observed Grade 3 or 4 laboratory abnormalities observed in placebo treated subjects were elevated ALT (Grade 3; 6 subjects [5.2%] and Grade 4; 2 subjects [1.7%]) consistent with ongoing HCV infection.

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

Conclusions

The conclusions from this interim analysis were as follows:

- The study met its primary efficacy endpoint demonstrating that the SVR12 rate of 99.0% (95% CI: 97.9% to 99.6%) in genotype 1, 2, 4, 5, and 6 HCV-infected subjects treated for 12 weeks with SOF/VEL was statistically superior to the prespecified SVR12 performance goal of 85% ($p<0.001$).
- High SVR12 rates were achieved across all HCV genotypes and subgroups
  - Among subjects with cirrhosis, the SVR rate was 99.2%
  - Among subjects with prior treatment failure, the SVR rate was 99.5%
  - Among subjects with baseline NS5A RAVs, the SVR12 rate was 99.2%
- Treatment with SOF/VEL for 12 Weeks was generally well tolerated with a safety profile similar to that of placebo treatment. There was a low incidence of SAEs, discontinuations due to AEs and no clinically relevant laboratory abnormalities.

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

Study Design

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

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

Disposition

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

Demographics and Baseline Characteristics

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

Efficacy Results

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

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

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

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

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

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

Virologic Resistance

Deep sequencing analyses indicated that genotype 2a and 2b were the predominant HCV subtypes in subjects who were randomized and treated in this study. Approximately 60% and 10% of subjects in the SOF/VEL 12 Week group had pretreatment NS5A and NS5B RAVs, respectively. The most prevalent NS5A RAV observed was L31M in 51% of subjects. Despite the presence of pretreatment NS5A and NS5B RAVs, no subjects in the SOF/VEL 12 Week group experienced virologic failure in this study. Two of the 6 subjects who relapsed in the SOF+RBV 12 Week group had low levels of the NS5B NI RAV L159F detectable at failure.

Safety Results

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

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

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

Serious adverse events (SAEs) were also rare (1.5%, 4 of 266 subjects [2 in each treatment group]). No SAE was reported in > 1 subject. All SAEs were considered by the investigators to be not related to study drug. Two non-treatment-emergent deaths were reported during the study (metastatic lung cancer and cardiac arrest after treatment completion). No pregnancies were reported during the study. Only 1 subject permanently discontinued any study drug (SOF/VEL)

due to AEs. After receiving 1 dose of SOF/VEL, the subject, who had a medical history of depression, insomnia and post-traumatic stress disorder, discontinued study treatment due to Grade 3 AEs of difficulty concentrating, headache, and anxiety that were assessed as related to study drugs by the investigator.

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

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

Conclusions

The conclusions from this interim analysis were as follows:

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

1.6. Study GS-US-342-1140 (ASTRAL-3)

Study Design

This ongoing, Phase 3, randomized, open-label, multicenter study is assessing the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL treatment compared with 24 weeks of SOF+RBV treatment in subjects with chronic genotype 3 HCV infection.

Subjects with genotype 3 HCV infection were randomized (1:1) to treatment with SOF/VEL for 12 weeks (SOF/VEL 12 Week group) or SOF+RBV for 24 weeks (SOF+RBV 24 Week group). Randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience (treatment naive vs. treatment-experienced).

Disposition

A total of 552 subjects were randomized and treated (277 subjects in the SOF/VEL 12 Week group and 275 subjects in the SOF+RBV 24 Week group). A total of 21 subjects (7.6%) in the SOF+RBV 24 Week group discontinued treatment compared with 2 subjects (0.7%) in the SOF/VEL 12 Week group. The most common reason for discontinuation of treatment for subjects in the SOF+RBV 24 Week group was AEs (9 subjects, 3.3%).

Demographics and Baseline Characteristics

The majority of subjects were male (62.3%), and 20.3% of subjects had a BMI $\geq$ 30 kg/m^2. Overall, the majority of subjects had HCV RNA $\geq$ 800,000 IU/mL (69.7%). A total of 163 subjects (29.5%) had cirrhosis at screening. Overall, 25.7% (142 subjects) were treatment experienced.

Efficacy Results

The study met the primary efficacy endpoint. The SVR12 rate for the SOF/VEL 12 Week group was statistically noninferior to the SVR12 rate for the SOF+RBV 24 Week group. The SVR12 rates were as follows:

- SOF/VEL 12 Week group: 95.3% (95% CI: 92.1% to 97.5%) of subjects (264 of 277) achieved SVR12.
- SOF+RBV 24 Week group: 80.4% (95% CI: 75.2% to 84.9%) of subjects (221 of 275) achieved SVR12.

The strata-adjusted difference (95% CI) in the proportions was 14.8% (9.6% to 20.0%). The superiority of treatment with SOF/VEL for 12 weeks over SOF+RBV for 24 weeks for SVR12 was also demonstrated ($p < 0.001$; CMH test stratified by cirrhosis status and prior treatment experience).

In the SOF/VEL 12 Week group, 13 of 277 subjects (4.7%) did not achieve SVR12. Of these, no subjects had on-treatment virologic failure, 11 subjects relapsed, and 2 subjects were lost to follow-up. In the SOF+RBV 24 Week group, 54 of 275 subjects (19.6%) did not achieve SVR12.

Of these, 1 subject had on-treatment virologic failure (nonresponse), 38 subjects relapsed, and 15 subjects did not achieve SVR12 for reasons other than virologic failure. These 15 subjects included 6 subjects who were lost to follow-up or who did not attend a Post-treatment Week 12 visit, 4 subjects who withdrew from the study due to AEs, 2 subjects who withdrew consent from the study, 2 subjects who died, and 1 subject who only received 2 days of study drug, did not achieve HCV RNA < LLOQ on treatment, and did not meet the protocol definition for virologic failure.

Most relapses occurred by the Post-treatment Week 4 visits. In the SOF/VEL 12 Week group, 8 of 11 relapses occurred by Post-treatment Week 4, and 3 of 11 relapses occurred between Post-treatment Weeks 4 and 12.

Across the 2 treatment groups, the SVR12 rates consistently favored the SOF/VEL 12 Week group over the SOF+RBV 24 Week group. Within each treatment group, the SVR12 rates for most subgroups were generally consistent with those observed in the overall population. In the SOF/VEL 12 Week group, the SVR12 rates for subjects with and without cirrhosis were 91.3% (73 of 80) and 97.0% (191 of 197), respectively, and the SVR12 rates for treatment-naive and treatment-experienced subjects were 97.1% (200 of 206) and 90.1% (64 of 71), respectively. In the SOF+RBV 24 Week group, subjects with cirrhosis had considerably lower SVR12 rates (66.3%; 55 of 83) than subjects without cirrhosis (87.2%; 163 of 187), and subjects with prior treatment experience had considerably lower SVR12 rates (63.4%; 45 of 71) than treatment-naive subjects (86.3%; 176 of 204).

HCV RNA levels ($\log_{10}$ IU/mL) declined rapidly, with similar decreases in HCV RNA observed in both treatment groups. Consistent with the rapid and sustained decline in HCV RNA, 91.7% of subjects in the SOF/VEL 12 Week group and 88.2% of subjects in the SOF+RBV 24 Week group had HCV RNA < LLOQ at Week 4. Time to virologic suppression did not impact virologic outcomes in the SOV/VEL 12 Week group: SVR12 rates were 96.0% and 95.7% among those subjects with HCV RNA < LLOQ and those with HCV RNA ≥ LLOQ at Week 4, respectively.

Virologic Resistance

Pretreatment NS5A and NS5B NI RAVs were present in 16% and 4% of subjects, respectively, in the SOF/VEL 12 Week group. There was a numerically lower SVR12 rate in SOF/VEL-treated subjects with baseline NS5A RAVs compared with subjects without NS5A RAVs (88% vs. 97%, respectively). All subjects with NS5B NI RAVs in the SOF/VEL 12 Week group achieved SVR12.

A total of 10 subjects in the SOF/VEL 12 Week group relapsed, and 1 subject was reinfected. All 10 subjects had the NS5A RAV Y93H detected at relapse time points. No SOF/VEL-treated subjects had NS5B NI RAVs emerge at relapse. The NS5B NI RAVs (N142T, L159F, or V321A) emerged in 7 of 39 subjects in the SOF+RBV 24 Week group who had virologic failure.

Safety Results

Overall, treatment with SOF/VEL for 12 weeks or SOF+RBV for 24 weeks was generally safe and well tolerated. A lower percentage of subjects in the SOF/VEL 12 Week group experienced any AE (88.4%; 245 of 277) compared with the SOF+RBV 24 Week group (94.5%; 260 of 275).

Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Grade 3 (severe) AEs were reported for 4.3% (12 subjects) in the SOF/VEL 12 Week group and 7.3% (20 subjects) in the SOF+RBV 24 Week group. Grade 4 (life-threatening) AEs were reported for no subjects in the SOF/VEL 12 Week group and 1.1% (3 subjects) in the SOF+RBV 24 Week group (death due to natural causes in 1 subject, cerebrovascular accident in 1 subject, and multiple gunshot wounds in 1 subject).

Of the most common AEs (ie, AEs reported in ≥ 10% of subjects in either treatment group), a lower percentage of subjects in the SOF/VEL 12 Week group compared with the SOF+RBV 24 Week group experienced fatigue (25.6% vs. 38.2%), insomnia (11.2% vs. 26.9%), nausea (16.6% vs. 21.1%), irritability (8.3% vs. 14.5%), cough (5.1% vs. 12.7%), pruritus (2.9% vs. 12.7%), and dyspepsia (3.2% vs. 10.9%).

Serious adverse events were reported for 2.2% (6 subjects) in the SOF/VEL 12 Week group and 5.5% (15 subjects) in the SOF+RBV 24 Week group. No SAE was reported in > 1 subject, and no SOV/VEL-treated subject had a treatment-related SAE. Three subject deaths were reported during the study (1 treatment-emergent death due to natural causes, 1 treatment-emergent death due to multiple gunshot wounds, and 1 nontreatment-emergent death due to an unknown cause); all 3 subjects were in the SOF+RBV 24 Week group. A total of 9 subjects (in the SOF+RBV 24 Week group) prematurely discontinued study drugs due to an AE. The most common AE resulting in discontinuation of study drug in the SOF+RBV 24 Week group was insomnia (1.1%, 3 subjects).

Most subjects had at least 1 laboratory abnormality reported, with the majority being Grade 1 (36.3%; 200 of 551 subjects) or Grade 2 (29.6%; 163 of 551 subjects) in severity. A lower percentage of subjects had Grade 3 laboratory abnormalities in the SOF/VEL 12 Week group (5.8%, 16 of 276) compared with the SOF+RBV 24 Week group (14.2%, 39 of 275). This difference was accounted for primarily by the expected decreases in hemoglobin observed during treatment with RBV. Grade 4 laboratory abnormalities were similarly low in the SOF/VEL 12 Week group (1.4%, 4 of 276) compared with the SOF+RBV 24 Week group (2.9%, 8 of 275).

The only Grade 3 or 4 hematology laboratory abnormality in the SOF/VEL 12 Week group occurring in more than 1 subject was decreased lymphocytes (1.1%, 3 of 276 subjects). One subject had normal lymphocytes throughout treatment and a Grade 3 decrease at the Post-treatment Week 4 visit. The other 2 subjects had Grade 2 or 3 decreased lymphocytes at baseline that transiently decreased by 1 grade during treatment.

The most common Grade 3 or 4 chemistry laboratory abnormalities in both treatment groups were increased lipase, increased serum glucose (hyperglycemia), and increased creatine kinase. Grade 3 or 4 increases in lipase were reported for 9 subjects (3.3%) in the SOF/VEL 12 Week

group and 5 subjects (1.8%) in the SOF+RBV 24 Week group. All of the Grade 3 or 4 increases in lipase were asymptomatic, with no cases of clinical pancreatitis. Grade 3 increases in serum glucose (hyperglycemia) were reported for 4 subjects (1.4%) in the SOF/VEL 12 Week group and 5 subjects (1.8%) in the SOF+RBV 24 Week group. All subjects with Grade 3 increased serum glucose had either a medical history of diabetes or $HbA_{1c} \geq 6.0\%$ at screening. Grade 3 or 4 increases in creatine kinase were reported for 2 subjects (0.7%) in the SOF/VEL 12 Week group and 4 subjects (1.5%) in the SOF+RBV 24 Week group. All of the Grade 3 or 4 creatine kinase elevations were transient and asymptomatic; the majority were associated with exercise. Grade 3 or 4 increases in total bilirubin (hyperbilirubinemia) were observed only in the SOF+RBV 24 Week group (Grade 3: 2 subjects, 0.7%; Grade 4: 1 subject, 0.4%). The timing and magnitude of the increases in total bilirubin were consistent with RBV-induced hemolysis.

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

Conclusions

The conclusions from this interim analysis were as follows:

- The study met its predefined primary efficacy endpoint: subjects with genotype 3 HCV infection in the SOF/VEL 12 Week group achieved an SVR12 rate of 95.3% that was statistically noninferior to the SVR12 rate of 80.4% achieved by subjects with genotype 3 HCV infection in the SOF+RBV 24 Week group.
  - The superiority of treatment with SOF/VEL for 12 weeks over SOF+RBV for 24 weeks for SVR12 was also demonstrated ($p < 0.001$).
- Across the 2 treatment groups, the SVR12 rates consistently favored the SOF/VEL 12 Week group over the SOF+RBV 24 Week group.
  - For subjects with cirrhosis, the SVR12 rates (SOF/VEL 12 Weeks vs. SOF+RBV 24 Weeks) were 91.3% and 66.3%, respectively.
  - For treatment-experienced subjects, the SVR12 rates (SOF/VEL 12 Weeks vs. SOF+RBV 24 Weeks) were 90.1% and 63.4%, respectively.
- Among the 16% of SOF/VEL-treated subjects with baseline NS5A RAVs, the SVR12 rate was numerically lower (88%) compared with subjects without baseline NS5A RAVs (SVR12 rate of 97%).
- SOF/VEL was generally well tolerated and, compared with SOF+RBV, lacked toxicities associated with RBV. No treatment-emergent deaths, Grade 4 AEs, treatment-related SAEs, discontinuations due to AEs, or clinically relevant laboratory abnormalities were observed in SOF/VEL-treated subjects.

1.7. Study GS-US-342-1137 (ASTRAL-4)

Study Design

This ongoing, Phase 3, randomized, open-label, multicenter study is assessing the antiviral efficacy, safety, and tolerability of SOF/VEL±RBV for 12 weeks and SOF/VEL for 24 weeks in subjects with chronic HCV infection and Child-Pugh-Turcotte (CPT) class B cirrhosis. The study was conducted in the US.

Subjects with genotype 1 to 6 HCV infection with CPT class B cirrhosis were randomized (1:1:1) to SOF/VEL for 12 weeks (SOF/VEL 12 Week group), SOF/VEL+RBV for 12 weeks (SOF/VEL+RBV 12 Week group), or SOF/VEL for 24 weeks (SOF/VEL 24 Week group). Randomization was stratified by HCV genotype (1, 2, 3, 4, 5, 6, and indeterminate).

Disposition

A total of 267 subjects were included in the Safety and Full Analysis Sets (90 subjects in the SOF/VEL 12 Week group, 87 subjects in the SOF/VEL+RBV 12 Week group, and 90 subjects in the SOF/VEL 24 Week group).

Of the 90 subjects in the SOF/VEL 12 Week group, 89 subjects (98.9%) completed study drug and 1 subject (1.1%) discontinued due to an AE.

Of the 87 subjects in the SOF/VEL+RBV 12 Week group, 82 subjects (94.3%) completed study drug; 4 subjects (4.6%) discontinued due to AEs and 1 subject (1.1%) discontinued due to virologic failure (pharmacokinetic [PK] data for this subject indicated noncompliance with study drugs).

Of the 90 subjects in the SOF/VEL 24 Week group, 84 subjects (93.3%) completed study drug; 4 subjects (4.4%) discontinued due to AEs, 1 subject (1.1%) discontinued due to virologic failure, and 1 subject (1.1%) discontinued due to noncompliance with study drug.

Demographics and Baseline Characteristics

Overall, demographics and baseline disease characteristics were balanced across the treatment groups. Of the 267 subjects randomized and treated, 207 subjects (77.5%) had genotype 1 HCV infection, 12 subjects (4.5%) had genotype 2 HCV infection, 39 subjects (14.6%) had genotype 3 HCV infection, 8 subjects (3.0%) had genotype 4 HCV infection, and 1 subject (0.4%) in the SOF/VEL 24 Week group had genotype 6 HCV infection. The majority of subjects were male (69.7%), and 42.3% of subjects had a BMI $\geq$ 30 kg/m^2. Most subjects (55.1%) had prior treatment experience and the majority of subjects had HCV RNA $\geq$ 800,000 IU/mL (55.8%).

Efficacy Results

The SVR12 rates were as follows:

- SOF/VEL 12 Week group: 83.3% (95% CI: 74.0% to 90.4%) of subjects (75 of 90) achieved SVR12

- SOF/VEL+RBV 12 Week group: 94.3% (95% CI: 87.1% to 98.1%) of subjects (82 of 87) achieved SVR12

- SOF/VEL 24 Week group: 85.6% (95% CI: 76.6% to 92.1%) of subjects (77 of 90) achieved SVR12

All 3 treatment groups met their primary efficacy endpoints with SVR12 rates that were statistically superior compared with the assumed spontaneous rate of 1%. The p-value was < 0.001 for the comparison with the SVR12 for each treatment group.

Among subjects with genotype 1 HCV infection, the SVR12 rate was higher for those in the SOF/VEL+RBV 12 Week group (95.6%, 65 of 68) compared with the SOF/VEL 12 Week group (88.2%, 60 of 68) or the SOF/VEL 24 Week group (91.5%, 65 of 71). Similarly, among subjects with genotype 3 HCV infection, the SVR12 rate was higher for those in the SOF/VEL+RBV 12 Week group (84.6%, 11 of 13) compared with the SOF/VEL 12 Week group (50.0%, 7 of 14) or the SOF/VEL 24 Week group (50.0%, 6 of 12).

All subjects with genotype 2, 4, or 6 HCV infection achieved SVR12 across all treatment groups with the exception of 1 subject with genotype 2 HCV infection in the SOF/VEL 24 Week group who died 39 days after completing 28 days of treatment.

Most virologic failures were due to relapse. One subject with genotype 3 HCV infection in the SOF/VEL+RBV 12 Week group had on-treatment breakthrough with PK data showing undetectable plasma drug levels consistent with non-adherence to study drug and 1 subject with genotype 3 HCV infection in the SOF/VEL 24 Week group had on-treatment breakthrough.

There was 1 subject (1.5%) with genotype 1 HCV infection with virologic failure in the SOF/VEL+RBV 12 Week group compared with 5 subjects (7.4%) in the SOF/VEL 12 Week group and 3 subjects (4.2%) in the SOF/VEL 24 Week group. Among subjects with genotype 3 HCV infection, the lowest rate of virologic failure was observed in the SOF/VEL+RBV 12 Week group with 2 failures (15.4%) compared with 6 (42.9%) in the SOF/VEL 12 Week group and 5 (41.7%) in the SOF/VEL 24 Week group.

There were no virologic failures in subjects with genotype 2, 4, or 6 HCV infection in any of the treatment groups.

Treatment with SOF/VEL+RBV for 12 weeks resulted in high SVR12 rates irrespective of genotype, prior treatment history, baseline HCV RNA, and presence of pretreatment NS5A or NS5B RAVs. Furthermore, there was no impact of demographic factors such as age, sex, BMI, or IL28B genotype on treatment outcome in the SOF/VEL+RBV 12 Week group.

Overall, 108 subjects (47.2%) had an improvement in CPT score (range: 1−5 points) while 99 subjects (43.2%) had no change. A minority of subjects (9.6%, 22 subjects) experienced an increase (worsening) in CPT score from baseline to Post-treatment Week 12. A higher percentage of subjects receiving SOF/VEL for 24 weeks (54.7%) compared with subjects receiving SOF/VEL±RBV for 12 weeks (40.7%−46.6%) had improvements in CPT score from

baseline to Post-treatment Week 12; this difference likely reflects the longer time of observation with HCV RNA suppression. The improvements in CPT score were largely due to improvements in bilirubin and albumin.

Overall, the majority of subjects who achieved SVR12 also had a decrease (improvement) (55.5%, 127 of 229 subjects) in MELD score between baseline and Post-treatment Week 12 (range: 1−11 points). Among subjects who had MELD score < 15 at baseline and achieved SVR12, 197 of 203 subjects (97.0%) remained < 15 at Post-treatment Week 12. A total of 16 subjects (61.5%) with baseline MELD score ≥ 15 who achieved SVR12 improved to < 15. Improvements in MELD score were largely due to improvements in total bilirubin.

Virologic Resistance

Pretreatment NS5A RAVs were observed in 26% to 29% of subjects across the treatment groups. The presence of pretreatment NS5A RAVs did not impact treatment outcome in the SOF/VEL+RBV 12 Week group. Slightly lower SVR rates were observed in subjects with genotype 1 HCV infection with NS5A RAVs treated with SOF/VEL for 12 or 24 weeks compared to subjects without pretreatment NS5A RAVs. No virologic failures were observed in subjects with genotype 2, 4, or 6 HCV infection. The small numbers of subjects with genotype 3 HCV infection with pretreatment NS5A RAVs precluded meaningful subgroup analysis. The presence of pretreatment NS5B RAVs did not impact treatment outcome in any treatment group.

The majority of subjects had NS5A RAVs present at virologic failure with Y93H being the most common variant. NS5B NI RAVs were less common and typically observed at low levels. Of the 9 subjects with genotype 1 HCV infection with virologic failure, 6 had NS5A RAVs at failure (5 treatment emergent and 1 maintained from pretreatment). Two genotype 1 HCV-infected subjects had L159F and S282T NS5B NI RAVs present at failure; both of these subjects had multiple NS5A RAVs at pretreatment that reduce susceptibility to VEL. All 13 subjects with genotype 3 HCV infection with virologic failure had Y93H at failure (10 were treatment emergent). Three genotype 3 HCV-infected subjects had low levels of NS5B NI RAVs emerge at virologic failure.

Safety Results

Overall, treatment with SOF/VEL±RBV for 12 weeks or SOF/VEL for 24 weeks was generally safe and well tolerated. Adverse events were consistent with the expected clinical sequelae in the setting of decompensated cirrhosis and, in addition, with the known toxicities of RBV in the SOF/VEL+RBV 12 Week group.

A smaller percentage of subjects in the SOF/VEL 12 Week and SOF/VEL 24 Week groups experienced any AE (81.1% in each group) compared with the SOF/VEL+RBV 12 Week group (90.8%). The higher frequency of AEs observed in the SOF/VEL+RBV 12 Week group was primarily due to AEs consistent with RBV-associated toxicity. No treatment-related Grade 3 AEs were reported in > 1 subject in any group or overall.

Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Overall, the most commonly reported Grade 3 or 4 AEs were hepatic encephalopathy and sepsis (5 subjects each), which are consistent with the natural history of disease progression in a population with decompensated liver disease.

Serious adverse events (SAEs) occurred in 17.6% of subjects in similar proportions across treatment groups, and only 1 subject (0.4%) experienced SAEs considered related to SOF/VEL. The most commonly reported SAEs were hepatic encephalopathy and sepsis (5 subjects each). Nine deaths occurred during the study, 2 of which were treatment emergent, and none of which was assessed as related to study drugs. One subject in the SOF/VEL 24 Week group underwent a liver transplantation on Post-treatment Day 8 after completing 35 days of treatment.

Nine subjects discontinued all study drugs due to an AE (SOF/VEL 12 Week group: 1.1%, 1 subject; SOF/VEL+RBV 12 Week group: 4.6%, 4 subjects; SOF/VEL 24 Week group: 4.4%, 4 subjects). No AE leading to discontinuation of study drugs was reported in > 1 subject. A total of 31.0% (27 of 87) of subjects had modified or interrupted RBV dosing due to AEs, and 10.3% (9 of 87) of subjects permanently discontinued RBV due to AEs while continuing SOF/VEL.

The majority of subjects had at least 1 Grade 3 or 4 laboratory abnormality (42.7% and 12.4%, respectively) with the highest rates observed in the SOF/VEL+RBV group (Grade 3: 43.7%; Grade 4 18.4%) due to a higher rate of hematologic abnormalities. The most commonly observed Grade 3 or 4 hematology laboratory abnormalities were decreased lymphocytes, hemoglobin, and platelet counts, all of which are a known effect of RBV therapy or expected in a subject population with decompensated liver disease.

The most commonly observed Grade 3 or 4 chemistry laboratory abnormalities were increased glucose and increased total bilirubin. All of the Grade 3 or 4 increased glucose abnormalities occurred in subjects with a history of diabetes mellitus or had elevated glucose at baseline or continuing through the Post-treatment period. The majority of subjects with Grade 3 or 4 increased total bilirubin (71.7%, 22 of 31 subjects) were in the SOF/VEL+RBV 12 Week group, primarily in a pattern that was consistent with RBV-induced hemolysis.

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) were reported during the study. No trends in electrocardiogram findings suggestive of cardiotoxicity were observed.

Conclusions

The conclusions from this interim analysis were as follows:

- Treatment with SOF/VEL±RBV for 12 or 24 weeks in subjects with decompensated cirrhosis resulted in high SVR12 rates:
  - In the SOF/VEL 12 Week group, the SVR12 rate was 83.3% (75 of 90 subjects).
  - In the SOF/VEL+RBV 12 Week group, the SVR12 rate was 94.3% (82 of 87 subjects).
  - In the SOF/VEL 24 Week group, the SVR12 rate was 87.8% (79 of 90 subjects).

- The SVR12 rates were highest in subjects treated with SOF/VEL+RBV for 12 weeks with few virologic failures:

  — In subjects with genotype 1 HCV infection, the virologic failure rate was 1.5% (1 of 68 subjects).

  — In subjects with genotype 3 HCV infection, the virologic failure rate was 15.4% (2 of 13 subjects), of which 1 subject had on-treatment breakthrough with PK data showing undetectable plasma drug levels consistent with non-adherence to study drug.

- Overall, there were no virologic failures in subjects with genotype 2, 4, or 6 HCV infection.

- The SVR12 rates between the SOF/VEL 12- and 24-week treatment durations were similar across all genotypes.

- The presence of pretreatment NS5A and NS5B RAVs did not impact treatment outcome with SOF/VEL+RBV for 12 weeks.

- Approximately half of subjects who achieved SVR12 experienced an early improvement in CPT and MELD scores, primarily related to improvements in synthetic function (albumin) and decreases in bilirubin.

- SOF/VEL was generally well tolerated in these subjects with decompensated liver disease, as evidenced by low rates of study treatment discontinuation and the majority of Grade 3 and 4 AEs, SAEs, and laboratory abnormalities being consistent with clinical sequelae of advanced liver disease and RBV toxicity.

1.8. Rationale for This Study

This is a Phase 2 study designed to evaluate the efficacy and safety of the SOF/VEL tablet administered for 4 weeks to subjects starting in the perioperative period of liver transplantation.

After transplantation, recurrence of HCV infection occurs in almost all patients {Feray et al 1992}, {Wright et al 1992} who have HCV RNA detectable prior to transplantation. HCV recurrence is associated with cirrhosis, fibrosing cholestatic hepatitis, graft loss, liver re-transplantation, and death {Prieto et al 1999}, {Wiesner et al 2003}, {Berenguer et al 2002}, {Gane et al 2008}, {Crespo et al 2012}, {Charlton et al 2014}, {Berenguer et al 2000}, {Forman et al 2002}, {Firpi et al 2009}. HCV RNA levels fall significantly in the anhepatic phase of liver transplantation and continue to fall during the first 12-24 hours post transplantation. Serum HCV RNA then begin to rise rapidly from the second post-operative week and peak by the fourth month {Charlton 2003}.

Deposition of fibrotic tissue in most HCV transplanted livers is highly accelerated with the development of bridging fibrosis and cirrhosis in 20-54% at 5 years and 32-51% at 7 years {Berenguer et al 2013}. Once cirrhosis is established, the probability of liver graft failure is 42% within 12 months {Berenguer et al 2002}.

There is great advantage to administering a well-tolerated direct acting antiviral without the use of PEG-IFN or RBV in the immediate postoperative period while the HCV RNA virus is at its lowest level. We hypothesize that the time period prior to re-infection is unique and mimics that of acute infection, as the nidus of HCV chronic infection (pretransplant liver) has been removed. For this reason, we believe that a short course of therapy (eg, 4 weeks), is likely to be successful. If the progression of the HCV virus can be halted before the progressive liver fibrosis activity is initiated both the new graft and the patient stand a greater chance of survival.

Additionally, patients who start HCV treatment pre-transplant may not have time to complete the full duration of treatment when a liver becomes available. The results of this study can inform on the safety and efficacy of continuing SOF/VEL treatment through transplantation.

1.8.1. Rationale for the Dose of SOF/VEL

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

VEL 100 mg was administered in combination with SOF 400 mg for 12 weeks to 237 HCV-infected subjects in Phase 2 studies. VEL 100 mg was selected for co-formulation with SOF based on the Phase 2 safety, PK and antiviral activity (studies GS-US-342-0102, GS-US-342-0109, and GS-US-337-0122 [Cohort 4]). The Phase 1 study GS-US-281-0102 established the anti-HCV activity of VEL and indicated that the exposures achieved following administration of doses > 25 mg provide at least 80% of maximal antiviral response in all HCV genotypes. SOF/VEL (400 mg /100 mg) as a FDC tablet was evaluated in the phase 3 ASTRAL program.

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

1.9. Risk/Benefit Assessment for the Study

The regimen to be assessed in this study combines a potent HCV nucleotide inhibitor with a potent HCV NS5A inhibitor in patients who are in the immediate post-transplant operative period. 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 the first once-daily, PEG-free, RBV-free, pangenotypic regimen for the treatment of chronic HCV infection in patients who have received a liver transplant. The potential benefits of early treatment in the peritransplant period with SOF/VEL:

- The once-daily, single tablet, short duration, pangenotypic HCV regimen would offer a simple algorithm for patients infected with HCV undergoing liver transplants, regardless of genotype
- 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 25mg or VEL 100mg administered for 8 or 12 weeks has been established in over 800 patients in Phase 2 studies. The safety profile of the proposed therapeutic regimen of SOF 400 mg and VEL 100 mg administered for 12 weeks has been established in 237 subjects enrolled in Phase 2 studies. No clinical safety issues specifically related to VEL or SOF + VEL have been identified to date. No clinical safety issues specifically related to the NS5A inhibitor class including daclatasvir (DCV) and LDV have been identified to date {Afdhal et al 2014a}, {Afdhal et al 2014b}, {Kowdley et al 2014}.

The safety profile of SOF/VEL has been studied in 4 Phase 3 trials (ASTRAL 1-4) in 1302 patients. Twelve weeks of SOF/VEL was generally well tolerated, and lead to a similar incidence of AEs and SAEs compared to placebo in patients with GT 1, 2, 4, 5, or 6 HCV (See Section 1.2.2.1). When 12 weeks of SOF/VEL was compared to SOF + RBV for 12 weeks in patients with GT2 or 3 HCV, therapy with SOF/VEL was again well tolerated with few differences in AEs or SAEs, minus the avoidance of RBV associated toxicities (See Section 1.2.2.2). Patients who received SOF/VEL for either 12 or 24 weeks with decompensated cirrhosis experienced AEs and SAEs typical for patients with decompensated cirrhosis in no pattern that could be attributed to study drug. Patients with decompensated cirrhosis who received SOF/VEL + RBV for 12 weeks also experienced AEs and SAEs consistent with underlying liver disease as well as toxicities expected with RBV treatment.

In summary, there is currently no approved treatment for patients with recurrent HCV posttransplantation. Treatment during the time period prior to re-infection may be unique and mimics that of acute infection, as the nidus of HCV chronic infection (pretransplant liver) has been removed. Thus this may offer an opportunity for a short course of therapy (eg, 4 weeks), to be successful. If high rates of SVR can be obtained with a short, IFN-free, RBV-free, pangenotypic regimen in the peri-operative period, this would render the patient's new liver graft free from HCV and the sequelae of events towards end stage liver disease post transplantation could be avoided.

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

1.10. 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 explore the antiviral efficacy of treatment with SOF/VEL FDC therapy administered for four weeks following liver transplantation as measured by sustained virologic response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of SOF/VEL in HCV-infected subjects in the peri-operative and post-transplant period

The secondary objectives of this study are:

- To determine the percentage of subjects who attain SVR at 4 weeks after cessation of treatment (SVR4)
- To evaluate the proportion of subjects with virologic failure
- To assess rates of graft survival, graft function, acute rejection and immunosuppressive therapy during treatment with SOF/VEL
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To characterize pharmacokinetics of SOF/VEL

The exploratory objectives of this study are:

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3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- The primary efficacy endpoint is SVR12 (HCV RNA < lower limit of quantification [LLOQ] 12 weeks after the date of last dose of study drug) for subjects in the Full Analysis Set.

The secondary endpoint of this study is:

- The proportion of subjects with HCV RNA < LLOQ at 4 weeks after cessation of treatment (SVR4)
- The proportion of subjects with HCV RNA < LLOQ on treatment
- The proportion of subjects with virologic failure (defined as HCV RNA ≥ LLOQ at end of treatment or relapse during Post-treatment follow-up)

3.2. Study Design

This is an open-label study that will evaluate the safety, tolerability and antiviral efficacy of SOF/VEL administered for 4 weeks in HCV-infected adult male and female subjects who are undergoing liver transplantation.

HCV RNA will be assessed at each visit.

3.3. Study Treatments

For all subjects SOF/VEL tablet (400 mg/100 mg) once daily will be started the day of the subject's liver transplant if the transplant is completed before noon and the following day if it is completed after noon and will continue for 4 weeks. The planned first dose may be delayed for up to 1 day if, in the investigators opinion, delay is in the subject's medical interest. The subject will receive 4 weeks of study drug.

3.4. Visit Schedule

All subjects will complete the following study visits: Screening; Pre-surgery (if needed); On-Treatment visits Days 1, 3, 5, 7, 14, 21, and 28; and Post-treatment Visits at Weeks 1, 2, 4, and 12 following the last dose of study drug.

Screening assessments will be completed at the time a subject is identified as a potential study participant to give sufficient time for the subject to provide informed consent and perform screening assessments. Subject's screening data will be confirmed in the pre-operative period (within 48 hours of the planned transplant) at the Pre-surgery visit if the screening visit occurs more than 48 hours before the liver transplant surgery is started.

If a separate informed consent is signed, samples of the explanted liver will be taken during surgery.

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

3.5. 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 7.6 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
- If a subject experiences graft dysfunction (including primary graft non-function) requiring relisting for liver transplant, treatment will be stopped
- If subject is relisted for transplantation for any reason treatment will be stopped
- Subject receives a 2nd liver transplant while on study treatment
- Pregnancy of female subject
- 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**)** Subjects who permanently discontinue all study drugs for any reason including safety and/or tolerability concerns prior to completion of the assigned dosing period will be followed according to the Post-treatment study assessments to determine whether the subject achieves SVR.

3.6. Subject Stopping Rules

The Gilead Medical Monitor must be consulted prior to discontinuation of study drug unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject.

Administration of study medication may be discontinued due to a clinical or laboratory event. There is no option for SOF/VEL dose reduction. If SOF/VEL is stopped due to toxicity, it must

not be restarted and the subject must complete an ET visit. Any interruptions of study medication must be discussed with the Sponsor Medical Monitor prior to restarting.

Subjects who meet any of the following laboratory or medical criteria must stop all study medication(s):

- Any medical condition (in the opinion of the Medical Monitor) for which the risks of treatment outweigh the benefits
- Commencement of dialysis
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 adverse event assessed as related to SOF/VEL

3.7. End of Study

Subjects are considered to have completed the study after the Post-treatment Week 12 follow-up visit, regardless of treatment duration, unless the subject early terminates because HCV RNA is ≥ LLOQ. If the subject terminates early due to HCV RNA ≥ LLOQ, the subject will complete the post treatment Week 4 visit as their final visit.

3.8. Substudies

3.8.1. Optional Archive Sample


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4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 10 subjects with chronic HCV awaiting liver transplantation will be enrolled.

In order to manage the total study enrollment, Gilead Sciences, Inc. at its sole discretion, may suspend screening and/or discontinue the enrollment at any site at any time (upon written notice to the site). Discontinuation of the enrollment phase may result in the immediate ineligibility of all subjects screened but not yet enrolled, regardless of the progress or outcome of the screening assessments performed.

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 or for those subjects where hepatic encephalopathy affects their ability to provide initial or ongoing consent, has an appropriate and legally-authorized representative (LAR) willing and able to provide consent on behalf of the subject.

2) Male or female, age ≥ 18 years

3) HCV RNA infection with quantifiable virus at Screening or documented in the patient's medical record.

4) Chronic HCV infection (≥ 6 months) as documented by either prior medical history or liver biopsy

5) Currently on the liver transplantation wait list (both transplant from deceased or living donor will be considered acceptable)

6) Screening ECG without clinically significant abnormalities.

7) A negative serum pregnancy test is required for female subjects (unless surgically sterile or greater than two years post-menopausal; see Appendix 4 for definitions).

8) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 4.

9) Male subjects must agree and refrain from sperm donation from the date of screening until at least 30 days after the last dose of study drug.

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

11) Subject must be able to comply with the dosing instructions for study drug administration and be able to complete the study schedule of assessments, including all required Post-treatment visits.

4.3. Exclusion Criteria

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

1) Receipt of an HCV infected liver

2) Any serious or active medical or psychiatric illness which, in the opinion of the investigator, would interfere with subject treatment, assessment, or compliance

3) HIV infection or a positive hepatitis B virus surface antigen result

4) Current malignancy (with exception of HCC within local listing criteria, certain resolved skin cancers or other early cancer for which surgical resection is considered to be completely curative)

5) Treatment with any approved or experimental medication with known anti-HCV activity within 1 month prior to screening date

6) Prior exposure to a HCV NS5B nucleotide/side inhibitor including SOF or to an HCV NS5A inhibitor

7) Patients on hemodialysis prior to or at the time of transplantation will be excluded

8) Participation in a clinical study with an investigational drug or biologic within 28 days prior to screening visit, unless information on the investigational drug is available to indicate that there is no potential drug interaction (safety or efficacy)

9) Use of any prohibited concomitant medications as described in Section 5.3.Known hypersensitivity to the SOF, VEL, the metabolites, or formulation excipient.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Description and Handling of SOF/VEL FDC

5.1.1. Formulation

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

5.1.2. Packaging and Labeling

SOF/VEL (400 mg/100 mg) FDC 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.

5.1.3. Storage and Handling

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

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study 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 FDC tablets to complete the entire study will be shipped to the investigator or qualified designee from the Gilead Clinical Supply Management Team (or its designee).

5.2. 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. If the subject is unable to swallow the SOF/VEL tablet, the tablet may be crushed and delivered by nasograstric tube.

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:

- 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 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)
Other	Modafinil [b], Sulfasalazine[c], Methotrexate[c]	

a Proton pump inhibitor (PPI) doses comparable with omeprazole 20 mg can be administered with SOF/VEL when SOF/VEL is administered with food. H2-receptor antagonists must not exceed a dose of 40 mg famotidine or equivalent and can be taken simultaneously with SOF/VEL and/or staggered by 12 hours. Antacids that directly neutralize stomach acid (ie 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, rosuvastatin. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

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

Should subjects have a need to initiate treatment with any excluded concomitant medication, the Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication.

5.4. 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 accountability records will be provided to each study site to:

- 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 IMP returned, along with the initials of the person recording the information.

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

5.4.1. Investigational Medicinal Product Return or Disposal

Please refer to Section 9.1.7 for Investigational Medicinal Product Accountability and Return.

6. STUDY PROCEDURES

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

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

6.1. Subject Enrollment and Treatment Assignment

6.2. Pretreatment Assessments

6.2.1. Screening Visit/Pre-Surgery

Subjects will be initially screened to determine their eligibility for participation in the study (they are required to be on the waitlist for liver transplantation). If the screening visit occurs more than 48 hours before the liver transplant surgery is started, the subject will also be reassessed within 48 hours of transplantation to determine their continued eligibility at the pre-surgery visit.

Screening period is the time from initial screen (ie, identification of the subject as being on the liver transplant waitlist and potentially meeting inclusion/exclusion criteria for the study) until administration of the first dose of study treatment.

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

6.2.2. Day 1 Assessments

Day 1 will be the morning following the transplant (if the subject is out of transplant before 12:00 pm the Day 1 dose will occur that day. If the subject is out of transplant after 12:00 pm the Day 1 dose will occur the following morning).

6.3. Treatment Assessments (± 2 days)

Subjects meeting all of the inclusion and none of the exclusion criteria will begin study treatment on Day 1. In addition to those assessments listed in the Schedule of Events, study personnel will observe the subject taking their first dose of study drug and record the date and time the first dose was taken.

For all subjects receiving 4 weeks of therapy, treatment procedures/assessments are to be completed on Days 3, 5, 7, 14, 21, and 28 post start of Day 1 treatment. Please refer to Appendix 2 for a schedule for assessments.

6.4. Early Termination (ET) Visit

For subjects who have completed an ET visit, the Post-treatment Weeks 1, 2, and 4, and 12 follow-up visits will be scheduled from the date of the last dose of study drug.

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

6.5. Unscheduled Visits

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.

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

6.6. Post-Treatment Assessments

Post-treatment Weeks 1, 2, 4, and 12 visits must be scheduled from the date of the last dose of study drug.

Subjects who have HCV RNA ≤LLOQ at end of treatment and do not relapse will complete all post-treatment visits at Weeks 1, 2, 4, and 12. Subjects that experience relapse will have confirmatory testing as soon as possible and will not be required to complete additional visits.

If a subject must undergo a second transplantation while on study treatment or is relisted for transplantation, all study treatment must be stopped.

If a subject is in the Post-treatment follow-up and undergoes a second liver transplant, the subject will continue with the follow-up visits from the first transplantation (for the assessment of Post-transplant recurrence). If the subject is more than 4 weeks after the last dose of study drug at the time of the second transplant and had completed the safety follow-up period, it is not necessary to resume adverse event collection.

6.7. Assessments for Premature Discontinuation from Study

Discontinuation from study drug dosing and discontinuation from the overall study including follow-up will be collected as two separate events. If a subject discontinues study treatment dosing every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.6).

6.8. End of Study

Subjects are considered to have completed the study after the post-treatment Week 12 visit, regardless of treatment duration or early termination of study drug. If the subject terminates early due to HCV RNA ≥ LLOQ, the subject may discontinue follow up after the post treatment Week 4 visit.

6.9. Procedures and Specifications

6.9.1. Central 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 MCV.

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

Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatinine, Total Bilirubin (reflex Direct Bilirubin if Total is abnormal), Glucose, Lipase, Potassium, Sodium, and Gamma-glutamyl transferase (GGT). Creatinine clearance will be calculated based on the lesser of actual weight and ideal body weight.

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

Virological Tests: Serologies for HCV, HBV, and HIV. HCV RNA will be measured using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV genotype should the above assays become unavailable or is not definitive.

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

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

6.9.2. Medical History

Medical history including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history will be collected on all subjects during screening up to the day of dosing. This will include information regarding the subject's HCV treatment history.

6.9.3. Complete Physical Examination

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

6.9.4. 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.

6.9.5. MELD Score/Child-Pugh Score

MELD Score and Child-Pugh-Turcotte score should be assessed at Screening and on Day 1.

Table 6-1. Child-Pugh-Turcotte Classification of the severity of cirrhosis

	Points		
	1	**2**	**3**
Encephalopathy	None	Grade 1-2 (medication-controlled)	Grade 3-4 (medication-refractory)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3

Note: if the either ascites or encephalopathy is "none" because the patient is taking medication which has controlled the symptoms, the scoring should be 2 points (not 1 point).
CPT score is obtained by adding the points for each parameter
CPT class is scored as: A = 5-6 points
B = 7-9 points
C = 10-15 points

MELD Score Calculation

The MELD score is calculated as:

$$10 \times \{[0.957 \times \text{Ln(Scr)}] + [0.378 \times \text{Ln(Tbil)}] + [1.12 \times \text{Ln(INR)}] + 0.643)\}$$

Where Scr = serum creatinine (in mg/dL), Tbil = Total Bilirubin (in mg/dL), INR = international normalized ratio, and Ln = natural log. If any lab value is less than 1.0, then set to 1.0 in the calculation. If the subject received dialysis at least twice in the past week, then Scr is set to 4.0 mg/dL in the above formula. The result will be rounded to the nearest whole number.

For the components of the MELD score and the components of the CPT score which are based on laboratory values, the data will be obtained from the central laboratory, and the scores will be calculated within the clinical database.

6.9.6. Creatinine Clearance (CrCL)

Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft et al 1976}. Creatinine clearance will be calculated based on the lesser of actual weight and ideal body weight.

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

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

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

6.9.7. Ideal Body Weight (IBW)

Estimated ideal body weight in (kg)

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet

6.9.8. Body Mass Index (BMI)

BMI is calculated by the following equation.

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

6.9.9. 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 Day 1 as part of routine safety monitoring.

6.9.10. Pharmacokinetic (PK) Sample

Single PK blood samples will be collected at each on-treatment visit for all subjects except on Days 1, 3 and 5. PK analysis of SOF (and its metabolites GS-566500 and GS-331007), and VEL may be conducted.

The exact date and time of the most recent dose of SOF/VEL taken prior to collection of the PK sample and the exact date and time the PK sample is drawn will be recorded on the appropriate eCRF.

All subjects will also be required to participate in an intensive PK sub-study (samples obtained over 24 hours) on Day 1 post-transplant. Serial PK samples will be collected at the following time points: 0 (pre-dose), 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose. The PK of SOF, its metabolites GS-566500 and GS-331007, and VEL will be assessed.

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

6.9.11. Viral RNA Sequencing / Phenotyping Sample

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

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

6.9.12. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing at the Screening/pre-surgery visit, and Day 28 during the dosing period and for 30 days following the last dose of study drug. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drugs immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion)performed; the condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

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

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

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study 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 AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

Severity should be recorded and graded according to the GSI Grading Scale for Severity of AEs and Laboratory Abnormalities (Appendix 3). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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

Requirements for collection prior to study drug initiation:

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

Adverse Events

All AEs, expect those described in Section 7.5, regardless of cause or relationship, that occur from initiation of study medication until 30-days after last administration of study drug must be reported to the eCRF database as instructed.

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

Serious Adverse Events

All SAEs, except those described in Section 7.5, regardless of cause or relationship, that occur from initiation of study medication until 30 days after last administration of study drug, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period ;however, if the investigator learns of any SAEs that occur after study participation has

concluded and the event is deemed relevant to the use of 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
Gilead Medical Monitor	Name:	Benedetta Massetto, MD
	Phone:	PPD PPD
	Fax:	PPD
	Email:	PPD

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

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

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

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

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

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to

worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

7.5. Reporting Requirements for Liver Transplant and Complications of Liver Transplant

Due to the nature of the subject population and the inclusion criteria, events that are clearly related to liver transplant should not be collected or reported as AEs and SAEs. In addition, these events will be exempt from global expedited reporting requirements for the duration of the study. These include:

1) The liver transplant procedure itself (and related hospitalization)

2) Events that are direct sequelae of the liver transplant or peri-operative care (central line insertions, etc)

3) Planned hospitalizations for testing or procedures that are part of the liver transplant assessment and preparation process

These events should be reported as AEs/SAEs only if it is assessed that the events (including transplant itself) were not an anticipated or predictable part of the underlying disease transplant process or procedure. Events that are considered possibly or probably related to study medication must be reported using the usual reporting procedures, as described in Section 7.3. In addition, concomitant medications related to the transplant procedure do not need to be recorded (anesthetics, peri-operative pain medication, etc). If there are any questions about how an event should be reported, please contact the study Medical Monitor.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study 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 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.3 and 7.4. 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 using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead 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.

7.6.2.2. Reporting Other Special Situations

All special situations reports (SSRs) will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Special Situations Report (eSSR) Reporting Process

- Site personnel record all SSR data in the eCRF database and from there transmit the SSR 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 SSR information electronically, i.e., the eCRF database is not functioning, record the SSR 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
Gilead Medical Monitor	Name:	Benedetta Massetto
	Phone:	PPD PPD
	Fax:	PPD PPD
	Email:	PPD

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To explore the antiviral efficacy of treatment with SOF/VEL FDC therapy administered for four weeks following liver transplantation as measured by sustained virologic response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of SOF/VEL in HCV-infected subjects in the peri-operative and post-transplant period

The secondary objectives of this study are:

- To determine the percentage of subjects who attain SVR at 4 weeks after cessation of treatment (SVR4)
- To evaluate the proportion of subjects with virologic failure
- To assess rates of graft survival, graft function, acute rejection and immunosuppressive therapy during treatment with SOF/VEL
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To characterize pharmacokinetics of SOF/VEL

The exploratory objectives of this study are:

PPD

8.1.2. Primary Endpoint

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

8.1.3. Secondary Endpoint

Secondary efficacy endpoints include the following:

- The proportion of subjects with HCV RNA < LLOQ at 4 weeks after cessation of treatment (SVR4)
- The proportion of subjects with HCV RNA < LLOQ on treatment
- The proportion of subjects with virologic failure (defined as HCV RNA ≥ LLOQ at end of treatment or relapse during Post-treatment follow-up)

8.1.4. Safety Endpoint

The primary safety endpoint is any AE leading to premature discontinuation of study drug. Other important safety endpoints include deaths, graft losses, and rejection episodes.

8.1.5. Other Endpoints of Interest

Other endpoints of interest include changes to immunosuppression and the emergence of viral resistance to SOF or VEL during and after treatment discontinuation, and HCV RNA levels (IU/mL) at each on-treatment visit, if relevant.

8.2. Analysis Conventions

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

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

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The analysis set for antiviral activity analyses will be the FAS which includes subjects who were enrolled into the study, received a liver transplant while on study, and took at least one dose of study drug.

8.2.1.2. Safety

The analysis set for safety analyses will include all subjects who took at least one dose of study drug.

All safety data collected from the first dose of any study drug (including the perioperative dose of SOF/VEL) through the date of last dose of study drug plus 30 days will be included in safety summaries, unless otherwise specified.

8.2.1.3. Pharmacokinetics

The PK analysis set will include subjects who were enrolled and received at least one dose of study drug, and have at least one nonmissing postdose concentration value for the corresponding analyte (VEL, SOF and its metabolite[s], as appropriate) in serum or plasma. The PK analysis set will be used for general analyses of PK.

The PK Substudy analysis set will include all subjects who were enrolled in the PK Substudy, have been administered at least one dose of study drug, and have at least one nonmissing postdose concentration value for the corresponding analyte (VEL, SOF and its metabolite[s], as appropriate) in serum or plasma. The PK Substudy analysis set will be used for intensive PK profiles of these analytes.

8.3. Data Handling Conventions

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

For the analysis of post-Day 1 categorical efficacy endpoints, if a data point is missing and is preceded and followed in time by values that are deemed successes, then the missing data point will be termed a success; otherwise the data point will be termed a failure.

If no HCV RNA values are obtained after the last dose of study medication, the subject will be considered a treatment failure for the SVR endpoints. Subjects who have HCV RNA ≥ LLOQ at end of treatment or relapse in off-treatment follow-up will be counted as failures at subsequent follow-up visits (ie, where no data is available).

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 the most recent non-missing screening result, if available.

Values for missing vital signs data will not be imputed; however, a missing Day 1 result will be replaced with the most recent non-missing 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 value. 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).

PK concentration values below the lower limit of quantitation (BLQ) will be treated as zero at predose time points, and one-half the value of the lower limit of quantitation (LLOQ) at postbaseline time points, where LLOQ is corrected for the dilution factor (ie, reported LLOQ/dilution factor) for determination of summary and order statistics. For purposes of data presentation, individual values that are BLQ will be presented as "BLQ" in the concentration data listing. For the presentation of summary and order statistics, if at least 1 subject has a concentration value BLQ for the time point, then the minimum value will be displayed as "BLQ". If more than 25% of subjects have a concentration data value of BLQ for a given time point, then the minimum and the first quartile [Q1] will be displayed as "BLQ". If more than 50% of the subjects have a concentration data value BLQ for the time point, then the minimum, first quartile [Q1], and median values will be displayed as "BLQ". If more than 75% of the subjects have a concentration value of BLQ for a given time point, then the minimum, 1st quartile [Q1], median, and 3rd quartile [Q3] values will be displayed as "BLQ". If all subjects have concentration data values BLQ for the time point, then all order statistics (minimum, first quartile [Q1], median, third quartile [Q3], maximum) will all be displayed as "BLQ".

Pharmacokinetic parameters that are BLQ will be imputed as one-half LLOQ before log transformation or statistical model fitting.

8.4. 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 characteristic data will include body mass index, Day 1 HCV RNA level ($\log_{10}$ IU/mL), HCV genotype, IL28B genotype, MELD and CPT scores, and additional endpoints as necessary.

8.5. Efficacy Analysis

8.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is SVR12 (HCV RNA <LLOQ 12 weeks after cessation of treatment) for subjects in the FAS. The number and percentage of subjects who attain SVR12

will be presented. A 2-sided 95% confidence interval using the Clopper-Pearson method will also be constructed.

8.5.2. Secondary Efficacy Endpoint

The number and percentage of subjects who attain SVR4 will be presented. Two-sided 95% confidence intervals using the Clopper-Pearson method will also be constructed.

The number and percentage of subjects who are <LLOQ will be presented by visit while on treatment. On-treatment HCV RNA visit windows will be calculated from the date of first dose of SOF/VEL after liver-transplantation (ie, from Study Day 1 as described in this protocol). Two-sided 95% confidence intervals using the Clopper-Pearson method will be provided.

A virologic outcome table will present the number and percentage of subjects with end of treatment virologic failure and relapse (ie, virologic failure).

8.6. Safety Analysis

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

All safety data collected while "on treatment" (ie, on or after Study Day 1 up to 30 days after the last dose of study drug) will be summarized for subjects who receive SOF/VEL.

Safety endpoints will be summarized as the number (percentage) of subjects with events or abnormalities for categorical data or as an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the eCRF. Exposure data will be summarized for subjects who receive SOF/VEL.

8.6.2. Adverse Events

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

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any 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 for subjects receiving SOF/VEL provided for:

- All AEs,
- All study drug-related AEs,
- Combined Grade 2, 3 and 4 AEs,
- Combined Grade 3 and 4 AEs,
- Combined Grade 2, 3 and 4 study drug-related AEs,
- Combined Grade 3 and 4 study drug-related AEs,
- All AEs that caused permanent discontinuation from study drug,
- All AEs that caused temporary interruption of study drug,
- All SAEs (including death), and
- All study drug-related SAEs

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

8.6.3. Laboratory Evaluations

Selected laboratory tests (ie, bilirubin, ALT, AST, platelets and creatinine) will be summarized by study visit to assess the effect of SOF/VEL treatment in combination with liver transplantation on liver and renal function over time. Visit windows will be assigned based on the Day 1, and last dose date of any study drug.

Values for missing safety laboratory data will not be imputed.

All laboratory values, whether they were low or high relative to the reference range, and the assigned laboratory toxicity grade will be included in the listings of laboratory data.

8.7. Pharmacokinetic Analysis

Plasma concentrations of the study drug over time may be summarized using descriptive statistics, provided sufficient data is available. PK parameters (eg C_{max} AUC_{0-24}) may be listed and summarized (as appropriate) for study drug (VEL, SOF and its metabolite[s], as appropriate) using descriptive statistics. Details of the pharmacokinetic analysis plan will be provided in the pharmacokinetic reporting and analysis plan.

8.8. Sample Size

With a sample size of 10 subjects, a two-sided 95% exact confidence interval will extend at most 63% in length.

8.9. Data Monitoring Committee

A data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data. The initial meeting will occur after the first 5 subjects have completed the study treatment period. The following one will be held after the remaining planned subjects have completed the treatment period. The DMC will provide recommendations, and whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The investigator, medical monitor, and study biostatistician will be members of the DMC.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

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

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

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

9.1.3. Informed Consent

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

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

9.1.4. Confidentiality

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

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

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

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

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

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

9.1.6. Case Report Forms

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

the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

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

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

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT
A Phase 2, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir Fixed Dose Combination Administered for Four Weeks in Patients Infected with Chronic HCV in the Peri-Operative Liver Transplantation Setting

Original Protocol
26 February 2016

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

PPD

DIANA BRAINARD FOR
Name (Printed) BENEDETTA MASCETTO
Author

1-March-2016
Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed) Signature

Date Site Number

Appendix 2. Study Procedures Table

Appendix Table 1. Screening, On-Treatment Visits

Clinical Assessments	Screening	Pre-Surgery (if more than 48 hours from screening to transplant)	Day 1[a]	Days on Treatment (±2 days)						
				3	5	7	14	21	28	ET/ Unscheduled[e]
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X	X								
Physical Examination	X	X								X
Height and Weight[b]	X	X	X							X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X
12-lead ECG[d]	X	X								
CPT and MELD Scores	X	X								
Adverse Events and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling	X	X	X							X
Hematology & Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation (PT, PTT and INR)	X	X	X	X	X	X	X	X	X	X
CrCL calculation	X	X	X	X	X	X	X	X	X	X
HCV RNA (Plasma) [e]	X	X	X	X	X	X	X	X	X	X
Viral RNA Sequencing /Phenotyping Sample (Plasma)			X	X	X	X	X	X	X	X
Single Pharmacokinetic Sample						X	X	X	X	X
Pregnancy Testing[f]	X	X	X						X	X
Urinalysis	X	X								

Clinical Assessments	Screening	Pre-Surgery (if more than 48 hours from screening to transplant)	Day 1[a]	Days on Treatment (±2 days)						
				3	5	7	14	21	28	ET/ Unscheduled[e]
IL28B Genotype			X							
HCV Genotype	X									
HCV, HIV, HBV Serology	X	X								
Archive Sample[g]			X						X	X
PPD										
PK Sub-study Collection[i]			X							
Study Drug Dosing			X	X	X	X	X	X	X	
Review of Study Drug Adherence and Drug Accountability[j]				X	X	X	X	X	X	X

a If the transplant is completed before noon, the subject will take their first dose that day after the transplant which will be considered Day 1. If the transplant is completed after noon, the subject will take their first dose the following morning which will be considered Day 1. The planned first dose may be delayed for up to 1 day if, in the investigators opinion, delay is in the subject's medical interest. ET = Early Termination; at all unscheduled visits initiated for the purpose of confirmatory testing, a viral sequence analysis plasma sample must be obtained.

b Weight should be done with inner clothing and without shoes and Height should be done at screening only. Height will be performed only at initial screening visit. Weight will be assessed at screening and Day 1 for CrCL calculations. CrCL calculation for all post-transplant visits will use the Day 1 weight.

c Vital signs include resting blood pressure, pulse, respiratory rate and temperature.

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

e HCV RNA samples will be collected at all visits. An additional HCV RNA sample will be collected just before but as close to the transplant as possible.

f For females of childbearing potential only: serum β-hCG at Screening, urine test thereafter. If urine is positive, confirm immediately with serum β-hCG. .

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i All subjects will have intensive serial PK samples drawn before the SOF/VEL dose on Day 1, then dose is given, then remaining samples are collected for 24hrs. The 24 hr sample should be collected before the dose of study drug on Day 2. Detailed instructions will be provided to each study site and will also be included in the lab manual.

j Study drug will be reconciled at every post-Day 1 visit by the investigator in order to monitor the subject's adherence with the dosing regimen. Subjects must be instructed to bring back all bottles of study drug in the original container at every post Day 1 study visits through the end of treatment.

Appendix Table 2. Post-Treatment Study Visits

Clinical Assessments[a]	Visit identified by Post-Treatment study week			
	Post-Treatment Week 1 (± 3 days)	**Post-Treatment Week 2 (± 3 days)**	**Post-Treatment Week 4 (± 5 days)**	**Post-Treatment Week 12 (±5 days)**
Weight and Vital Signs[b]			X	
Adverse Events and Concomitant Medications	X	X	X	
Pregnancy Prevention Counseling	X			
Hematology & Chemistry	X	X	X	X
Coagulation (PT, PTT and INR)	X	X	X	X
HCV RNA and Viral Sequencing Sample (Plasma)	X	X	X	X
Pregnancy Testing[c]	X	X	X	

a If a subject is in Post-treatment follow-up and undergoes liver transplant, they will continue the follow-up schedule.
b Weight should be done with inner clothing and without shoes. Vital signs include resting blood pressure, pulse, respiratory rate and temperature.
c For females of childbearing potential only: serum β-hCG at Screening, urine test thereafter. If urine is positive, confirm immediately with serum β-hCG.

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

Antiviral Toxicity Grading Scale Version: 01 April 2015

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Infant <1 Year	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 t o <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant <1 Year	>ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
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
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

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

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

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

Notes:

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

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

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

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

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

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

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)

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

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

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

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

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

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

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

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

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

1) Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following 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 GS-5816 have demonstrated no adverse effect on fertility or embryo-fetal development.

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

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 randomization. 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 or etonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the 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) Unacceptable Methods of Contraception

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

6) 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 7.6.2.1.