CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination (FDC) and Sofosbuvir/Velpatasvir FDC and Ribavirin in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis
Sponsor:	Gilead Sciences, Inc.
IND Number:	This is a non-IND study
EudraCT Number:	2016-000417-73
Clinical Trials.gov Identifier:	Not Available
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-342-2097
Gilead Study Director *or* Medical Monitor:	Name: Brian McNabb, MD Telephone: PPD Fax: PPD Cell Phone: PPD
Protocol Version/Date:	Original: 16 March 2016 Amendment 1: 04 April 2016

TABLE OF CONTENTS

TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 5
LIST OF IN-TEXT FIGURES 5
PROTOCOL SYNOPSIS 5
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 10
1. INTRODUCTION 13
1.1. Background 13
1.2. Sofosbuvir/Velpatasvir Fixed Dose Combination 14
1.2.1. General Information 14
1.2.2. Additional Clinical Experience 15
1.3. Ribavirin (RBV) 39
1.4. Rationale for This Study 40
1.5. Rationale for Dose Selection 40
1.6. Overall Risk/Benefit Assessment 41
1.7. Compliance 42
2. OBJECTIVES 43
3. STUDY DESIGN 44
3.1. Treatment Plan and Regimen 44
3.2. Visit Schedule 44
3.3. Virologic Response 44
3.3.1. HCV Virologic Response-Based Treatment Stopping Criteria 44
3.3.2. HIV Virologic Rebound Criteria 45
3.4. Stopping Rules for Individual Subjects 47
3.5. Discontinuations 47
3.6. Assessments for Premature Discontinuation from Study 48
3.7. Criteria for Discontinuation of Study Treatment 48
3.8. Biomarker Testing 48
3.8.1. Biomarker Samples for Optional Future Research 48
3.8.2. Biomarker Samples for Optional Pharmacogenomic Research 49
4. SUBJECT POPULATION 50
4.1. Number of Subjects and Subject Selection 50
4.2. Inclusion Criteria 50
4.3. Exclusion Criteria 52
5. INVESTIGATIONAL MEDICINAL PRODUCTS 55
5.1. Randomization, and Study Drug Supply 55
5.2. Description and Handling of SOF/VEL FDC 55
5.2.1. Formulation 55
5.2.2. Packaging and Labeling 55
5.2.3. Storage and Handling 55
5.3. Dosage and Administration of SOF/VEL FDC 56
5.4. Description and Handling of Ribavirin (RBV) 56
5.4.1. Formulation 56
5.4.2. Packaging and Labeling 56
5.4.3. Storage and Handling 56
5.4.4. Dosage and Administration 57

5.5. Prior and Concomitant Medications 58
5.6. Acceptable HIV Antiretroviral Regimens 59
5.7. Study Drug Adherence and Drug Accountability 60
5.8. Study Drug Return or Disposal 61

6. STUDY PROCEDURES 62

6.1. Subject Enrollment and Treatment Assignment 62
6.2. Screening Assessments 62
6.2.1. Screening Visit (Day 28 to Day 0) 62
6.3. Treatment Assessments 64
6.3.1. Baseline/Day 1 Visit 64
6.3.2. Week 2 (±3 days) 65
6.3.3. Weeks 4 and 8 (± 3 days) 66
6.3.4. Week 12 or Early Termination (± 3 days) 66
6.3.5. Unscheduled Visit 67
6.4. Posttreatment Assessments 67
6.4.1. Post-treatment Week 4 (±5 days) 67
6.4.2. Post-treatment Week 12 (± 5 days) 68
6.5. Confirmatory Visit 69
6.6. End of Study 69
6.7. Procedures and Specifications 69
6.7.1. Clinical Laboratory Analytes 69
6.7.2. Medical History 70
6.7.3. Complete Physical Examination 70
6.7.4. Vital Signs 70
6.7.5. Creatinine Clearance 70
6.7.6. 12-Lead ECGs 71
6.7.7. HCV Viral RNA Sequencing / Phenotyping Sample (Archive) 71
6.7.8. HIV Viral RNA Genotyping/Phenotyping Sample (Archive) 71
6.7.9. Single Pharmacokinetic (PK) Sample 71
6.7.10. Pharmacogenomics Testing 71
6.7.11. Sample Storage 72
6.7.12. Pregnancy Testing 72

7. TOXICITY MANAGEMENT 73

7.1. Dose Modification Due to Toxicity 73
7.2. Group 1: Subjects administered SOF/VEL 73
7.3. Group 2: Subjects administered SOF/VEL+ RBV 73
7.3.1. Subject Stopping Rules 73
7.4. Subject Stopping Rules 73
7.5. Special Situations Reports 73
7.5.1. Definitions of Special Situations 73

8. ADVERSE EVENTS MANAGEMENT 75

8.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events 75
8.1.1. Adverse Events 75
8.1.2. Serious Adverse Events 75
8.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events 76
8.2. Assessment of Adverse Events and Serious Adverse Events 76
8.2.1. Assessment of Causality for Study Drugs and Procedures 76
8.2.2. Assessment of Severity 77
8.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead 77

8.4. Gilead Reporting Requirements 78
8.5. Toxicity Management 79
8.5.1. Instructions for Reporting Special Situations 79

9. STATISTICAL CONSIDERATIONS 81

9.1. Analysis Objectives and Endpoints 81
9.1.1. Analysis Objectives 81
9.1.2. Primary Endpoints 81
9.1.3. Secondary Endpoints 81
9.1.4. Other Endpoints of Interest 82
9.2. Analysis Conventions 82
9.2.1. Analysis Sets 82
9.3. Data Handling Conventions 82
9.4. Demographic Data and Baseline Characteristics 84
9.5. Efficacy Analysis 84
9.5.1. Primary Analysis 84
9.5.2. Secondary Analyses 84
9.6. Safety Analysis 85
9.6.1. Extent of Exposure 85
9.6.2. Adverse Events 85
9.6.3. Laboratory Evaluations 86
9.6.4. Other Safety Evaluations 86
9.6.5. HIV RNA Analysis 86
9.7. Pharmacokinetic Analysis 86
9.8. Sample Size 86

10. RESPONSIBILITIES 87

10.1. Investigator Responsibilities 87
10.1.1. Good Clinical Practice 87
10.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval 87
10.1.3. Informed Consent 87
10.1.4. Confidentiality 88
10.1.5. Study Files and Retention of Records 88
10.1.6. Case Report Forms 89
10.1.7. Investigational Medicinal Product Accountability and Return 90
10.1.8. Inspections 90
10.1.9. Protocol Compliance 90
10.2. Sponsor Responsibilities 91
10.2.1. Protocol Modifications 91
10.2.2. Study Report and Publications 91
10.3. Joint Investigator/Sponsor Responsibilities 91
10.3.1. Payment Reporting 91
10.3.2. Access to Information for Monitoring 92
10.3.3. Access to Information for Auditing or Inspections 92
10.3.4. Study Discontinuation 92

11. REFERENCES 93

12. APPENDICES 96

Appendix 1. Investigator Signature Page 97
Appendix 2. Study Procedures Table 98
Appendix 3. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities 100

Appendix 4. Child-Pugh-Turcotte Classification of the severity of cirrhosis 122
Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements 123
Appendix 6. Opportunistic Infections 126

LIST OF IN-TEXT TABLES

Table 1-1. GS-US-342-1138: SVR12 Overall and by HCV Genotypes 16
Table 1-2. NGMN, NG, EE, and VEL Plasma PK Parameters Following Administration of NGM/EE alone or with VEL 32
Table 1-3. Summary of LH, FSH, and Progesterone Concentrations Following Administration of NGM/EE alone or with VEL 32
Table 1-4. Summary of Changes in SOF/VEL PK following administration with Representative H2RAs and PPIs 34
Table 1-5. GS-US-342-1167: Summary of Changes in PK Parameters of SOF, its Metabolites GS-566500 and GS-331007, GS-5816, and Evaluated ARVs (EFV, RPV, DTG, EVG, COBI, FTC, TAF, and TFV) (PK Analysis Sets) 35
Table 1-6. GS-US-342-1326: Preliminary Summary of Changes in PK Parameters of SOF, its Metabolites GS-566500 and GS-331007, GS-5816, and Evaluated ARVs (EVG, COBI, DRV, ATV, LPV, RTV, RAL, FTC, and TFV) 37
Table 5-1. List of Disallowed /Use with Caution Medications 59
Table 7-1. Ribavirin Dose Modification Guideline for Coadministration with SOVALDI 73

LIST OF IN-TEXT FIGURES

Figure 3-1. HIV Virologic Rebound Schema 46

PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination (FDC) and Sofosbuvir/Velpatasvir FDC and Ribavirin in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis
IND Number:	This is a non-IND study
EudraCT Number:	2016-000417-73
Clinical Trials.gov Identifier:	Not Available
Study Centers:	Approximately 30 centers in Spain
Number of Subjects Planned:	Approximately 200 subjects with chronic genotype 3 HCV infection and compensated cirrhosis
Target Population:	Male and non-pregnant/non-lactating female subjects with chronic genotype 3 HCV infection and compensated cirrhosis, ages 18 years or older with and without HIV-1 coinfection.
Duration of Treatment:	Following randomization, enrolled subjects will receive assigned study treatment for 12 weeks
Objectives:	The primary objectives of this study are: • To evaluate the efficacy of study treatment with Sofosbuvir(SOF)/Velpatasvir(VEL, GS-5816) FDC and SOF/VEL FDC and Ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained virologic response 12 weeks after cessation of treatment regimen (SVR12) • To evaluate the safety and tolerability of each treatment regimen The secondary objectives of this study are: • To determine the proportion of subjects who attain SVR at 4 weeks after cessation of each treatment regimen (SVR4) • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of each treatment regimen • To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

	The exploratory objective of this study is: • PPD [redacted]
Study Design:	Approximately 200 subjects with chronic genotype 3 HCV infection and compensated cirrhosis will be randomized (1:1) to either: 1. Group 1 (n = 100): SOF/VEL once daily for 12 weeks or 2. Group 2 (n = 100): SOF/VEL + RBV for 12 weeks Randomization will be stratified by prior treatment experience (treatment naïve/treatment-experienced).
Substudy	Pharmacogenomics (PG) Substudy In consenting participants, a blood sample will be drawn at baseline or during the study for pharmacogenomics research.
Diagnosis and Main Eligibility Criteria:	Chronic genotype 3 HCV infected, male and non-pregnant/ non-lactating female subjects with compensated cirrhosis, ages 18 years or older. HIV-1 coinfected patients are eligible to participate. They must meet the HIV specific eligibility criteria. Refer to Sections 4.2 and 4.3 of the protocol for detailed Inclusion and Exclusion Criteria
Study Procedures/ Frequency:	Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. The screening window can be extended to 42 days for subjects requiring liver biopsy, additional HCV genotype testing, or for extenuating circumstances. All subjects will complete the following study visits: Screening, Baseline/Day 1, on-treatment visits at the end of Weeks 2, 4, 8, and 12, and posttreatment Week 4. Patients who achieve SVR4 will also be required to attend a posttreatment Week 12 visit. Screening assessments will include physical examination, medical history, height, weight, vital signs, 12-lead ECG, adverse events related to screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation),

	HCV RNA, HIV-1 RNA, CD4 T-cell count and percent, serology (HIV, HCV, HBV), hemoglobin A1c (HbA1c), assessment of the presence or absence of cirrhosis, screening for hepatocellular carcinoma (HCC), serum β-hCG (females of child bearing potential only), IL28B genotyping, urinalysis and urine drug screen. Subjects with HIV co-infection will also have the following laboratory tests: HIV-1 RNA, CD4 T-cell count and percent. On-treatment assessments include adverse events (AEs), concomitant medications, study medication pill count, physical examination, weight, vital signs, safety laboratory tests, HCV RNA, pharmacokinetic samples, and urine pregnancy tests (females of child bearing potential only). Subjects with HIV co-infection will also have the following laboratory tests: HIV-1 RNA, CD4 T-cell count and percent. Post-treatment assessments include AEs, concomitant medications, vital signs, safety laboratory tests, HCV RNA, and urine pregnancy tests (females of child bearing potential only). Subjects with HIV co-infection will also have the following laboratory tests: HIV-1 RNA, CD4 T-cell count and percent. Samples for HCV RNA sequencing / phenotyping will be collected at Baseline and every visit thereafter. Subects' with HIV co-infection will also have samples for HIV RNA genotyping/phenotyping collected at Baseline/Day 1 and at Weeks 2, 4, 8, 12, ET and Posttreatment Week 4. Samples will be collected during on-treatment visits for pharmacokinetic (PK) analysis of study drugs. For subjects who provide their additional and specific consent, an appropriate blood sample will be collected at the Baseline/Day 1 visit for PG (this sample may be drawn after Baseline/Day 1 if necessary). For subjects who provide their additional and specific consent, PPD
Test Product, Dose, and Mode of Administration:	SOF/VEL fixed dose combination (FDC) is manufactured as a 400/100mg FDC tablet for oral administration. All subjects will take 1 tablet daily with or without food. Subjects in Group 2 will take RBV with food at a total daily oral dose of 1000 or 1200 mg (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg) in a divided daily dose.

Criteria for Evaluation:	
Safety:	AEs and laboratory tests will be collected throughout the study
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0
Pharmacokinetics:	A single PK blood sample will be collected at each on-treatment visit for all subjects. The PK of SOF (and metabolites), VEL and RBV may be assessed.
Statistical Methods:	The primary efficacy endpoint for the study is SVR12 in all randomized and treated subjects. In the primary efficacy analysis, point estimate and 95% confidence interval of SVR12 will be computed for each treatment group. Secondary efficacy endpoints include SVR4 and the proportion of subjects with virologic failure. All continuous endpoints (except for safety endpoints) will be summarized using an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) by treatment group and stratification within group (as appropriate). All categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition. Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data by treatment group. With a sample size of 100 for each treatment, a two-sided 95% exact confidence interval will extend at most 21% in length for each treatment.

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
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
APRI	AST: platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUCtau	area under the plasma concentration versus time curve over the dosing interval (tau)
ß-hCG	ß-human chorionic gonadotropin
BLQ	below the lower limit of quantification
BMI	body mass index
CD4	cluster of differentiation 4
CI	confidence interval
CLcr	creatinine clearance
Cmax	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CK	creatine kinase
CPT	Child-Pugh-Turcotte Classification
CRF	case report form(s)
CRO	Contract (or clinical) research organization
CSA	colony stimulating agents
DAA	direct acting antiviral
DCV	daclatasvir (HCV NS5A Inhibitor)
DDI	drug-drug interaction
DSPH	Drug Safety and Public Health
EC	Ethics committee
ECG	electrocardiogram
EDC	electronic data capture
eCRF	Electronic case report form(s)
ESA	Erythropoiesis-stimulating agents
ET	early termination
EU	European Union
EudraCT	European clinical trials database
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination

FSH	follicle stimulating hormone
GCP	Good Clinical Practice (Guidelines)
GM-CSF	Granulocyte macrophage colony stimulating factor
GSI	Gilead Sciences, Inc.
GT	genotype (viral)
H2RA	Histamine-2 receptor antagonist
Hb	Hemoglobin
HBV	Hepatitis B virus
HbA1C	Hemoglobin A1C
HCC	Hepatocellular carcinoma
hCG	human chorionic gonadotropin
HDPE	high-density polyethylene
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HLGT	high-level group term
HLT	high-level term
IB	investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	interferon
IL28B	interleukin-28B gene
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
INR	international normalized ratio of prothrombin time
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
LAM	lactational amenorrhea method
LDV	ledipasvir
LFT	liver function test
LH	luteinizing hormone
LLN	lower limit of the normal range
LLOQ	lower limit of quantification
LLT	lower-level term
LT	liver transplantation
MELD	Model for End Stage Liver Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute

mL	milliliter
mmHg	millimeters mercury
MCV	mean cellular volume
NDA	New Drug Application
ng	nanogram
ng•h/mL	nanograms times hours per milliliter
NG	norgestrel
NGM	norgestimate
NGM/EE	norgestimate/ethinyl estradiol
NGMN	norelgestromin
NS (3/4A/5A/5B)	Non-structural protein
OC	oral contraceptive
PCR	Polymerase chain reaction
Peg-IFN	Pegylated-Interferon-α
pg	pictogram
pg•h/mL	picograms times hours per milliliter
P-gp	P-glycoprotein
PK	pharmacokinetic
PPI	Proton pump inhibitor
PT	Preferred term or prothrombin time
RBV	ribavirin
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
SOF	Sovaldi® or Sofosbuvir, formerly GS-7977
SOF/VEL	SOF/VEL fixed dose combination
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
t_{max}	The time (observed time point) of C_{max}
$t_{½}$	An estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
ULN	upper limit of the normal range
US	United States
VA	Veterans Affairs
VEL	Velpatasvir, formerly GS-5816
WBC	White blood cell count

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) infection is a global health challenge with estimates ranging up to 150 million individuals infected worldwide {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 transplantation, 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 and in the European Union for GT1-6 with different regimens and durations dependent on the HCV genotype and the presence or absence of cirrhosis {Gilead Sciences Inc 2013}.The next wave of therapies for the treatment of HCV includes combinations of direct acting antivirals (DAAs) including SOF in Peg-IFN and RBV free regimens. The first of these treatments, a fixed dose combination (FDC) of SOF and the HCV nonstructural protein 5A (NS5A) inhibitor ledipasvir (LDV), has been approved in the US and Europe. The Phase 3 studies GS-US-337-0102 (ION 1), GS-US-337-0109 (ION 2), and GS-US-337-0108 (ION 3) demonstrated that treatment with LDV/SOF with or without RBV for 8, 12 or 24 weeks resulted in high SVR12 rates in subjects with GT1 HCV infection {Afdhal et al 2014b}, {Afdhal et al 2014a}, {Kowdley et al 2014}. LDV/SOF with RBV is currently approved as a 24 week regimen for the treatment of genotype 3 HCV infection in Europe, but is not approved for GT3 HCV infections in the US.

Despite the recent advances of DAA based therapy for HCV, there remains room for improvement in therapy for certain subgroups of patients based on genotype, previous HCV treatment experience, and the presence or absence of cirrhosis. For example, while there are good treatment options available for patients with GT3 HCV infections without cirrhosis (12 weeks of SOF plus daclatasvir has been shown to lead to SVR12 rates as high as 98% in patients with GT 3 HCV infections) {Nelson et al 2015}, this regimen has not been as effective in patients with concomitant cirrhosis, where SVR12 rates are around 60%. Treatment options for patients with GT 3 HCV infections and cirrhosis are limited to longer regimens (24 weeks) that include the use of ribavirin or 12 week regimens that require the use of ribavirin and pegylated interferon {Gilead Sciences Inc 2013}. Considering these subgroups is critical as over half of all HCV infections are non-GT1: estimates from 2 recent meta-analyses indicate GT3 HCV is the next most common after GT1 accounting for 22-30% of HCV infections. The availability of a well-tolerated, all oral, ribavirin-free, pegylated interferon-free, short duration therapy that is effective in all HCV genotypes, including patients with GT3 HCV and cirrhosis

would be a major advance for the treatment of HCV infection globally. Moreover, a pangenotypic regimen that does not require HCV genotyping, response guided therapy, or intensive safety monitoring due to use of Peg-IFN or RBV would allow a greater number of patients to be treated in regions where HCV genotyping or careful safety monitoring of treated patients is not part of routine medical care for HCV infection.

1.2. Sofosbuvir/Velpatasvir Fixed Dose Combination

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

SOF is a nucleotide analog HCV NS5B polymerase inhibitor currently approved in the US and other regions for the treatment of HCV infection as described in Section 1.1. VEL (formerly known as GS-5816) is a HCV NS5A inhibitor that has demonstrated activity against HCV in phase 1, phase 2, and phase 3 studies. VEL showed activity against genotypes 1, 2, 3 and 4 HCV in a phase 1, 3 day, monotherapy study. Phase 2 studies of SOF + VEL administered as single agents have demonstrated that the combination of SOF 400 mg and VEL 100 mg administered for 12 weeks is well tolerated and results in high SVR rates across a broad range of HCV genotypes. In the Phase 2 study GS-US-342-0109 all patients with GT3 HCV infections without cirrhosis achieved SVR12, regardless of the addition of RBV. Patients with compensated cirrhosis achieved higher SVR12 rates with the addition of RBV, suggesting that RBV provides additional efficacy when added to regimens of SOF + VEL in these patients. The SOF/VEL FDC (400/100 mg) is a co-formulation of SOF 400 mg and VEL 100 mg has been shown to be effective in the treatment of GT1-6 HCV in four Phase 3 trials (ASTRAL 1-4), including patients with GT3 HCV infections and cirrhosis.{Feld et al 2015, Foster et al 2015} {Curry et al 2015}. The ASTRAL studies and several ongoing phase 3 trials are described in detail in Section 1.2.2.1.

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

1.2.1. General Information

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

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

1.2.2. Additional Clinical Experience

1.2.2.1. Sofosbuvir/Velpatasvir Phase 3 Studies

Four Phase 3 studies have been completed 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). Three Phase 3 trials enrolling patients with HIV-1 coinfection (GS-US-342-1202 [ASTRAL-5]), patients who failed to achieve SVR12 in previous Gilead sponsored HCV treatment studies (GS-US-342-1553), and patients who received placebo during ASTRAL-1 (GS-US-342-1446) are currently ongoing. Summaries of results from the completed Phase 3 studies and descriptions of the ongoing Phase 3 studies are presented below.

1.2.2.1.1. 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 Begium, 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 1-1 presents the SVR12 results for the SOV/VEL FDC12 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 posttreatment week 4; one treatment-naïve 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 posttreatment Week 12 visit, and 1 subject died prior to the posttreatment Week 4 visit).

Table 1-1. 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 posttreatment 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 posttreatment 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 posttreatment 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 $\geq 5 \times$ 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.

1.2.2.1.2. 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; 134 in the SOF/VEL 12 Week group and 132 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 posttreatment Week 4 visit and 2 relapses occurred between the posttreatment 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 posttreatment Week 4 and 2 subjects relapsed between the posttreatment 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.

1.2.2.1.3. 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. This study was conducted in Australia, Canada, France, Germany, Italy, New Zealand, United Kingdom and United States.

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+RBV24 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 posttreatment 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 posttreatment Week 4 visit. In the SOF/VEL 12 Week group, 8 of 11 relapses occurred by posttreatment Week 4, and 3 of 11 relapses occurred between posttreatment 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 SOF/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 posttreatment 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.

1.2.2.1.4. 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 posttreatment 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 posttreatment 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 posttreatment 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 posttreatment 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 posttreatment 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 posttreatment 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.

1.2.2.1.5. Study GS-US-342-1202 (ASTRAL-5)

Study Design

This ongoing, Phase 3, open-label, multicenter study is assessing the antiviral efficacy, safety, and tolerability of SOF/VEL for 12 weeks in subjects with chronic HCV infection and HIV-1 coinfection. This study is being conducted in the US, New Zealand, and Australia.

Approximately 100 subjects with genotype 1 to 6 HCV infection with HIV-1 coinfection on a stable regiment of HIV antiretroviral therapy (ARV) are all scheduled to receive SOF/VEL for 12 weeks. The primary outcome is the proportion of subjects who achieve SVR12.

1.2.2.1.6. Study GS-US-342-1553

Study Design

This ongoing, open-label, multicenter study is assessing the antiviral efficacy, safety, and tolerability of SOF/VEL ±RBV for 24 weeks in subjects with chronic HCV infection who have participated in prior Gilead sponsored HCV treatment studies. This study is being conducted in the US, New Zealand, and Australia.

Approximately 150 subjects with and without cirrhosis with genotype 1 to 6 HCV infection who did not achieve SVR12 in previous Gilead sponsored HCV treatment studies will all receive SOF/VEL + RBV for 24 weeks). The primary outcome is the proportion of subjects who achieve SVR12.

1.2.2.1.7. Study GS-US-342-1446

Study Design

This ongoing, open-label, multicenter study is assessing the antiviral efficacy, safety, and tolerability of SOF/VEL for 12 weeks in subjects who received placebo in study GS-US-342-1138 (ASTRAL 1). This study is being conducted in the US, Canada, Europe, and Asia.

Approximately 100 subjects with genotype 1, 2, 4, 5, and 6 HCV infection who received placebo in ASTRAL 1 will all receive SOF/VEL 12 weeks. The primary outcome is the proportion of subjects who achieve SVR12.

1.2.2.2. Clinical Pharmacology Studies

1.2.2.2.1. Study GS-US-281-1058

GS-US-281-1058 is an open-label, Phase 1, multiple-dose drug-drug interaction (DDI) study in healthy female subjects of childbearing age evaluating the effect of VEL on the pharmacokinetics of a representative hormonal oral 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 oral 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 1-2 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 1-2. 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 1-3. 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 1-3. Summary of LH, FSH, and Progesterone Concentrations Following Administration of NGM/EE alone or with VEL

PD Analyte	Median (Q1, Q3)	
	OC Alone (N = 15)	OC + GS-5816 (N = 13)
LH (mIU/mL)	8.0 (2.9, 12.7)	9.3 (5.4, 14.4)
FSH (mIU/mL)	3.6 (2.0, 5.9)	2.6 (2.2, 5.1)
Progesterone (ng/mL)	0.24 (0.17, 0.39)	0.27 (0.18, 0.80)

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

1.2.2.2.2. 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. A summary of results from these studies are 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 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. Largest decreases were observed in subjects with highest exposure at reference, and those with low exposure at reference 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 1-4. 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%
	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%.

1.2.2.2.3. Study GS-US-342-1167

Study GS-US-342-1167 evaluated safety, tolerability, and pharmacokinetics of SOF, its metabolites GS-566500 and GS-331007, and GS-5816 following administration of SOF/VEL (400/100 mg) with Atripla® (ATR; efavirenz/emtricitabine/tenofovir disoproxil fumarate [EFV/FTC/TDF]), Eviplera® (emtricitabine/rilpivirine/tenofovir disoproxil fumarate [FTC/RPV/TDF]), Tivicay® (dolutegravir [DTG]), or elvitegravir/cobicistat/emtricitabine/tenofovir alafemamide fumarate (EVG/COBI/FTC/TAF).

Table 1-5 summarizes the differences in PK parameters of SOF, its metabolites GS-566500 and GS-331007, GS-5816, and evaluated ARVs (EFV, RPV, DTG, EVG, COBI, FTC, TAF, and TFV) when SOF/GS-5816 or the ARVs were administered alone compared with administration of SOF/GS-5816 + ARVs.

Table 1-5. GS-US-342-1167: Summary of Changes in PK Parameters of SOF, its Metabolites GS-566500 and GS-331007, GS-5816, and Evaluated ARVs (EFV, RPV, DTG, EVG, COBI, FTC, TAF, and TFV) (PK Analysis Sets)

	SOF/GS-5816+ARV / ARV				SOF/GS-5816+ARV / SOF/GS-5816									
	ARV PK Parameters			ARVs	SOF PK Parameters		GS-566500 PK Parameters		GS-331007 PK Parameters			GS-5816 PK Parameters		
Analyte	AUC_{tau}	C_{max}	C_{tau}		AUC_{tau}	C_{max}	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}	C_{tau}	AUC_{tau}	C_{max}	C_{tau}
EFV/FTC/TDF														
EFV	↔	↔	↔	**EFV/ FTC/ TDF**	↔	**↑38%**	↔	↔	↔	↔	↔	**↓53%**	**↓47%**	**↓57%**
FTC	↔	↔	↔											
TFV	**↑81%**	**↑77%**	**↑121%**											
FTC/RPV/TDF														
RPV	↔	↔	↔	**FTC/ RPV/ TDF**	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
FTC	↔	↔	↔											
TFV	**↑40%**	**↑44%**	**↑84%**											
DTG														
DTG	↔	↔	↔	**DTG**	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
EVG/COBI/FTC/TAF														
EVG	↔	↔	↔	**EVG/ COBI/ FTC/ TAF**	**↑37%**	↔	↔	↔	**↑48%**	↔	**↑58%**	**↑50%**	**↑30%**	**↑60%**
COBI	↔	↔	**↑103%**											
FTC	↔	↔	↔											
TAF	↔	**↓20%**	NC											
TFV	↔	↔	↔											

NC = not calculable
Note: 90% CIs of the %GLSM ratios were within (↔), extended above (↑), or extended below (↓) the predetermined alteration boundaries of 70% to 143%.

Effect of EFV/FTC/TDF, FTC/RPV/TDF, DTG (Dolutegravir), or EVG/COBI/FTC/TAF on Sofosbuvir, GS-566500, GS-331007, and GS-5816 Pharmacokinetics

No alteration in the overall exposure of SOF, GS-566500, and GS-331007 was observed following coadministration of SOF/GS-5816 + EFV/FTC/TDF, FTC/RPV/TDF, or DTG. Other than a small increase in SOF C_{max} when administered with EFV/FTC/TDF, the 90% CIs for the %geometric least-squares mean (%GLSM) ratios for all primary PK parameters (AUC_{tau}, C_{max}, and C_{tau} [if measurable]) were within predetermined lack of PK alteration boundaries of 70% to 143%, confirming a lack of an effect on the PK of SOF and metabolites by EFV/FTC/TDF, FTC/RPV/TDF, or DTG. An increase in SOF AUC (37%) and GS-331007 AUC (48%) and C_{tau} (58%) were observed when administered with EVG/COBI/FTC/TAF. Of note, GS-331007 exposure when administered with EVG/COBI/FTC/TAF was within the range of GS-331007 exposures observed in the LDV/SOF Phase 3 studies, as well as similar to exposures seen in subjects with mild renal impairment where dosing of SOF is permitted without dose adjustment.

The PK of GS-5816 was not altered by FTC/RPV/TDF or DTG. A reduction (approximately 50%) in GS-5816 systemic exposures was observed following administration of SOF/GS-5816 + EFV/FTC/TDF compared to SOF/GS-5816 alone. A modest increase (approximately 50%) in GS-5816 systemic exposures was observed following administration of SOF/GS-5816 + EVG/COBI/FTC/TAF compared to SOF/GS-5816 alone.

Effect of Sofosbuvir/VEL on Efavirenz, Rilpivirine, Dolutegravir, Elvitegravir, Cobicistat, Emtricitabine, Tenofovir, and Tenofovir Alafenamide Pharmacokinetics

The PK of EFV, RPV, DTG, EVG, and FTC were not altered following coadministration of EFV/FTC/TDF, FTC/RPV/TDF, DTG, or EVG/COBI/FTC/TAF with SOF/GS-5816. The 90% CIs for the %GLSM ratios for EFV, RPV, DTG, EVG, and FTC AUC_{tau}, C_{max}, and C_{tau} remained within the protocol-predefined lack of PK alteration boundaries of 70% to 143%. An increase in COBI C_{tau} (103%) was observed with no increase in AUC_{tau} or C_{max} following coadministration of EVG/COBI/FTC/TAF with SOF/GS-5816. A small decrease in TAF C_{max} (20%) was observed with no decrease in AUC_{tau} following coadministration of EVG/COBI/FTC/TAF with SOF/GS-5816.

The PK of TFV was not altered following coadministration of EVG/COBI/FTC/TAF with SOF/GS-5816. The 90% CIs for the %GLSM ratios for TFV AUC_{tau}, C_{max}, and C_{tau} remained within the protocol predefined lack of PK alteration boundaries of 70% to 143%. Modest increases in TFV AUC_{tau}, C_{max}, and C_{tau} of approximately 81%, 77%, and 121%, respectively, were observed following coadministration of EFV/FTC/TDF with SOF/GS-5816. Similarly, modest increases in TFV AUC_{tau}, C_{max}, and C_{tau} of approximately 40%, 44%, and 84%, respectively, were observed following coadministration of FTC/RPV/TDF with SOF/GS-5816. Similar absolute TFV plasma exposures were achieved following administration of SOF/GS-5816 + EFV/FTC/TDF and SOF/GS-5816 + FTC/RPV/TDF. Furthermore, TFV exposures were also comparable to those achieved upon coadministration of TDF with HIV protease inhibitor (PIs), which did not warrant dose adjustment {Hoetelmans et al 2007}, {Agarwala et al 2005}. Accordingly, administration of TDF as part of FTC/RPV/TDF or FTC/TDF does not warrant dose adjustment when administered with SOF/GS-5816.

Based on the safety and PK data from this study in addition to safety, efficacy, and PK of the agents respectively, SOF/GS-5816 may be coadministered with FTC/RPV/TDF, DTG, FTC/TDF, or EVG/COBI/FTC/TAF without dose adjustment to any of the agents. SOF/GS-5816 should not be administered with EFV/FTC/TDF or EFV as part of other ARV regimens.

1.2.2.2.4. Study GS-US 342-1326

Study GS-US-342-1326 evaluated safety, tolerability, and pharmacokinetics of SOF, its metabolites GS-566500 and GS-331007, and GS-5816 following administration of SOF/GS-5816 (400/100 mg) with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; Stribild®), emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; Truvada®) plus ritonavir (RTV)-boosted darunavir (DRV; Prezista®), atazanavir (ATV; Reyataz®), and lopinavir (LPV/RTV; Kaletra®), and raltegravir (RAL; Isentress®).

Table 1-6 summarizes the differences in preliminary PK parameters of SOF, its metabolites GS-566500 and GS-331007, GS-5816, and evaluated ARVs (EVG, COBI, DRV, ATV, LPV, RTV, RAL, FTC, and TFV) when SOF/GS-5816 or the ARVs were administered alone compared with administration of SOF/GS-5816 + ARVs.

Table 1-6. GS-US-342-1326: Preliminary Summary of Changes in PK Parameters of SOF, its Metabolites GS-566500 and GS-331007, GS-5816, and Evaluated ARVs (EVG, COBI, DRV, ATV, LPV, RTV, RAL, FTC, and TFV)

	SOF/GS-5816+ARV / ARV				**SOF/GS-5816+ARV / SOF/GS-5816**									
	ARV PK Parameters			**ARVs**	**SOF PK Parameters**		**GS-566500 PK Parameters**		**GS-331007 PK Parameters**			**GS-5816 PK Parameters**		
Analyte	**AUC_{tau}**	**C_{max}**	**C_{tau}**		**AUC_{tau}**	**C_{max}**	**AUC_{tau}**	**C_{max}**	**AUC_{tau}**	**C_{max}**	**C_{tau}**	**AUC_{tau}**	**C_{max}**	**C_{tau}**
EVG/COBI/FTC/TDF				**EVG/ COBI/ FTC/ TDF**	↔	↔	↔	↔	**↑35%**	↔	**↑45 %**	↔	↔	**↑37 %**
EVG	↔	↔	↔											
COBI	↔	↔	**↑71%**											
FTC	↔	↔	↔											
TFV	**↑35%**	**↑36%**	**↑45%**											
DRV + RTV + FTC/TDF				**DRV+ RTV+ FTC/ TDF**	**↓27%**	**↓39%**	↔	↔	↔	↔	↔	↔	**↓24%**	↔
DRV	↔	↔	↔											
RTV	↔	↔	↔											
FTC	↔	↔	↔											
TFV	**↑38%**	**↑55%**	**↑51%**											

	SOF/GS-5816+ARV / ARV			ARVs	SOF/GS-5816+ARV / SOF/GS-5816									
	ARV PK Parameters				SOF PK Parameters		GS-566500 PK Parameters		GS-331007 PK Parameters			GS-5816 PK Parameters		
Analyte	**AUC_{tau}**	**C_{max}**	**C_{tau}**		**AUC_{tau}**	**C_{max}**	**AUC_{tau}**	**C_{max}**	**AUC_{tau}**	**C_{max}**	**C_{tau}**	**AUC_{tau}**	**C_{max}**	**C_{tau}**
ATV + RTV + FTC/TDF				**ATV+ RTV+ FTC/ TDF**	↔	↔	↔	↔	↔	↔	**↑42 %**	**↑142%**	**↑55%**	**↑301 %**
ATV	↔	↔	**↑39%**											
RTV	↔	↔	**↑29%**											
FTC	↔	↔	↔											
TFV	↔	**↑55%**	**↑39%**											
LPV/RTV + FTC/TDF				**LPV/ RTV+ FTC/ TDF**	**↓29%**	**↓41%**	↔	↔	↔	↔	↔	↔	**↓31%**	**↑62 %**
LPV	↔	↔	↔											
RTV	↔	↔	↔											
FTC	↔	↔	↔											
TFV	↔	**↑42%**	↔											
RAL + FTC/TDF				**RAL+ FTC/ TDF**	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
RAL	↔	↔	**↓21%**											
FTC	↔	↔	↔											
TFV	**↑40%**	**↑46%**	**↑70%**											

NC = not calculable
Note: 90% CIs of the %GLSM ratios were within (↔), extended above (↑), or extended below (↓) the predetermined alteration boundaries of 70% to 143%.

Effect of EVG/COBI/FTC/TDF, DRV+RTV+FTC/TDF, ATV+RTV+FTC/TDF, LPV/RTV+FTC/TDF, or RAL+FTC/TDF on Sofosbuvir, GS-566500, GS-331007, and GS-5816 Preliminary Pharmacokinetics

No alteration in the exposure (AUC_{tau}, C_{max}, or C_{tau}) of SOF, GS-566500, GS-331007, or GS-5816 was observed following administration of SOF/GS-5816 with RAL+FTC/TDF. A small increase in GS-331007 overall exposure (~35%) was observed with no alteration in the overall exposure of SOF, GS-566500, or GS-5816 when administered with EVG/COBI/FTC/TDF. Administration of SOF/GS-5816 with DRV+RTV+FTC/TDF or LPV/RTV+FTC/TDF resulted in a modest decrease in the overall exposure of SOF (~27% and ~29%, respectively) with no alteration in the overall exposure of GS-566500, GS-331007, or GS-5816. Administration of SOF/GS-5816 with ATV+RTV+FTC/TDF resulted in an increase in GS-5816 AUC_{tau} (~142%), C_{max} (~55%), and C_{tau} (~301%) with no change in the overall exposure of SOF or its metabolites (GS-566500 and GS-331007).

Effect of Sofosbuvir/GS-5816 on Elvitegravir, Cobicistat, Darunavir, Atazanavir, Lopinavir, Ritonavir, Raltegravir, Emtricitabine, and Tenofovir Preliminary Pharmacokinetics

The overall exposure (AUC_{tau}) and maximal exposure (C_{max}) of EVG, COBI, DRV, ATV, LPV, RTV, RAL, and FTC were not altered when administered with SOF/GS-5816, as the 90% CIs for the %GLSM ratios for AUC_{tau} were within the protocol-predefined lack of PK alteration boundaries of 70% to 143%. An increase in the C_{tau} of COBI (~71%), ATV (~39%), and RTV (~29%) when administered as part of ATV+RTV+FTC/TDF was observed following coadministration with SOF/GS-5816. A small decrease in the C_{tau} of RAL (~21%) was observed following coadministration with SOF/GS-5816 with no change in overall or maximal RAL exposure.

Modest increases in TFV AUC_{tau} (Range: 35-40%), C_{max} (Range: 36-55%), and C_{tau} (Range: 45-70%) were observed following administration of EVG/COBI/FTC/TDF, DRV+RTV+FTC/TDF, or RAL+FTC/TDF with SOF/GS-5816. A modest increase in TFV C_{max} (~55%) and C_{tau} (~39%) with no alteration in TFV AUC_{tau} was observed following administration of ATV+RTV+FTC/TDF with SOF/GS-5816. A modest increase in TFV C_{max} (~42%) with no alteration in TFV AUC_{tau} or C_{tau} was observed following administration of LPV/RTV+FTC/TDF with SOF/GS-5816.

Based on available safety and PK data from this study in addition to the safety, efficacy, and PK of these agents respectively, SOF/GS-5816 may be coadministered with EVG/COBI/FTC/TDF, DRV+RTV+FTC/TDF, ATV+RTV+FTC/TDF, LPV/RTV+FTC/TDF, or RAL+FTC/TDF without dose adjustment to any of the agents.

1.3. Ribavirin (RBV)

Ribavirin is a guanosine analogue that inhibits the *in vitro* replication of a wide range of RNA and DNA viruses {Roche Laboratories Inc. 2010}, {Roche Products Limited 2010}. Ribavirin monotherapy has little or no effect on the replication of HCV *in vivo* but can result in normalization of serum ALT activity and improvement in liver histology. When combined with IFN or PEG therapy, RBV decreases substantially the relapse rate seen after cessation of IFN therapy {Poynard et al 1998}, {McHutchison et al 1998}.

Ribavirin is a known teratogen (FDA category X). Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment, and in the case of males, impregnating a female while on RBV and up to7 months following completion of therapy.

A comprehensive review of RBV is contained in the SmPC.

1.4. Rationale for This Study

This Phase 2 study is designed as a multicenter, randomized, open-label study evaluating SOF/VEL FDC for 12 weeks and SOF/VEL + RBV for 12 weeks in subjects with Chronic GT3 HCV infection and compensated cirrhosis. Patients with genotype 3 HCV infection and cirrhosis have previously been studied as subgroups within 1 Phase 2 study (GS-US-342-0109) and 2 Phase 3 studies (GS-US-342-1140 [ASTRAL-3] and GS-US-342-1137 [ASTRAL-4]) evaluating either SOF + VEL or SOF/VEL FDC. GS-US-342-0109 is described in detail in the investigators brochure. Briefly, 27 and 26 patients with GT3 HCV infections without cirrhosis received SOF 400 mg + VEL 100 mg and SOF 400 mg + VEL 100mg + RBV, respectively, for 12 weeks, while 26 and 26 patients with compensated cirrhosis received SOF 400 mg + VEL 100mg and SOF 400 mg + VEL 100 mg + RBV, respectively, for 12 weeks. All patients without cirrhosis achieved SVR12, regardless of the addition of RBV, suggesting the RBV provides no additional efficacy when given to such patients. Among the patients with compensated cirrhosis, 88.5% achieved SVR12 without RBV while 96.2% achieved SVR12 with the addition of RBV, suggesting that RBV provides additional efficacy when added to regimens of SOF + VEL FDC in patients with GT3 HCV infections and cirrhosis. In ASTRAL-3 (described in Section 1.2.2.1.3), 277 patients with genotype 3 HCV were given SOF/VEL for 12 weeks, 80 (29%) of whom had underlying cirrhosis. The SVR12 rate for the cirrhotic patients was 91% compared to 97% for the non-cirrhotic patients. In ASTRAL-4 (described in Section 1.2.2.1.4) 14, 13, and 12 patients with genotype 3 HCV and decompensated cirrhosis (CPT B) received 12 weeks of SOF/VEL , 12 weeks of SOF/VEL + RBV, and 24 weeks of SOF/VEL, respectively. Of those patients, 7 (50%), 11 (85%), and 6 (50%) subjects achieved SVR12, suggesting that RBV provides additional efficacy on top of SOF/VEL when given to patients with GT3 HCV infections and decompensated cirrhosis.

In this study, approximately 200 subjects with genotype 3 HCV and compensated cirrhosis will be randomized 1:1 into 2 treatment groups: SOF/VEL for 12 weeks and SOF/VEL + RBV for 12 weeks. This study design will approximately double the number of patients with genotype 3 HCV and compensated cirrhosis treated with a non-RBV SOF/VEL regimen in clinical trials to better characterize the efficacy and safety of SOF/VEL in this important subgroup. Furthermore, though based on small numbers of patients with GT3 HCV infections and cirrhosis, both GS-US-342-0109 and ASTRAL-4 suggest that the regimen of SOF/VEL + RBV for 12 weeks is potentially an important regimen in these patients. This study design will also provide safety and efficacy data of the SOF/VEL + RBV regimen in patients with genotype 3 HCV and cirrhosis.

In summary, this study will expand the knowledge of the safety and efficacy of SOF/VEL ± RBV in patients with genotype 3 HCV and cirrhosis, and will further characterize the use of SOF/VEL as a once-daily pangenotypic regimen for the treatment of chronic HCV infection.

1.5. Rationale for Dose Selection

Sofosbuvir 400 mg, once daily, when dosed in combination with RBV with or without PEG has demonstrated broad genotypic efficacy and favorable safety profile in over 1700 HCV-infected subjects across multiple patient populations in Phase 2 and 3 trials. This dose is the approved

marketed dose of sofosbuvir for the treatment of HCV-infection and as such, has been selected for co-formulation with VEL into a fixed-dose combination tablet.

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

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

1.6. Overall Risk/Benefit Assessment

This study will provide information on the safety and efficacy of SOF/VEL ± RBV, a potent HCV nucleotide inhibitor and a potent HCV NS5A inhibitor, in patients with GT3 HCV infections and cirrhosis. The potential benefits of SOF/VEL ± RBV over the current standard of care for the treatment of chronic GT3 HCV in patients with cirrhosis are:

- Increasing the cure rate of GT3 HCV beyond that of currently approved therapies for patients with concomitant cirrhosis
- Providing the first PEG and RBV-free treatment option for patients with GT3 HCV and cirrhosis
- A once-daily, single tablet, single duration, pangenotypic therapy for HCV infection could simplify treatment algorithms and impact worldwide disease prevalence
- A reduction in the AEs currently associated with the use of PEG and RBV
- A short duration of therapy which should lead to better outcomes through improved adherence.

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

The safety profile of SOF + VEL 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 2014b}, {Afdhal et al 2014a}, {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 led to a similar incidence of AEs and SAEs compared to placebo in patients with GT 1, 2, 4, 5, or 6 HCV. When 12 weeks of SOF/VEL was compared to SOF + RBV for 12 or 24 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. 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, SOF/VEL ± RBV has the potential to increase SVR12 rates of GT3 HCV infections among patients with cirrhosis. If high rates of SVR can be obtained with a short, PEG-free ± RBV regimen, the anticipated improvements in safety and tolerability would offer a favourable risk-benefit determination for patients with chronic GT3 HCV infection and cirrhosis.

1.7. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the efficacy of study treatment with Sofosbuvir/Velpatasvir (SOF/VEL) FDC and SOF/VEL FDC and Ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained viralogic response 12 weeks after cessation of treatment regimen (SVR12)

- To evaluate the safety and tolerability of each treatment regimen

The secondary objectives of this study are:

- To determine the proportion of subjects who attain SVR at 4 weeks after cessation of each treatment regimen (SVR4)

- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of each treatment regimen

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

The exploratory objective of this study is:

- PPD [redacted]

3. STUDY DESIGN

3.1. Treatment Plan and Regimen

This is a multicenter, randomized, open-label study that will evaluate the safety, tolerability and antiviral efficacy of SOF/VEL FDC with and without RBV for 12 weeks in subjects with chronic genotype 3 HCV infection and compensated cirrhosis with or without HIV co-infection.

Approximately 200 subjects with chronic genotype 3 HCV infection and compensated cirrhosis will be randomized (1:1) to either:

- Group 1 (n = 100): SOF/VEL once daily for 12 weeks

OR

- Group 2 (n = 100): SOF/VEL + RBV for 12 weeks

Randomization will be stratified by prior treatment experience (treatment naïve/treatment-experienced).

3.2. Visit Schedule

All subjects will complete screening, on-treatment, and post-treatment assessments.

Screening assessments will be completed within 28 days of the Day 1 visit. The screening window can be extended to 42 days for subjects requiring liver biopsy, additional HCV genotyping or for extenuating circumstances.

All subjects will complete the following study visits: Screening, Baseline/Day 1, on-treatment visits at the end of Weeks 2, 4, 8 and 12. All subjects will complete the post-treatment Week 4 visit. Subjects with HCV RNA < LLOQ at the post-treatment Week 4 visit will complete the post-treatment Week 12 visit. Subjects with HCV RNA ≥LLOQ at post-treatment Week 12 visit will be asked to return for a confirmatory visit.

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

3.3. Virologic Response

3.3.1. HCV Virologic Response-Based Treatment Stopping Criteria

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

- Confirmed HCV RNA ≥ LLOQ after 2 consecutive HCV RNA < LLOQ
- Confirmed > 1 log10 increase from nadir
- HCV RNA ≥ LLOQ through 12 weeks of treatment

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

If HCV viral relapse is detected at post-treatment Week 4 or 12 visits, subjects will be asked to return for a confirmatory visit.

3.3.2. HIV Virologic Rebound Criteria

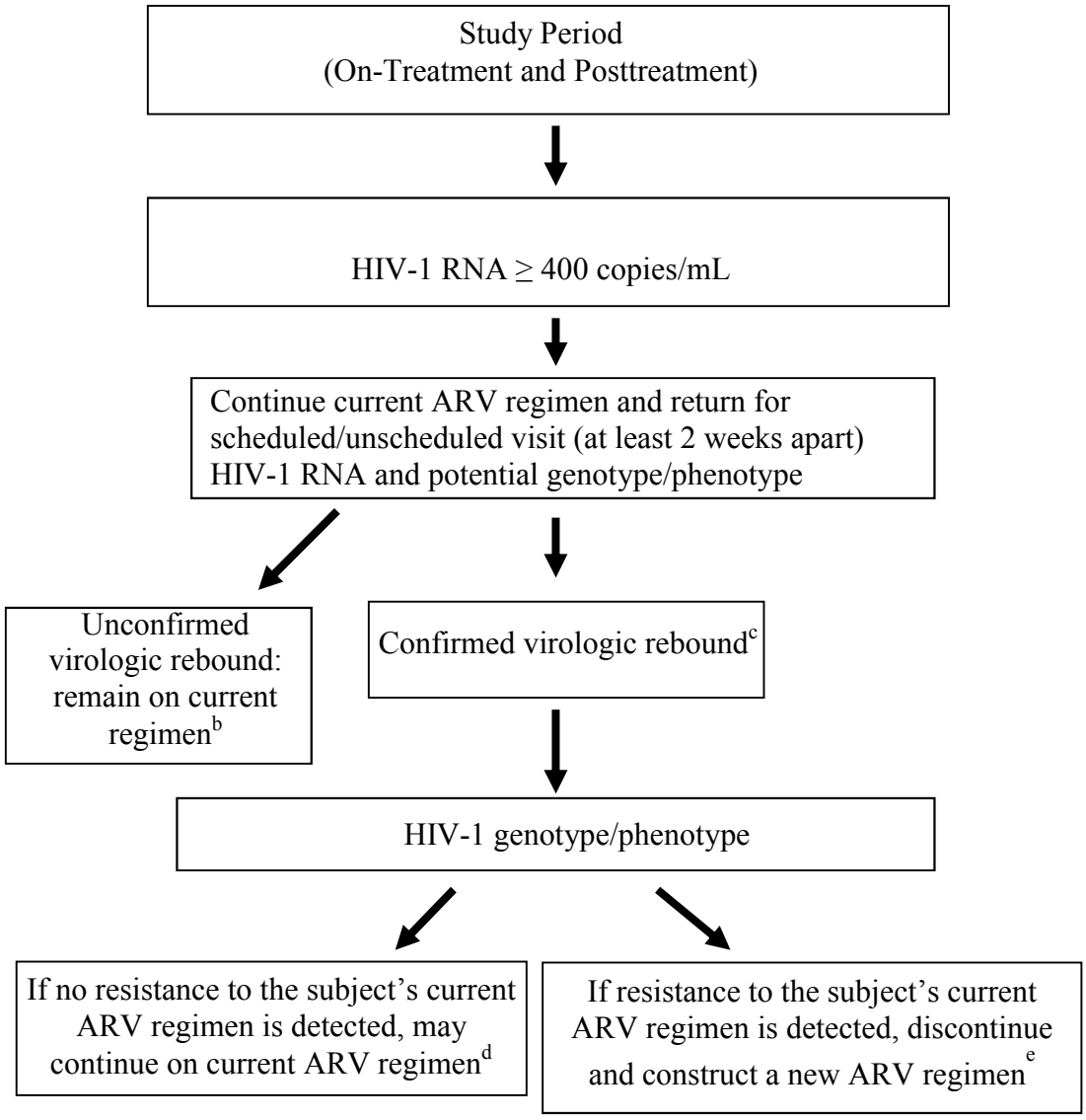
Subjects who have at least two consecutive post-baseline visit plasma HIV-1 RNA levels ≥ 400 copies/mL (at least two weeks apart) will be considered to have HIV virologic rebound.

Following an initial HIV-1 RNA result of ≥ 400 copies/mL, subjects will continue to take their current ARV regimen and be asked to return to the clinic after 2 weeks for a scheduled or unscheduled blood draw for confirmation of HIV virologic rebound. If HIV virologic rebound is confirmed at the scheduled or unscheduled visit, the blood samples from this visit will be used for HIV-1 genotype/phenotype testing. If no resistance to the subject's current ARV regimen is detected, the subject may continue on current ARV regimen. If resistance to the subject's current ARV regimen is detected, then it is strongly recommended that whenever possible, the subject be switched to an alternative approved regimen, as outlined in Section 4.2 of this protocol.

HCV study drug should be continued unless safety events warrant the discontinuation of the study drug, as outlined is Section 3.5 of the protocol, or if a subject must be switched to an unapproved HIV regimen based upon acquired resistance.

Please refer to Figure 3-1 for the management of subjects who meet the criteria for HIV virologic rebound.

Figure 3-1. HIV Virologic Rebound Schema



a HCV study drug should be continued unless safety events warrant the discontinuation of these study drugs, as outlined in Section 3.5 of the protocol
b If virologic rebound is not confirmed, the subject should remain on their current ARV regimen.
c If virologic rebound is confirmed, the HIV-1 genotype and phenotype (reverse transcriptase and protease) will be analyzed.
d Based on the results of the genotype and phenotype assays, the subject may remain on their ARV regimen at the discretion of the Investigator (e.g. virologic rebound due to non-adherence). If the genotype and/or phenotype assay fails to provide results, a new ARV regimen may be configured at the discretion of the Investigator in consultation with the Medical Monitor.
e A new ARV regimen should be configured or the ARV regimen held for the duration of SOF/VEL dosing at the Investigator's discretion in consultation with the Medical Monitor. If a new ARV regimen is required, it is strongly recommended to use an alternative regimen that is approved in this protocol. If an unapproved ARV regimen is prescribed, then SOF/VEL ± RBV must be discontinued after consultation with the medical monitor.

3.4. Stopping Rules for Individual Subjects

Subjects who meet any of the following criteria should be discontinued from the study and complete an Early Termination Visit and return for Posttreatment Follow-up visits:

- Elevation of ALT and/or AST that is greater than the ULN and > 5x baseline or nadir confirmed by immediate repeat testing unless laboratory results are assessed by both the investigator and Gilead Medical Monitor as having an explanation other than drug induced liver injury and it is deemed in the best interest of the subject to continue HCV treatment
- Confirmed elevation of ALT >15 x ULN (unrelated to any interventional procedures)
- Confirmed total bilirubin >10 x ULN (unrelated to any interventional procedures)
- Confirmed total bilirubin >3x baseline or 3x nadir (unrelated to any interventional procedures)
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any non-laboratory Grade 4 events assessed as related to administration of SOF/VEL
- Worsening of disease state as evidenced by progressing hepatic decompensation and/or progression of Child-Pugh Score (CPT) to ≥ 10

The Gilead Medical Monitor should be consulted prior to discontinuation of SOF/VEL and /or RBV unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject.

Any questions regarding toxicity management should be directed to Gilead Medical Monitor.

3.5. Discontinuations

If the subject meets the Virologic Response-Based Stopping Criteria (Section 3.3.1), they should complete an Early Termination Visit as soon as possible after SOF/VEL is discontinued and complete post-treatment visits up to 30 days after the last dose of SOF/VEL and/or 60 days after the last dose of RBV to assess for safety.

If the subject meets the Stopping Rules for Individual Subjects (Section 3.4) or other criteria for discontinuation of study treatment (Section 3.7), prior to completion of SOF/VEL dosing period, the subject should complete an Early Termination Visit as soon as possible after SOF/VEL is discontinued and complete the post-treatment assessments as described in Section 6.3 and in Study Procedures Appendix 2.

Subjects discontinuing treatment prior to completion of dosing period for reasons other than those described in Sections 3.3, 3.4 and 3.7 should complete an Early Termination Visit as soon

as possible after SOF/VEL is discontinued. The subject should also complete the post-treatment assessments as described in Section 6.3 and in Study Procedures Appendix 2.

3.6. Assessments for Premature Discontinuation from Study

If a subject discontinues SOF/VEL dosing (for example, as a result of an adverse event [AE]), every attempt should be made to keep the subject in the study and continue to perform the required study-related post-treatment assessments and procedures (see Section 6.3). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

3.7. Criteria for Discontinuation of Study Treatment

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

Study drug must be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section 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
- Subject requests to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy , or other reason
- Subject non-compliance
- Pregnancy of female subject. Subjects randomized to Group 2 who have female partners who become pregnant must immediately contact the Principal Investigator in order to discuss the risks and benefits of continuing treatment with RBV. It is permissible to stop RBV but continue SOF/VEL in subjects that have pregnant female partners.
- Discontinuation of the study at the request of Gilead, regulatory agency or an IRB/IEC

3.8. Biomarker Testing

3.8.1. Biomarker Samples for Optional Future Research

PPD

PPD

3.8.2. Biomarker Samples for Optional Pharmacogenomic Research

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 200 chronic HCV Genotype 3 infected subjects will be randomized 1:1 into 2 treatment groups in this study. Patients will be stratified by treatment experience (treatment naïve versus treatment experienced).

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

4.2. Inclusion Criteria

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

1. Willing and able to provide written informed consent
2. Male or female age ≥ 18 years
3. Chronic HCV infection (≥ 6 months) as documented by prior medical history or liver biopsy
4. Genotype 3 HCV at Screening as determined by the central laboratory. Any non-definitive HCV genotype results will exclude the subject from participation.
5. HCV RNA $\geq 10^4$ IU/mL at Screening
6. Confirmation of cirrhosis by any of the following methods:
    a. Liver biopsy showing cirrhosis (eg., Metavir score=4 or Ishak score ≥ 5)
    b. Fibroscan results > 12.5 kPa
    c. Fibrotest result >0.75 AND an AST platelet ratio index (APRI) >2 during Screening
    d. Liver imaging within 6 months of Baseline/Day 1 to exclude hepatocellular carcinoma (HCC)
7. Subjects must have a determination of treatment experience (treatmenet naïve v. treatment experienced). Treatment naïve is defined as having never been exposed to an approved or experimental HCV-specific direct acting antiviral agents or prior treatment of HCV with interferon or ribavirin. All other patients will be considered treatment experienced.
8. If treatment experienced, the subject's medical records must include details of prior treatment regimen(s). Any prior use of SOF or other nucleotide analogue HCV NS5B inhibitors should be documented. Previous use of an NS5A inhibitor is not allowed.

9. A negative serum pregnancy test is required for female subjects (unless permanently sterile or greater than two years post-menopausal).

10. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5.

11. Lactating females must agree to discontinue nursing before the first dose of study drug is administered.

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

Subjects with **HIV coinfection** may be eligible, provided they satisfy these additional inclusion criteria:

13. Completed at least 3 months of any prior HIV ARV therapy and maintained HIV RNA <50 copies/mL (or <LLOQ if the local laboratory assay's LLOQ is 50≥ copies/mL) and CD4 T-cell count > 100 cells/mm^3 prior to Screening. Subjects with an isolated or unconfirmed HIV RNA >50 copies/mL (or >LLOQ if the local laboratory assay's LLOQ is 50≥ copies/mL) are not excluded

14. No history of HIV-associated opportunistic infections within 6 months of Screening. (see Appendix 6)

15. On a stable, protocol-approved, ARV regimen for ≥ 8 weeks prior to Screening and is expected to continue the current ARV regimen through the end of study. HIV ARV agents allowed in this study are the following and should be administered per the prescribing information in the package insert:

— cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil fumarate (Stribild)

OR

— emtricitabine/tenofovir disoproxil fumarate, emtricitabine/tenofovir alafenamide, or abacavir/lamivudine plus:

- ritonavir boosted atazanvir; or
- ritonavir boosted darunavir; or
- ritonavir boosted lopinavir; or
- raltegravir; or
- rilpivirine

OR

— cobicistat/elvitegravir/emtircitabine/tenofovir alafenamide (Genvoya®)

a) Single tablet regimens containing emtricitabine/tenofovir disoproxil fumarate (Truvada®) plus rilpivirine (Eviplera®) or emtricitabine/tenofovir alafenamide plus rilpivirine) respectively are permitted.

b) Alternative combinations of the above listed medications may be allowed after discussion and approval by the Gilead Medical Monitor. Subjects taking ARV regimens not on the above list are excluded from this study.

4.3. Exclusion Criteria

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

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

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

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

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

   d. Solid organ or bone marrow transplantation.

   e. Significant pulmonary disease, significant cardiac disease, or porphyria.

   f. Clinically significant hemoglobinopathy (e.g., sickle cell disease, thalassemia).

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

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

i. Active, serious infection (other than HIV or HCV) requiring parental antibiotics, antivirals or antifungals within 30 days prior to baseline.

2. Child-Pugh-Turcotte (CPT) Score >7 at Screening

3. Current, uncontrolled ascites, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, or other signs of decompensated cirrhosis

4. Screening ECG with clinically significant abnormalities

5. Subjects with the following laboratory parameters at screening:

- HIV-1 RNA >50 copies/mL
- CD4 T-cell count <100 cells/mm^3
- ALT > 10 × the upper limit of normal (ULN)
- AST > 10 × ULN
- Direct bilirubin > 1.5 × ULN
    - For subjects receiving ritonavir boosted atazanavir regimen, a direct bilirubin > 1.5 x ULN will be allowed if < 25% of the total bilirubin
- Platelets < 50,000/μL
- HbA1c > 8.5%
- Creatinine clearance (CLcr) < 60 mL /min as calculated by the Cockcroft-Gault equation {Cockcroft et al 1976}
- Hemoglobin < 10 g/dL
- Albumin < 3 g/dL
- INR > 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR
- HIV-2 positive test
- Presence of HBV surface antigen

6. Prior exposure to VEL or any HCV NS5A inhibitor.

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

8. Females who may wish to become pregnant and/or plan to undergo egg harvesting during the course of the study and up to 6 months of the last dose of study drug

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

10. Active infection with hepatitis B virus (HBV).

11. Infection with HIV 2

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

13. Use of any prohibited concomitant medications as described in Section 5.5

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

15. Known hypersensitivity to VEL, SOF (and metabolites), or RBV.

16. The presence of contraindications to RBV.

17. Participation in a clinical study with an investigational drug or biologic within 3 months prior to Baseline/Day 1.

18. Treatment for HCV infection with experimental or approved regimens within 3 months of Baseline/Day 1.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, and Study Drug Supply

An Interactive Web Response System (IWRS) will be employed to manage subject randomization, treatment assignment, and study drug re-supply. Randomization will be stratified by prior treatment experience. Treatment naïve is defined as having never been exposed to an approved or experimental HCV-specific direct acting antiviral agents or prior treatment of HCV with interferon or ribavirin. All other patients will be considered treatment experienced. If treatment experienced, the subject's medical records must include details of prior treatment regimen (See Section 6.2.1).

5.2. Description and Handling of SOF/VEL FDC

5.2.1. Formulation

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

5.2.2. Packaging and Labeling

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

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

5.2.3. Storage and Handling

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

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures

that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling SOF/VEL tablets.

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

5.3. Dosage and Administration of SOF/VEL FDC

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

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

5.4. Description and Handling of Ribavirin (RBV)

5.4.1. Formulation

RBV tablets, 200 mg, are blue, capsule-shaped, film-coated tablets debossed with "3RP" on one side and "200" on the other side. In addition to the active ingredient, RBV tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, FD&C blue #2.

The RBV tablets being supplied by Gilead Sciences are a US marketed formulation of RBV.

5.4.2. Packaging and Labeling

The RBV tablets are packaged in white, HDPE bottles. Each bottle contains 168 tablets and rayon coil packing material and is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

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

RBV tablets (200 mg) will be supplied by Gilead Sciences for all Group 2 subjects.

5.4.3. Storage and Handling

RBV tablets should be stored at 25 °C (77 °F); excursions are permitted between 15 and 30 °C (59 and 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 RBV.

5.4.4. Dosage and Administration

Subjects in Group 1 will take SOF/VEL once daily with or without food.

Subjects in Group 2 will take SOF/VEL once daily and RBV 1000–1200 mg taken in a divided daily dose (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg). Subjects who are to receive total daily doses of 1000 mg will take 3 × 200 mg tablets in the morning and 2 × 200 mg tablets in the evening (or 2 x 200 mg tablets in the morning and 3 x 200 mg tablets in the evening). For those who are to receive 1200 mg of RBV, subjects should take 3 × 200 mg tablets twice daily. RBV should be taken with food.

Body Weight kg (lbs.)	RBV Daily Dose	RBV Number of tablets
< 75 kg	1000mg	3 X 200mg tablets A.M. 2 X 200mg tablets P.M.
≥ 75 kg	1200mg	3 X 200mg tablets A.M. 3 X 200mg tablets P.M

All subjects should be instructed to maintain approximately the same daily dosing interval between study drug doses. To aid compliance, it is suggested that SOF/VEL is administered with either the morning or evening dose of RBV with food.

For missed dose(s) of SOF/VEL, 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 of SOF/VEL with a missed dose under any circumstances.

For missed dose(s) of RBV, subjects should be instructed to take the missed dose(s) of study drug as soon as possible, unless more than 6 hours has elapsed since the scheduled time of the missed dose. In this case, the subject should be instructed to wait and take the next dose at the regularly scheduled time. No more than the daily dose of RBV (1000 mg or 1200 mg) should be taken on any calendar day. Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

No food restrictions apply to SOF/VEL. However as RBV must be taken with food hence it is suggested that when SOF/VEL is taken with RBV, both drugs should be taken together and with food for optimal adherence.

Dose modifications due to anemia or other reasons, may be made at the discretion of the Investigator.

5.5. Prior and Concomitant Medications

Concomitant medications taken within 30 days of Screening, up to and including the date of the visit four weeks after discontinuation of study drug, need to be recorded in the source documents and eCRFs. All concomitant medications should be recorded in the source documents (including all blood products).

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

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

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

- Investigational agents or devices for any indication

Concomitant use of certain medications or herbal/natural supplements (inducers of drug transporters i.e. P-gp) with study drug may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug or these medication. The use of such agents is prohibited from 21 days prior to Baseline/Day 1 through the end of study drug dosing. The use of amiodarone is prohibited from 60 days prior to Baseline/Day 1 through the end of study drug dosing.

Examples of representative medications which are prohibited or are to be used with caution are listed below:

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[f]	Diltiazem, Verapamil, Dronedarone, Quinidine, Ranolazine, Bosentan, Olmesartan, Valsartan, Digoxin[d]
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[e]		Rosuvastatin (≤10 mg/day),
Other	Modafinil [b], Sulfasalazine[c], Methotrexate[c]	

a Proton pump inhibitor (PPI dose comparable with omeprazole (20 mg) can be administered with SOF/VEL when SOF/VEL is administered with food. H2-receptor anagonist 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 (i.e. Tums, Maalox) may not be taken within 4 hours (before or after) SOF/GS-5816 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 Monitor for signs and sympotoms of digoxin toxicity.
e Use with SOF/VEL may result in an increase in the concentration of HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis
f 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.

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

Subjects may not take any approved HCV medications during their participation in the study period.

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.

5.6. Acceptable HIV Antiretroviral Regimens

Acceptable HIV antiretroviral medications allowed in this study include the following and should be administered per the prescribing information in the package insert:

- cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil fumarate (Stribild)

  OR

- emtricitabine/tenofovir disoproxil fumarate, emtricitabine/tenofovir alafenamide, or abacavir/lamivudine plus:

  — ritonavir boosted atazanvir; or

  — ritonavir boosted darunavir; or

  — ritonavir boosted lopinavir; or

  — raltegravir; or

  — rilpivirine

  OR

  — cobicistat/elvitegravir/emtircitabine/tenofovir alafenamide (Genvoya®)

Single tablet regimens containing emtricitabine/tenofovir disoproxil fumarate (Truvada®) plus rilpivirine (Eviplera®) or emtricitabine/tenofovir alafenamide plus rilpivirine) respectively are permitted.

Alternative combinations of the above listed medications may be allowed on a case by case basis with approval from the Gilead Medical Monitor. ARV regimens not on the above list are excluded from this study at enrollment. ARVs not on the approved list may be allowed in the cases of HIV virologic breakthrough during the study period if approved by the Medical Monitor. HIV medications will not be supplied by Gilead.

5.7. Study Drug Adherence and Drug Accountability

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

SOF/VEL FDC ± RBV accountability records will be provided to each study site:

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

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

- Subjects will be dispensed bottles of RBV based on their weight-based dose of RBV at the Baseline/Day 1 visit, as applicable. Subjects should bring back the study drug in the original container at every post Day 1 study visit through the end of study treatment. Any extra bottles dispensed should be brought back to each on-treatment visit for accountability purposes and will be re-dispensed to the subject except at Week 12 or EOT visit.

5.8. Study Drug Return or Disposal

Refer to Section 10.1.7 for information on return and disposal of study drugs.

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. All eligible subjects will complete Screening, Baseline/Day 1, On-Treatment visits at the end of Weeks 2, 4, 8 and 12 and post-treatment Visits at Weeks 4 and 12, as appropriate. Subjects with HCV RNA ≥LLOQ at post-treatment Week 4 visit will complete a confirmatory visit within 2 weeks of the Week 4 post-treatment visit. Subjects with HCV RNA ≥LLOQ at post-treatment week 12 visit will be asked to return for confirmatory visit within 2 weeks of the Week 12 post-treatment visit. Viral breakthrough or relapse must be confirmed.

Information on the specific laboratory parameters to be measured and clinical assessment to be performed are provided in Section 6.5.

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

This is an open-label study. An Interactive Web Response System (IWRS) will be employed to manage subject enrollment, treatment assignment (Group 1 or Group 2), and study drug dispensing and re-supply. Randomization will be stratified by prior treatment experience (treatment naïve/treatment-experienced).

6.2. Screening Assessments

6.2.1. Screening Visit (Day 28 to Day 0)

Subjects will be screened within 28 days of the Baseline/Day 1 visit. The screening window can be extended to 42 days for subjects requiring liver biopsy, additional HCV genotype testing or for extenuating circumstances.

The following will be performed and documented at screening:

- Obtain written informed consent
  - PPD
- Determine inclusion and exclusion eligibility
- Appropriate diagnostic imaging (CT or Ultrasound) must be performed within 6 months of Baseline/Day 1 to exclude the presence of hepatocellular carcinoma

- Obtain medical history, including
  - Hepatitis C history
  - Liver biopsy results (if applicable)
  - Determine cirrhosis status as defined in Section 2
  - Exclusion of hepatocellular carcinoma (HCC). Appropriate diagnostic imaging (CT or Ultrasound) should be performed or confirmed to have been performed within 6 months of Screening to exclude the presence HCC.
  - Determine treatment experience status as defined in Section 4.2
    - If treatment experience, record the duration(s) and type(s) of the prior treatment administered.
    - If treatment experienced, record whether or not any past treatment regimens contained SOF or other nucleotide analogue HCV NS5B inhibitors
- Complete physical examination including, vital signs (resting blood pressure, pulse, respiratory rate and temperature), body weight, and height
- Obtain details of concomitant medications
- Perform 12-lead ECG
- Calculate CPT score
- Obtain blood samples for tests as listed in Section 6.7.1:
  - Hematology
  - Chemistry
  - Coagulation tests
  - HCV RNA
  - Determination of HCV viral genotype and subtype
  - HCV antibody, HIV, and HBV antibody
  - HbA_{1c}
  - IL28B

  - — Serum β-hCG pregnancy test for females of childbearing potential only
  - — HIV-1 RNA will only be collected and analyzed for co-infected subjects
- Obtain urine sample for:
  - — Urinalysis
  - — Urine drug screen
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.
- Retests of Screening labs are permitted only if there is reason to believe the retest value will be within accepted parameters, for example, if the initial exclusionary value was either due to a sample processing error or due to an extenuating circumstance such as intercurrent illness.
- Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the Baseline/Day 1 Visit assessments and enrollment into the study

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

6.3. Treatment Assessments

6.3.1. Baseline/Day 1 Visit

The following baseline tests and procedures must be completed prior to enrollment and dosing/dispensation of study drug:

- Confirm eligibility (Reference Sections 4.2 & 4.3)
- Perform complete physical examination, including body weight
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Obtain blood samples for:
  - — Hematology
  - — Chemistry

  - Coagulation tests
  - HCV RNA
  - Viral sequencing
  - HIV-1 RNA will only be collected and analyzed for co-infected subjects
- Obtain blood sample for Pharmacogenomics testing (for subjects who have consented)
- PPD
- Obtain urine samples for the following procedures:
  - Urinalysis
  - Pregnancy test for females of child bearing potential only
- Study Drug Administration
  - Dispense study drug as directed by the IWRS
  - Instruct the subject on the packaging, storage and administration of the study drugs
  - Observe the subject taking the first dose of study drug and record the time of first dose and whether it was taken with or without food.

6.3.2. Week 2 (±3 days)

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

- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing
  - PK sample
  - HIV-1 RNA will only be collected and analyzed for co-infected subjects
- Assess adherence with study drug dosing regimen including pill count

6.3.3. Weeks 4 and 8 (± 3 days)

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

- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications
- Conduct pregnancy prevention counseling
- Obtain blood samples for:
  - — Hematology
  - — Chemistry
  - — HCV RNA
  - — Viral sequencing
  - — PK sample
  - — HIV-1 RNA will only be collected and analyzed for co-infected subjects
- Obtain urine sample for pregnancy test (for females of child bearing potential only)
- Assess adherence with study drug dosing regimen including pill count
- Dispense study drugs as directed by the IWRS

6.3.4. Week 12 or Early Termination (± 3 days)

The following procedures/assessments are to be completed at the end of Week 12 or ET:

- Perform complete physical examination, including weight
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Calculate CPT score
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Obtain blood samples for:
  - — Hematology
  - — Chemistry

  - Coagulation tests
  - HCV RNA
  - Viral sequencing
  - PK sample
  - HIV-1 RNA will only be collected and analyzed for co-infected subjects
- PPD
- Obtain urine samples for
  - Urinalysis
  - Pregnancy test for females of child bearing potential only
- Assess adherence with study drug dosing regimen including pill count. Study drug should be returned at this visit

6.3.5. Unscheduled Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments are at the investigator's discretion. At all unscheduled visits initiated for the purpose of confirming HCV or HIV virologic failure, a sample for HCV RNA Sequencing / Phenotyping, or a sample for HIV RNA Genotyping/Phenotyping, respectively, must be collected.

The Sponsor (e.g. Medical Monitor and Clinical Trial Manager) and CRO must be informed, as soon as possible, when a subject comes off treatment due to an AE.

6.4. Posttreatment Assessments

The post-treatment Week 4 and 12 visits should be timed from the date of last administration of study drug. All subjects must complete the post-treatment Week 4 visit. All subjects who achieve SVR4 will attend the Week 12 visit. The end of study will occur at the post-treatment Week 4 visit in the case of subjects who do not achieve SVR4, and the post-treatment Week 12 visit in the case of patients who do achieve SVR4.

6.4.1. Post-treatment Week 4 (±5 days)

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

- Perform complete physical examination
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)

- Assessment of AEs and concomitant medications
- Pregnancy Prevention Counseling
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing
  - HIV-1 RNA will only be collected and analyzed for co-infected subjects
- Obtain urine sample for pregnancy test (for females of child bearing potential only)

6.4.2. Post-treatment Week 12 (± 5 days)

The following procedures/assessments are to be completed for all subjects who achieve SVR4, 12 weeks after taking the last dose of study drug:

- Perform complete physical examination
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - Viral sequencing
  - HIV-1 RNA will only be collected and analyzed for co-infected subjects
- Obtain urine sample for pregnancy test (for females of child bearing potential only)

6.5. Confirmatory Visit

Subjects with HCV RNA ≥LLOQ at either post-treatment Week 4 or 12 visits will be asked to return for confirmatory visit within 2 weeks. A sample for viral HCV RNA sequencing/phenotyping will be collected.

6.6. End of Study

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

The end of study will occur at the post-treatment Week 4 visit in the case of subjects who do not achieve SVR4, and the post-treatment Week 12 visit in the case of patients who do achieve SVR4.

6.7. Procedures and Specifications

6.7.1. Clinical Laboratory Analytes

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

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

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

Virological Tests: Serologies for HCV and HBV, Serology and/or antigen testing for HIV, including reflex testing, as necessary. HCV RNA will be measured using the COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV genotype INNO-LiPA 2.0 Assay. HIV RNA will be measured using the AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0. If HIV-1 virologic rebound is confirmed, HIV-1 genotype/phenotype will be determined using the PhenoSense™ Integrase HIV, GeneSeq™ Integrase HIV, PhenoSense™ HIV, GenoSure MG, GeneSeq™ HIV, and PhenoSense GT™. Gilead reserves the right to use alternate assays for HCV RNA, HIV RNA, HCV genotype, and HIV-1 genotype/phenotype should the above assays become unavailable or the results are indefinitive.

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

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

Additional Tests: Urine Drug screen (for Amphetamines, Cocaine, Methadone, Opiates) and Hemoglobin A1c (HbA1c), CD4 T-lymphocyte Absolute Count and %

Urinalysis: Appearance, Blood, Color, Glucose, Leukocyte esterase, pH, Protein, Urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal. At each visit this is tested, it will be recorded whether female subjects of childbearing potential are currently menstruating.

6.7.2. Medical History

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

6.7.3. Complete Physical Examination

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

6.7.4. Vital Signs

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

Blood pressure will be measured using the following standardized process:

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

6.7.5. Creatinine Clearance

Creatinine clearance will be calculated at all visits where blood is drawn. Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft et al 1976} using actual body weight (BW).

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

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

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

6.7.6. 12-Lead ECGs

Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording.

The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities. On treatment ECGs should be compared to the subject's baseline as part of routine safety monitoring.

6.7.7. HCV Viral RNA Sequencing / Phenotyping Sample (Archive)

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

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

6.7.8. HIV Viral RNA Genotyping/Phenotyping Sample (Archive)

Plasma samples will be collected at Baseline/Day 1 and each subsequent visit for HIV viral sequence analysis. At any unscheduled visit initiated for the purpose of confirming HIV virologic failure, an HIV genotype/phenotype plasma sample must also be collected. Unused samples may be archived.

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

6.7.9. Single Pharmacokinetic (PK) Sample

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

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

6.7.10. Pharmacogenomics Testing

An additional and distinct informed consent document will be provided to allow the Sponsor to obtain and test a subject's blood sample taken on Baseline/Day 1 for pharmacogenomics discovery research. If not obtained at Baseline/Day 1, the sample may be drawn at any time during the study. PPD

6.7.11. Sample Storage

PPD

[redacted]

6.7.12. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period and 30 days after last dose of SOF/VEL, 6 months after the last dose of RBV, or last visit of the study, whichever comes last.

If a positive urine pregnancy test is reported, an immediate confirmation with Serum β-hCG is required.

7. TOXICITY MANAGEMENT

7.1. Dose Modification Due to Toxicity

7.2. Group 1: Subjects administered SOF/VEL

There is no option for dose reduction or modification of SOF/VEL

7.3. Group 2: Subjects administered SOF/VEL+ RBV

Dose modification for subjects administered SOF/VEL+RBV should be performed according to the prescribing information.

Dose reduction of SOF/VEL is not permitted.

Table 7-1. Ribavirin Dose Modification Guideline for Coadministration with SOVALDI

Laboratory Values	Reduce Ribavirin Dose to 600 mg/day[a] If:	Discontinue Ribavirin If:[b]
Hemoglobin in patients with no cardiac disease	<10 g/dL	<8.5 g/dL
Hemoglobin in patients with history of stable cardiac disease	≥2 g/dL decrease in hemoglobin during any 4 week treatment period	<12 g/dL despite 4 weeks at reduced dose

a The daily dose of ribavirin is administered orally in two divided doses with food.
b Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the original assigned dose (1000 mg to 1200 mg daily).

If RBV is permanently discontinued, SOF should also be discontinued.

7.3.1. Subject Stopping Rules

See Section 3.4 for individual subject stopping rules..

7.4. Subject Stopping Rules

See Section 3.4 for individual subject stopping rules.

7.5. Special Situations Reports

7.5.1. Definitions of Special Situations

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

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

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

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

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

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

8. ADVERSE EVENTS MANAGEMENT

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

8.1.1. Adverse Events

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

An AE does not include the following:

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

8.1.2. Serious Adverse Events

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

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

- A congenital anomaly/birth defect

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

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

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to SOF/VEL interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 8.1.1 and 8.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 3.4.

8.2. Assessment of Adverse Events and Serious Adverse Events

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

8.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

- **Yes**: There is reasonable possibility that the event may have been caused by the study drug.

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

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

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

8.2.2. Assessment of Severity

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

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

Requirements for collection prior to study drug initiation:

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

Adverse Events

- Following initiation of study medication, all AEs, regardless of cause or relationship, pregnancy and other special situation reports, until 30 days after last administration of study drug must be collected/ reported to the eCRF database as instructed.
- All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

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

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

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

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

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

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

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

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

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

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

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

8.4. Gilead Reporting Requirements

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

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

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

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

8.5. Toxicity Management

8.5.1. Instructions for Reporting Special Situations

8.5.1.1. Instructions for Reporting Pregnancies

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

Refer to Section 8.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 8.1.1 and 8.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows:

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

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.

Clinical staff should also report any pregnancies to the Ribavirin Pregnancy Registry at 1-800-593-2214 (see also https://www.ribairinpregnancyregistry.com) Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

8.5.1.2. Reporting Other Special Situations

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

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

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

Refer to Section 8.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

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

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Objectives and Endpoints

9.1.1. Analysis Objectives

The primary objectives of this study are as follows:

- To evaluate the efficacy of study treatment with SOF/VEL FDC and SOF/VEL FDC and Ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained viralogic response 12 weeks after cessation of treatment regimen (SVR12)
- To evaluate the safety and tolerability of each treatment regimen

The secondary objectives of this study are:

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

The exploratory objective of this study is:

- PPD [redacted]

9.1.2. Primary Endpoints

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

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

9.1.3. Secondary Endpoints

The secondary efficacy endpoints include the proportion of subjects who attain sustained virologic response at 4 weeks after cessation of the study treatment regimen (SVR4); the proportion of subjects who have HCV RNA < LLOQ by visit while on study treatment; absolute and change from baseline/Day 1 in HCV RNA through Week 12; and the proportion of subjects with virologic failure.

9.1.4. Other Endpoints of Interest

Additional efficacy evaluations may include ALT normalization.

9.2. Analysis Conventions

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

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

9.2.1. Analysis Sets

9.2.1.1. All Randomized

All Randomized Analysis Set includes all subjects who were randomized in the study.

9.2.1.2. Efficacy

The primary analysis set for efficacy analysis will be the FAS which include all randomized subjects who received at least 1 dose of study drug.

9.2.1.3. Safety

The primary analysis set for safety analyses will be the Safety Analysis Set which includes all subjects who took at least 1 dose of study drug.

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

9.2.1.4. Pharmacokinetics

The Pharmacokinetic (PK) Analysis Set includes all subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value for the corresponding analyte in plasma. The analytes of interest may include SOF (and its metabolites GS-566500 and GS-331007), VEL, and RBV if applicable. The PK analysis set will be used for analyses of general PK.

9.3. Data Handling Conventions

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

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

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

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

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

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

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

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

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

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

HIV RNA in this study will be measured using the AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0. The LLOQ of the assay is 20 cp/mL.

When the calculated HIV RNA value is within the linear range of the assay, then the result will be report as the "<< numeric value>> cp/mL". When HIV RNA is not detected, the result is

reported as "No HIV-1 RNA detected". When the calculated HIV RNA cp/mL is less than LLOQ of the assay, the result is reported as "<20 cp/mL HIV-1 RNA Detected".

For numerical HIV RNA data analysis, values returned as "<20 cp/mL HIV-1 RNA Detected" or "No HIV-1 RNA detected" will be set to the LLOQ minus 1 (ie, 19 HIV RNA cp/mL). If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (eg, log10 scale) or nonparametric analysis methods may be used, as appropriate.

9.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods

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

Baseline characteristic data will include body mass index, absence or presence of cirrhosis, baseline HCV RNA level (log_{10} IU/mL), HCV genotype, IL28B genotype, HIV co-infection and additional endpoints as necessary.

9.5. Efficacy Analysis

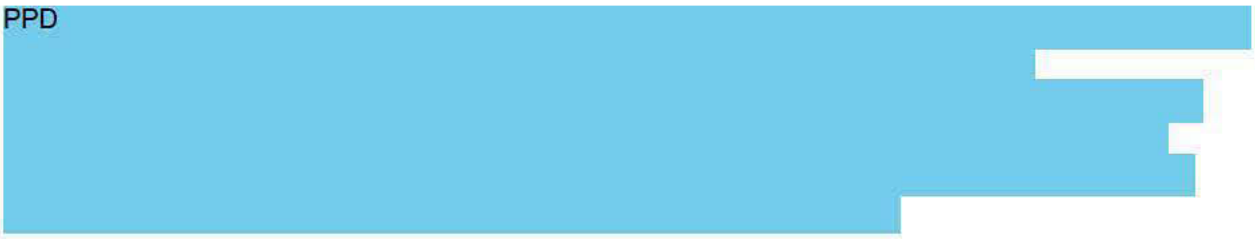
9.5.1. Primary Analysis

The primary efficacy endpoint for this study will be the proportion of subjects with SVR12 as defined as HCV RNA < LLOQ 12 weeks after cessation of study treatment regimen in the FAS population. Point estimate and 95% confidence interval (using the Clopper-Pearson method) of SVR12 will be computed for each treatment group.

9.5.2. Secondary Analyses

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

Descriptive summaries and listings will be provided for additional efficacy evaluations including serum HCV RNA actual values and change from baseline through Week 12, the proportion of subjects who experience virologic failure and ALT normalization.



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

9.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests (including HIV-1 RNA and CD4 T-cell count for HCV/HIV co-infection subjects), physical examinations, vital signs measurements and AEs will be documented at various time points during the study.

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

9.6.1. Extent of Exposure

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

9.6.2. Adverse Events

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

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

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

- All AEs
- AEs of Grade 3 or above
- AEs of Grade 2 or above
- All treatment-related AEs
- Treatment-related AEs of Grade 3 or above
- Treatment-related AEs of Grade 2 or above
- All SAEs
- All treatment-related SAEs
- All AEs leading to premature discontinuation of any study drug
- All AEs leading to premature discontinuation from SOF/VEL

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

9.6.3. Laboratory Evaluations

Selected laboratory data (including HIV RNA and CD4 T-cell count for HCV/HIV co-infection subjects) will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group and by study visit along with corresponding change from Baseline/Day 1.

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

Values for missing safety laboratory data will not be imputed; however, a missing Day 1 result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the Baseline/Day 1 value will be assumed to be normal (i.e., no grade [Grade 0]) for the summary of graded laboratory abnormalities. If Baseline/Day 1 data are missing, then any post-baseline graded abnormality (ie, at least Grade 1) will be considered treatment emergent.

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

9.6.4. Other Safety Evaluations

Individual data and change from baseline for vital signs measurements will be listed by subject and summarized by treatment group and overall by descriptive statistical summaries (n, mean, SD, median, Q1, Q3, minimum, and maximum).

9.6.5. HIV RNA Analysis

Subjects with HCV/HIV co-infection RNA < 50 copies/mL at Baseline/Day 1 will be summarized by visit to assess the proportion of subjects that maintain HIV-1 RNA < 50 copies/mL while on HCV treatment.

Details on HIV-1 RNA related safety analyses will be described in the statistical analysis plan.

9.7. Pharmacokinetic Analysis

Concentrations of SOF (and its metabolites GS-566500 and GS-331007) and VEL (GS-5816) in plasma may be determined using validated bioanalytical assays and listed.

9.8. Sample Size

Approximately 200 cirrhotic subjects with chronic genotype 3 HCV infection will be enrolled in this study. This sample size is based on the number of subjects who meet the eligibility criteria who could practically be enrolled. With a sample size of 100 for each treatment, a two-sided 95% exact confidence interval will extend at most 21% in length for each treatment.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, South Africa, Washington DC, Seoul and Brazil), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

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

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

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IEC. The investigator will not begin any study subject activities until approval from the 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 IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

10.1.3. Informed Consent

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

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

10.1.4. Confidentiality

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

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

10.1.5. Study Files and Retention of Records

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

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

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

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

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

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

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

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

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period of up to 15 years for purposes of this study

10.1.6. Case Report Forms

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

data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 10.1.5.

10.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused study drugs 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 study drug disposal procedures and provide appropriate instruction for destruction of unused study drugs. 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 study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

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

10.1.8. Inspections

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

10.1.9. Protocol Compliance

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

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

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

10.2.2. Study Report and Publications

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

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

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

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

No such communication, presentation, or publication will include Gilead's confidential information (see Section 10.1.4).

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

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Payment Reporting

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

10.3.2. Access to Information for Monitoring

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

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

10.3.3. Access to Information for Auditing or Inspections

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

10.3.4. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, both the sponsor and the investigator 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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12. APPENDICES

Appendix 1. Investigator Signature Page
Appendix 2. Study Procedures Table
Appendix 3. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities
Appendix 4. Child-Pugh-Turcotte Classification of the severity of cirrhosis
Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements
Appendix 6. Opportunistic Infections

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404, USA

STUDY ACKNOWLEDGEMENT

A Phase 2, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination (FDC) and Sofosbuvir/Velpatasvir FDC and Ribavirin in Subjects with Chronic Genotype 3 HCV Infection and Cirrhosis

GS-US-342-2097, Amendment 1, 04 April 2016

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

Brian McNabb

Brian McNabb, MD

PPD

Signature

04- April - 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

	Screen	Baseline/Day 1[b]	On-treatment Week				Post-treatment Week	
			2	4	8	12/ET	4	12
Clinical Assessments								
Informed Consent	X							
Determine Eligibility	X	X						
Medical History	X							
Physical Examination	X	X				X	X	X
Height	X							
Weight	X	X				X		
Vital Signs	X	X	X	X	X	X	X	X
12-Lead ECG	X							
CPT score	X					X		
Adverse Events and Concomitant Medications	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X		X	X	X	X	X
Review of Study Medication Compliance			X	X	X	X		
Study Drug Dispensing[a]		X		X	X			
Laboratory Assessments								
Hematology, Chemistry[g]	X	X	X	X	X	X	X	X
Coagulation Tests	X	X				X		
Urinalysis	X	X				X		
HCV RNA[c]	X	X	X	X	X	X	X	X[f]

			On-treatment Week				Post-treatment Week	
	Screen	**Baseline/Day 1[b]**	**2**	**4**	**8**	**12/ET**	**4**	**12**
HIV-1 RNA[h]	X	X	X	X	X	X	X	X
Viral Sequencing[c]		X	X	X	X	X	X	X[f]
Single PK			X	X	X	X		
Serum β-hCG or Urine Pregnancy Test[d]	X	X		X	X	X	X	X
Urine Drug Screen	X							
HCV Genotyping, IL28B	X							
HCV, HIV, HBV Serology	X							
HbA1c, Fibrotest®	X							
Archive Sample[e]		X				X		
Pharmacogenomic Sample[e]		X						

a The IWRS will provide direction on the specifics of each subject's study drug dispensing
b Baseline/Day 1 assessments must be performed prior to dosing
c Viral sequencing samples for virologic sequencing required at baseline and after any visit where a previously undetectable HCV RNA becomes detectable
d Serum β-hCG pregnancy test performed at screening and for confirmation of positive urine pregnancy test.
e Only for subjects who have provided consent for this sample and testing. The Week 12 / Early Termination visit will be the last opportunity for this to be collected.
f Only for subjects with HCV RNA ≥LLOQ at post-treatment week 12 visit will be asked to return after for a confirmatory visit where additional samples are collected.
g CrCl will be calculated at all visits where a blood sample is drawn
h HIV-1 RNA will only be collected and analyzed for co-infected subjects

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
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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	> 6.0 to 6.5 mg/dL	> 6.5 to 7.0 mg/dL	> 7.0 mg/dL
	> ULN to 1.50 mmol/L	> 1.50 to 1.63 mmol/L	> 1.63 to 1.75 mmol/L	> 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L	< 0.67 mg/dL < 0.6 mEq/L
	0.58 to <LLN mmol/L	0.43 to < 0.58 mmol/L	0.28 to < 0.43 mmol/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
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	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)
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. Child-Pugh-Turcotte Classification of the severity of cirrhosis

	POINTS*		
	1	**2**	**3**
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade3-4 (or chronic)
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
PT (sec prolonged) or INR	< 4 < 1.7	4-6 1.7-2.3	> 6 > 2.3

* CPT score is obtained by adding the score for each parameter
CPT class: A = 5-6 points
B = 7-9 points
C = 10-15 points

a U.S. Department of Veterans Affairs. Child -Pugh-Turcotte Classification of the severity of cirrhosis. Available at http://www hepatitis.va.gov/provider/tools/child-pugh-calculator.asp, Accessed May 29, 2012.

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Background

Ribavirin is contraindicated in pregnancy as significant teratogenic and embryocidal effects have been demonstrated in all animal species tested. Pregnancy must be excluded before the start of treatment with study drugs and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed regularly throughout this study. Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment (7 months for males). Please refer to the latest version of the product insert for additional information.

2) 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 $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause.

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

b. Definition of Male Fertility

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

3) Study Drug Effect 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.

4) 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 first dose of study drug. Pregnancy testing will occur at regular intervals throughout the duration of the trial. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from Screening until 30 days after the last dose of SOF/VEL or 6 months after the last dose of RBV, whichever occurs last.

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly used a condom from the date of Screening until 30 days after the last dose of SOF/VEL or 6 months after the last dose of RBV, whichever occurs last.
  - — Intrauterine device (IUD)
  - — Intrauterine hormone-releasing system (IUS)
  - — Tubal sterilization
  - — Essure micro-insert system
  - — Vasectomy in the male partner
  - — Barrier methods
    - ■ Female barriers: Diaphragm with spermicide or Cervical cap with 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 study treatment and until at least 30 days after the last dose of SOF/VEL or 6 months after the last dose of RBV, whichever occurs last.

5) 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 or 7 months after the last dose or RBV, whichever comes last, 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 or 7 months after last dose of RBV, whichever comes last.

Male subjects must also refrain from sperm donation during treatment and until at least 30 days after the last dose of SOF/VEL or 7 months after the last dose of RBV, whichever comes last.

6) Unacceptable Birth Control Methods

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

7) 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, if they become pregnant within 30 days of last dose of SOF/VEL , or if they become pregnant within 6 months of the last dose of RBV. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant within 30 days of the last dose of SOF/VEL or 7 months after the last dose of RBV, whichever occurs last, must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 8.5.1.1

Appendix 6. Opportunistic Infections

Non-inclusive list of opportunistic infections base on AIDS-Indicator Conditions from CDC Classification System for HIV Infection Clinical Category C:

1. Bacterial pneumonia, recurrent (two or more episodes in 12 months)

2. Candidiasis of the bronchi, trachea, or lungs

3. Candidiasis, esophageal

4. Cervical carcinoma, invasive, confirmed by biopsy

5. Coccidioidomycosis, disseminated or extrapulmonary

6. Cryptococcosis, extrapulmonary

7. Cryptosporidiosis, chronic intestinal (>1 month in duration)

8. Cytomegalovirus disease (other than liver, spleen, or nodes)

9. Encephalopathy, HIV-related

10. Herpes simplex: chronic ulcers (>1 month in duration), or bronchitis, pneumonitis, or esophagitis

11. Histoplasmosis, disseminated or extrapulmonary

12. Isosporiasis, chronic intestinal (>1-month in duration)

13. Kaposi sarcoma

14. Lymphoma, Burkitt, immunoblastic, or primary central nervous system

15. *Mycobacterium avium* complex (MAC) or *Mycobacterium kansasii*, disseminated or extrapulmonary

16. *Mycobacterium tuberculosis*, pulmonary or extrapulmonary

17. *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary

18. *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)

19. Progressive multifocal leukoencephalopathy (PML)

20. *Salmonella* septicemia, recurrent (nontyphoid)

21. Toxoplasmosis of brain

22. Wasting syndrome caused by HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (two or more loose stools per day for ≥1 month) or chronic weakness and documented fever for ≥1 month