GILEAD

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks in Subjects with Chronic HCV	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	
ClinicalTrials.gov Identifier:	Not Available	
Indication:	Hepatitis C Virus Infection	
Protocol ID:	GS-US-342-1518	
Gilead Sciences Study Director	Name: Telephone: Fax: Email:	PPD PPD PPD PPD
Protocol Version/Date:	Original:	16 January 2015

CONFIDENTIALITY STATEMENT

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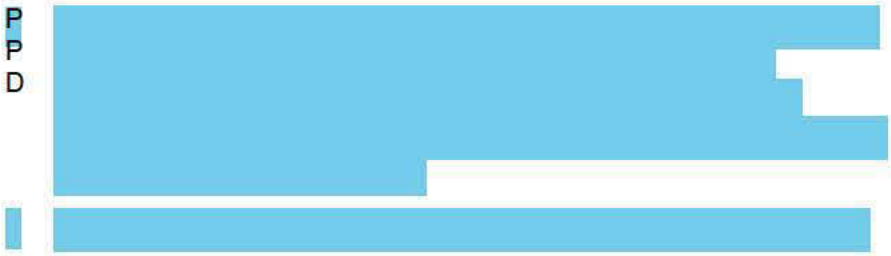
PROTOCOL SYNOPSIS

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

Study Title:	A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks in Subjects with Chronic HCV
ClinicalTrials.gov Identifier:	Not Available
Study Centers:	Approximately 32 sites in China, Malaysia, Singapore, Thailand, and Vietnam
Number of Subjects:	Approximately 360 subjects
Target Population:	Adults with chronic hepatitis C virus (HCV) infection
Treatment Duration:	Subjects will be treated for 12 weeks
Objectives:	The primary objectives of this study are: • To evaluate the efficacy of treatment with sofosbuvir (SOF)/GS-5816 fixed dose combination (FDC) for 12 weeks in subjects with chronic HCV infection as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR12) • To evaluate the safety and tolerability of treatment with SOF/GS-5816 for 12 weeks The secondary objectives of this study are: • To determine the proportion of subjects with SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24) • To evaluate the proportion of subjects with virologic failure • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment • To evaluate the emergence of viral resistance to SOF and GS-5816 during treatment and after cessation of treatment

The exploratory objectives of this study are:

PPD



Study Design:

International, multicenter, open-label study in treatment-naïve and treatment-experienced adults with chronic HCV infection. Subjects with or without cirrhosis will be enrolled.

Approximately 20% of subjects may be treatment experienced and approximately 20% of subjects may have compensated cirrhosis at screening.

Subjects with chronic HCV infection will be enrolled to receive SOF/GS-5816 once daily for 12 weeks.

This multi-regional clinical trial (MRCT) is planned to be conducted in China, Malaysia, Singapore, Thailand, and Vietnam. China will be considered Region 1. Malaysia, Singapore, Thailand, and Vietnam, which are all located in Southeast Asia, will be considered Region 2.

Approximately 360 subjects will be enrolled in the study in total. The approximate number of subjects to be enrolled in each region according to HCV genotype is represented in the table below:

HCV GT (Previous Rx History)	GT-1 (TN, TE)	GT-2 (TN, TE)	GT-3 (TN, TE)	GT-4,5,6 (TN, TE)	Total
Region 1 (China)	80	60	60	60	260
Region 2 (Malaysia, Singapore, Thailand, Vietnam)	100				100

GT = Genotype
Rx = Treatment
TN = Treatment Naïve, TE = Treatment Experienced

It is expected that a small number of subjects whose HCV genotype cannot be determined by the central laboratory (HCV genotype indeterminate) may also be enrolled.

Sub-Study:	PPD 
Diagnosis and Main Eligibility Criteria:	Chronic HCV-infected, male and non-pregnant/non-lactating female subjects, ages 18 years or older. Refer to Sections 4.2 and 4.3 for detailed Inclusion and Exclusion Criteria.
Study Procedures/ Frequency:	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 or additional HCV genotyping. All subjects will complete the following study visits: Screening, Day 1, on-treatment visits at the end of Weeks 1, 2, 4, 6, 8, 10, and 12. Following the last dose of study drug, all subjects will complete post treatment Week 4, including those subjects who terminate study drug treatment early. Subjects who achieve SVR4 (HCV RNA < LLOQ at the post treatment Week 4 visit) will attend the post treatment Week 12 visit and those who achieve SVR12 (HCV RNA < LLOQ) will complete the post treatment Week 24 visit. Viral breakthrough or relapse must be confirmed. Screening assessments will include physical examination, medical history, height, weight, vital signs, 12-lead ECG, adverse events related to screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry and coagulation), HCV RNA, serology (HIV, HCV, HBV), hemoglobin A1c (HbA1c), assessment of the presence or absence of cirrhosis, screening for hepatocellular carcinoma (HCC) for subjects with cirrhosis, serum β-hCG (females of child bearing potential only), IL28B and HCV genotyping, urinalysis and urine drug screen.

Based on the study visit, on-treatment assessments include physical examination, adverse events (AEs), concomitant medications, weight, vital signs, safety laboratory tests, HCV RNA, viral sequencing samples, 12-lead ECG, Health Related Quality of Life (HRQoL) Survey SF-36, study medication dispensing and pill count, and urine pregnancy tests and pregnancy prevention counseling (females of child bearing potential only) as applicable.

At the time of ECG collection, Day 1 (prior to study drug administration) and at Week 1 and Week 12 or Early Termination, printed copies (paper) will be reviewed by qualified study staff (as determined by the Investigator) and compared to the subject's Day 1 ECG as part of routine safety monitoring.

Post treatment assessments include weight, vital signs, AEs, concomitant medications, HRQoL SF-36, safety laboratory tests, HCV RNA, viral sequencing samples, and urine pregnancy tests (females of child bearing potential only).

PPD

PPD

Test Product, Dose, and Mode of Administration:

SOF/GS-5816 fixed dose combination (FDC) is manufactured as a 400 mg/100 mg FDC tablet for oral administration. Subjects will take 1 tablet daily with or without food.

Evaluation Criteria:

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® TaqMan® HCV Test, v2.0 for use with Ampliprep.

Statistical Methods:

The primary efficacy endpoint for the study is SVR12 in all enrolled and treated subjects.

The hypothesis to be tested will be that the SVR12 rate in Region 1 is superior to the pre-specified performance goal of 85%. A confidence interval approach will be used to estimate the SVR12 rates for Region 2 and for the overall population (ie, combined Region 1 and Region 2).

In the primary efficacy analysis, the SVR12 rate I Region 1 will be compared to 85% by using a two-sided exact one-sample binomial test at the 0.05 significance level. In addition, the point-estimate with the 2-sided 95% exact confidence interval (CI) using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rates by region and the overall population.

The sample size justification is based on the Region 1 population. A sample size of 260 subjects in Region 1 will provide more than 80% power to detect an improvement of at least 6 percentage points in SVR12 rate from the performance goal of 85% by using a two-sided exact one-sample binomial test at significance level of 0.05.

The point-estimate with the 2-sided 95% exact confidence interval (CI) using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rates by region and the overall study population.

Secondary efficacy endpoints include SVR4 and SVR24.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

β-hCG	β-human chorionic gonadotropin
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APRI	AST:platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BW	body weight
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CRF	case report form(s)
CRO	Contract (or clinical) research organization
DAA	Direct acting antiviral
DCV	Daclatasvir (HCV NS5A Inhibitor)
dL	Deciliter
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
ESA	Erythropoiesis stimulating agent
E_{max}	maximal effect
ESLD	End Stage Liver Disease
ET	Early Termination
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	Fixed dose combination
g	grams
GBD	Global Burden of Disease
GCP	Good Clinical Practice (Guidelines)
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
GT	Genotype (viral)
HbA_{1c}	Hemoglobin A_{1c}
HBV	Hepatitis B virus

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HLGT	High-Level Group Term
HLT	High-Level Term
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	Interferon
IL28B	IL28B gene
IND	Investigational New Drug (Application)
INR	International Normalized Ratio of prothrombin time
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
IWRS	interactive web response system
kg	Kilogram
L	Liter
LDL	low-density lipoprotein
LDV	ledipasvir
LLN	lower limit of the normal range
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
MCV	mean corpuscular volume or mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
Min	Minute
mmHg	millimeters mercury
NS (3/4A/5A/5B)	Non-structural Protein
PCR	Polymerase Chain Reaction
Peg-IFN	pegylated interferon
P-gp	P-glycoprotein
PG	Pharmacogenomic
PT	preferred term or prothrombin time
RBC	Red blood cell count
RBV	Ribavirin

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

RNA	ribonucleic acid
SADR	Serious adverse drug reaction
S_{cr}	serum creatinine (mg/dL)
SAE	serious adverse event
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOC	System Organ Class
SOF	Sofosbuvir, formerly GS-7977
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
ULN	upper limit of the normal range
US	United States
WBC	white blood cell count
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) infection is a global health challenge with estimates ranging up to 150 million individuals infected worldwide {28346}. In the United States (US), approximately 2.7 million people have chronic HCV infection {28338} and HCV infection causes over 15,000 deaths each year {20446}, although under-reporting of HCV infection on death certificates may contribute to as much as a 5-fold underestimation of the actual number of deaths {28339}. Successful treatment of chronic HCV infection reduces the need for liver transplant, the incidence of HCC and overall mortality {25891}. Thus, the public health benefit of safe and effective HCV treatment regimens is high.

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

Most current HCV drug development effort focuses on GT1 HCV infection as this is the most prevalent HCV genotype worldwide, including in developing countries {32174}, {31525}. However, over half of all HCV infections are non-GT1: estimates from 2 recent meta-analyses indicate GT3 HCV is the next most common accounting for 22-30% of infections, while GT2 and GT4 each account for approximately 8 to 13%, GT6 for approximately 2 to 5%, and GT5 for approximately 1% of HCV infections worldwide. The availability of a well-tolerated, all oral, short duration therapy that is effective across all HCV genotypes would be a major advance for the treatment of HCV infection globally, particularly in regions where HCV genotyping is not part of routine medical care.

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

1.2. HCV in China and Southeast Asia

The prevalence of HCV infection in East and Southeast Asia is difficult to quantify due to differences in the level of public health surveillance systems and access to general medical care. A recent literature review estimated the prevalence of anti-HCV antibodies in the Global Burden of Disease (GBD) regions as defined by the World Health Organization (WHO). In East Asia, which includes China, the prevalence was estimated to be 3.7% while in Southeast Asia, which includes Vietnam, Thailand, and Malaysia, the prevalence was estimated to be 2.0% {29744}. Although geographically Singapore is in Southeast Asia, it is classified by WHO as part of "High income Asia-Pacific" GBD and HCV prevalence in this region is 1.4% {29744}.

Genotype diversity is high in both these regions {31525}. Although there are inter- and intra-country differences, the most frequently observed HCV genotypes in both regions are GT1, 2, 3 and 6 (Table 1-1). In China, GT1, GT2 and GT6 are generally the most common, although regional differences in genotype distribution, such as GT3 in the South, are apparent {24217}. GT6 is also common in Vietnam and Thailand while GT3 is the most common genotype in Thailand and Malaysia, and GT2 is found in both countries. Although GT1 is the predominant genotype in Singapore, approximately 20% of infections are GT2 or GT3.

Table 1-1. Summary Characteristics by Country

	China	Vietnam	Thailand	Malaysia	Singapore
Estimated HCV Ab Seroprevalence	1.3[n,p]-3.2%[a]	2.5%[b]	2.7%[n,p]	1.5%[n,p]	
HCV Genotype Distribution	GT-1 – 58.2%[c] GT-2 – 15.5%[c] GT-3 – 8.7%[c] GT-6 – 6.3%[c] Other– 11.3%[c]	GT-1 ~ 47%[b] GT3 ~ 6%[b] GT-6 ~ 47%[b]	GT1 ~34%[n] GT2 ~ 4% GT3 ~41% GT4 <1% GT6 ~23%	GT1 ~39%[n] GT2 ~4% GT3 ~56% GT4 ~1%	GT1 ~81%[n] GT2 ~ 7% GT3 ~ 12%
Estimated % IL28B-CC Genotype	~85%-88%[c,g]	~90%[d]	77%[o]		
Estimated Peg-IFN +RBV SVR rates					
GT-1	~44-70%[h,j,k,m]	~53%[f]	74%		
GT-2	75%[j]	-			
GT-3		-	80%		
GT-6	~65-86%[h,i,l,m]	~74%[f]	65%[r]		

References: a{24428}; {24397}; {24800}; {24799}; {24798};{24235}; b{19682}; c{24217};{24212}; {24211}; {24388}; {24242}; {24382}; {24410}; {24209}; d{22075};f{24413}; g{24383}; h{24797}; i{24395}; j{13261}; k{24391}; l{24393}; m{24411},

In these Asian countries the predominant modes of HCV transmission have been iatrogenic in nature with large proportions of infected patients being exposed prior to the implementation of routine HCV antibody screening at blood banks, improved sterilization techniques for medical/dental equipment, and the widespread availability of disposable medical supplies

{24216}, {24239}, {24396}, {32905}, {32906}, {32907}. Transmission of HCV infection through traditional medical approaches including acupuncture is also common {24239}, {24428}. Due to the timing of introduction of practices aimed at reducing HCV transmission, the seroprevalence of HCV antibodies is seen to increase with age and is generally highest in those over 60 years of age in China {24384}. Elderly patients are more likely to be treatment-experienced and may be at higher risk of developing progressive liver disease. Comorbid conditions such as cardiovascular disease and diabetes are common with increasing age, which pose additional challenges to patient management {24398}, {22156}. The use of IFN is particularly challenging in elderly patients who generally report a higher frequency of adverse events and of greater severity compared to younger patients. Lower levels of treatment adherence are also observed. These factors likely contribute to the overall lower SVR rates generally observed in the elderly {24390}. As these patients continue to age, the number who will develop hepatic complications including cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease (ESLD) is significant {22077}, which will pose a significant burden on the healthcare systems in the region.

In addition to blood transfusions and medical procedures, intravenous drug abuse (IVDA) is a significant risk factor in Malaysia, Thailand and Vietnam, as well as parts of China {19682}, {32762}. The use of interferon (IFN)-based therapy is also problematic in the IVDA population. The risk for developing severe IFN-related psychiatric events including depression, suicidal ideation, cognitive disturbances, psychotic symptoms, fatigue, and habit relapse is high. Adherence to therapy may be low and effective treatment requires multidisciplinary support {25091}.

Treatment of chronic infection in many countries in Asia is currently based upon weekly subcutaneous administration of pegylated interferon (Peg-IFN) with orally administered ribavirin (RBV) for 24 to 48 weeks dependent upon genotype and virologic response. In Caucasians, this treatment regimen affords sustained virologic response rates (SVR) on the order of 42-46% in treatment-naïve patients with GT1 and 76-82% in patients with GT2/3 infection {23342}, {23351}. Observed SVR rates using the same interferon (IFN) based treatment regimens are generally higher in Asian patients: Yu and Chuang {24218} summarize SVR rates in Asian patients in general as approximately 70% for those with HCV GT1 infection, 90% for GT2/3 infection, and 80% for GT6 infection. Although data are limited, published SVR rates for the countries included in this study are included in Table 1-1. The higher SVR rates have been largely attributed to a higher proportion of Asian patients (>85%) possessing the host IL28B-CC genotype which confers a favorable virologic outcome following treatment with IFN-containing regimens {22075}, {24243}, {22156}, {21337}, {22098}. Although relatively high SVR rates can be achieved in Asian patients with IFN+RBV, the safety and tolerability of IFN-containing regimens is sub-optimal. Contraindications to IFN preclude its use by a significant number of patients {22156} while management of adverse effects commonly result in dose reductions and may lead to treatment discontinuation. Safety and tolerability are particularly problematic in an aging population with chronic hepatitis C. Moreover, lower SVR rates are also observed in older patients {24406}.

Recently, first generation protease inhibitors (PI) (i.e., telaprevir [TVR] and boceprevir [BCV]) have been approved in some countries for use in patients with GT1 infection when combined with Peg-IFN+RBV. The Peg-IFN+RBV+PI regimens have incrementally improved SVR rates in GT1 treatment-naïve patients to approximately 70%; however, they are associated with significant safety and tolerability concerns {17996}, {17492} and their use is limited to GT1 HCV.

1.3. Sofosbuvir/GS-5816 Fixed Dose Combination

SOF/GS-5816 fixed-dose combination (SOF/GS-5816 FDC) combines two HCV specific direct acting antivirals (DAAs) into a single tablet for the treatment of chronic HCV infection.

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

The development of SOF/GS-5816 may have a major impact of the global prevalence and burden of HCV as it may represent a simple, well tolerated, highly efficacious pangenotypic treatment for all HCV infected patients.

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

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

1.4. Additional Clinical Study Experience

1.4.1. Study GS-US-281-1058

GS-US-281-1058 is an open-label, Phase 1, multiple-dose drug-drug interaction study in healthy female subjects of childbearing age evaluating the effect of GS-5816 on the pharmacokinetics of a representative hormonal contraceptive medication, norgestimate/ethinyl estradiol (NGM/EE, OC). The study is summarized herein, as the data are relevant to the current study. Following

screening, eligible subjects were enrolled in a lead-in period (Part A) of 28 days during which they completed dosing with the hormonal contraceptive (OC) prior to baseline assessments and initiation of Cycle 1 (Part B). Subjects with a documented history of taking OC for at least 1 menstrual cycle could be enrolled directly into Cycle 1. The PK, safety, and tolerability of OC and OC + GS-5816 were assessed in Part B of the study, which consisted of 2 cycles: subjects received OC alone during Cycle 1, and OC plus GS-5816 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+GS-5816) 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 GS-5816. Steady-state GS-5816 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 GS-5816 relative to administration of NGM/EE alone. A modest increase in EE C_{max} was observed when administered with GS-5816 with no change in overall exposure (AUC) or C_{tau}. The magnitude of increase in EE C_{max} when administered with GS-5816 is similar to that observed with the concomitant administration of other drugs such as voriconazole and etravirine, which did not warrant dose adjustment {13886}, {24911}. GS-5816 exposures were consistent with historical data (Studies GS-US-281-0115, GS-US-342-0104).

Table 1-2. Preliminary NGMN, NG, EE, and GS-5816 Plasma PK Parameters Following Administration of NGM/EE alone or with GS-5816

PK Parameter	Mean (%CV)		GLSM Ratio (90% CI) NGM/EE + GS-5816 vs. NGM/EE
	NGM/EE Alone (N = 15)	NGM/EE + GS-5816 (N = 13)	
Norelgestromin			
AUC_{tau} (pg•h/mL)	17,700 (16.7)	15,700 (11.2)	0.89 (0.85, 0.94)
C_{max} (pg/mL)	1650 (16.8)	1600 (13.7)	0.97 (0.90, 1.04)
C_{tau} (pg/mL)	454 (18.5)	416 (14.3)	0.92 (0.86, 0.98)
Norgestrel			
AUC_{tau} (pg•h/mL)	47,000 (34.4)	43,000 (32.4)	0.91 (0.73, 1.14)
C_{max} (pg/mL)	2410 (30.6)	2330 (31.5)	0.96 (0.80, 1.17)
C_{tau} (pg/mL)	1760 (34.4)	1640 (35.7)	0.92 (0.74, 1.15)
Ethinyl Estradiol			
AUC_{tau} (pg•h/mL)	666 (30.7)	686 (27.3)[a]	1.06 (0.98, 1.14)
C_{max} (pg/mL)	57.5 (27.3)	80.0 (28.4)[a]	1.42 (1.28, 1.58)
C_{tau} (pg/mL)	14.8 (39.3)	12.4 (43.9)[a]	0.84 (0.77, 0.92)
GS-5816			
AUC_{tau} (ng•h/mL)	--	4680 (35.1)	--
C_{max} (ng/mL)	--	626 (22.0)	--
C_{tau} (ng/mL)	--	68.3 (47.6)	--

Note: preliminary data presented to 3 significant figures.

a N = 12

Preliminary luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone concentrations were similar in both treatment cycles, as presented in Table 1-3. Luteinizing hormone and progesterone median values were lower than those expected for ovulatory or luteal phases, respectively {25217}, {25218}, {25219}. Follicle stimulating hormone was lower or within the expected range for the ovulatory phase {25218}. These results are consistent with a possible decrease in serum LH and FSH by hormonal contraceptives and absence of ovulation, as assessed by very low progesterone values on cycle Day 21.

Table 1-3. Preliminary Summary of LH, FSH, and Progesterone Concentrations Following Administration of NGM/EE alone or with GS-5816

	Median (Q1, Q3)	
PD Analyte	**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 GS-5816. 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 GS-5816 as a single agent or as part of SOF/GS-5816 FDC is permitted.

1.5. Rationale for the Current Study

This Phase 3 study has been designed as a multicenter, open-label, non-randomized study evaluating SOF/GS-5816 for 12 weeks. Approximately 360 subjects will be enrolled.

The population of the study will be subjects with chronic HCV infection of any genotype, with approximately 20% having prior treatment failure and approximately 20% having evidence of compensated cirrhosis at screening.

Although favorable virologic response rates can be achieved in Asian patients with currently available therapy, there are significant advantages to the development of novel, all-oral, safe and effective IFN-free regimens. The NEUTRINO study (GS-US-334-0110) demonstrated that SOF + Peg-INF/RBV treatment for 12 weeks results in high SVR rates in subjects with genotype 1 and 4 HCV infection and in the small number of subjects with genotype 5 and 6 HCV infection {24715}. However, the side effects of SOF + Peg-INF/RBV occurred across multiple organ systems and the availability of a Peg-INF-and RBV-free regimen would be an advancement for patients with genotype 1, 4, 5, and 6 HCV infection. Although SOF +RBV for 12 or 24 weeks resulted in high SVR rates in subjects with genotype 2 or 3 HCV infections, respectively, the availability of a RBV-free regimen would be an advancement in treatment as well.

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

Phase 2 evaluation of SOF + GS-5816 demonstrated that co-administration of the single agents for 8 or 12 weeks was well tolerated and resulted in high SVR rates across a broad range of HCV genotypes. In the Phase 2 study GS-US-342-0102 , administration of SOF 400mg + GS-5816

100mg for 12 weeks to treatment-naïve subjects without cirrhosis with genotype 1, 2, 3, 4, or 6 HCV infection resulted in SVR12 rate of 100% (28/28), 100% (10/10), 93% (25/27), 86% (6/7), and 100% (5/5), respectively. In addition, one treatment naïve subject with genotype 5 HCV infection administered SOF +GS-5816 25mg for 12 weeks achieved SVR12. The GS-US-342-0109 study evaluated SOF + GS-5816 with and without RBV in populations of patients considered more difficult to cure, including subjects who had failed a prior interferon based regimen and those with cirrhosis. Administration of SOF 400mg + GS-5816 100 mg for 12 weeks resulted in SVR12 rates of 88% (23/26) and 100% (27/27) in treatment experienced subjects with genotype 3 HCV infection with and without cirrhosis, respectively. Administration of SOF 400mg + GS-5816 100mg for 12 weeks resulted in an SVR12 rates of 100% (27/27) in subjects with genotype 1 HCV infection who had failed prior treatment with a protease inhibitor with Peg-IFN/RBV. Seven of these 27 subjects had cirrhosis.

The Phase 2 data suggest that SOF 400 mg +GS-5816 100mg has the potential to cure HCV infected patients across a broad range of HCV genotypes, when administered for 12 weeks without RBV and regardless of prior treatment experience or cirrhosis status. The co-formulation of SOF/GS-5816 (400 mg/100 mg) adds to the simplicity of the regimen in allowing for a once daily pill. Data from this study will support the development of a well-tolerated, short duration, RBV-free regimen for all genotypes of HCV infection that has the potential to make an impact on the global prevalence and burden of HCV infection.

This study will assess the safety and efficacy of GS-5816/SOF in Asian patients. Each of the countries selected for inclusion in the study has a high burden of disease associated due to HCV infection. In China, estimates of the seroprevalence of HCV range from 1.3 to 3.2% which corresponds to approximately 15 to 30 million people. Seroprevalence estimates are similar in Malaysia, Thailand, and Vietnam although data is limited. The genotype distribution in the selected countries will facilitate enrollment of subjects with genotypes 1, 2, 3 and 6 HCV infection—the most common HCV genotypes across East and Southeast Asia.

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

1.6. Rationale for Dose Selection

Sofosbuvir 400 mg, once daily, when dosed in combination with RBV with or without Peg-IFN has demonstrated broad genotypic efficacy and favorable safety profile in over 1700 HCV-infected subjects across multiple patient populations in Phase 2 and 3 trials. This dose is the approved marketed dose of sofosbuvir for the treatment of HCV-infection and as such, has been selected for co-formulation with GS-5816 into a fixed-dose combination tablet.

GS-5816 100 mg has been administered in combination with SOF 400 mg for 12 weeks to 237 HCV-infected subjects in Phase 2 studies. GS-5816 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 GS-5816 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 GS-5816 100 mg support further evaluation of this combination in clinical development.

1.7. Overall Risk/Benefit Assessment

This study will provide information on the safety and efficacy of SOF/GS-5816, which combines a potent HCV nucleotide inhibitor and a potent HCV NS5A inhibitor. This combination has the potential to be a once-daily pangenotypic regimen for the treatment of chronic HCV infection.

The potential benefits of SOF/GS-5816 over the current standard of care for the treatment of chronic HCV are:

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

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

The safety profile of SOF/GS-5816 has not been established. The safety profile of SOF + GS-5816 25mg or GS-5816 100mg administered for 8 or 12 weeks has been established in over 800 subjects in Phase 2 studies. The safety profile of the proposed therapeutic regimen of SOF 400mg and GS-5816 100mg administered for 12 weeks has been established in 237 subjects enrolled in Phase 2 studies. No clinical safety issues specifically related to GS-5816 or SOF + GS-5816 have been identified to date. No clinical safety issues specifically related to the NS5A inhibitor class including daclatasvir (DCV) and LDV have been identified to date {28583}, {28585}, {28587}.

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

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

2. OBJECTIVES

The primary objectives of this study are:

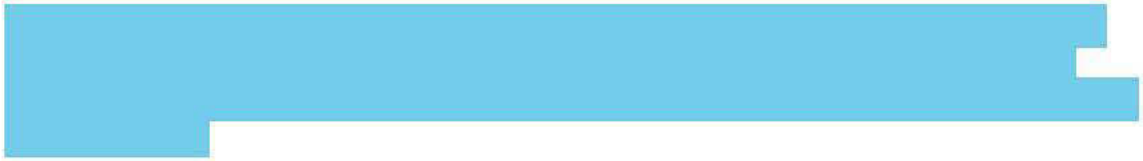
- To evaluate the efficacy of treatment with SOF/GS-5816 for 12 weeks in subjects with chronic HCV infection as measured by the proportion of subjects with SVR12
- To evaluate the safety and tolerability of treatment with SOF/GS-5816 for 12 weeks

The secondary objectives of this study are:

- To determine the proportion of subjects with SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF and GS-5816 during treatment and after cessation of treatment

The exploratory objectives of this study are:

P
P
D



3. STUDY DESIGN

3.1. Treatment Plan and Regimen

This is an international, multicenter, open-label study that will evaluate the safety, tolerability and antiviral efficacy of SOF/GS-5816 for 12 weeks in treatment-naïve and treatment-experienced adults with chronic HCV infection. Subjects with or without cirrhosis will be enrolled.

Approximately 20% of subjects may be treatment experienced and approximately 20% of subjects may have compensated cirrhosis at screening.

Subjects with chronic HCV infection will be enrolled to receive SOF/GS-5816 once daily for 12 weeks.

This multi-regional clinical trial (MRCT) is planned to be conducted in China, Malaysia, Singapore, Thailand, and Vietnam. China will be considered Region 1. Malaysia, Singapore, Thailand, and Vietnam, which are all located in Southeast Asia, will be considered Region 2.

Approximately 360 subjects will be enrolled in the study in total. The approximate number of subjects to be enrolled in each region according to HCV genotype is represented in the table below:

HCV GT (Prior Rx History)	GT-1 (TN, TE)	GT-2 (TN, TE)	GT-3 (TN, TE)	GT-4,5,6 (TN, TE)	Total
Region 1 (China)	80	60	60	60	260
Region 2 (Malaysia, Singapore, Thailand, Vietnam)	100				100

Rx = Treatment
TN = Treatment Naïve, TE = Treatment Experienced

It is expected that a small number of subjects whose HCV genotype cannot be determined by the central laboratory (HCV genotype indeterminate) may also be enrolled.

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 or additional HCV genotyping.

All subjects will complete the following study visits: Screening, Day 1, on-treatment visits at the end of Weeks 1, 2, 4, 6, 8, 10, and 12. Following the last dose of study drug, all subjects will complete post treatment Week 4, including those subjects who terminate study drug treatment early. Subjects who achieve SVR4 (HCV RNA < LLOQ) will attend the post treatment Week 12 visit and those who achieve SVR12 (HCV RNA < LLOQ) will complete the post treatment Week 24 visit. Viral breakthrough or relapse must be confirmed.

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

3.3. Virologic Response-Based Stopping Criteria

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

- Confirmed HCV RNA ≥ LLOQ after 2 consecutive HCV RNA < LLOQ
- Confirmed > 1 $\log_{10}$ increase from on-treatment nadir
- HCV RNA ≥ LLOQ through 8 weeks of treatment

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

All subjects who terminate treatment early will complete the early termination (ET) and post treatment Week 4 visit. Subjects who achieve SVR4 will attend the post treatment Week 12 visit and those who achieve SVR12 will complete the post treatment Week 24 visit.

3.4. Treatment Discontinuation Criteria

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

Study drug(s) must be discontinued in the following instances:

- Unacceptable toxicity, as defined in Section 7 of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Pregnancy of female subject
- Efficacy failure as defined in Section 3.3
- Significant protocol violation
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy or other reason
- Discontinuation of the study at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

3.5. Discontinuations

Subjects discontinuing treatment prior to completion of the assigned dosing period should complete an early termination visit (see Section 6.4). All subjects who terminate treatment early will complete the early termination (ET) visit and post treatment Week 4 and Week 12 visits.

3.6. Substudies

3.6.1. PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 360 subjects will be enrolled in this study. A detailed breakdown of the number of subjects to be enrolled in each region according to HCV genotype is presented in Section 3.1. Approximately 20% of subjects may be treatment experienced and approximately 20% of subjects may have compensated cirrhosis at screening.

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

4.2. Inclusion Criteria

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

1) Willing and able to provide written informed consent
2) Male or female, age ≥ 18 years
3) Bodyweight ≥ 40 kg
4) HCV RNA ≥ 10^4 IU/mL at Screening
5) HCV genotype 1, 2, 3, 4, 5, 6, or indeterminate as assessed at Screening by the Central Laboratory
6) Chronic HCV infection (≥ 6 months) documented by prior medical history or liver biopsy
7) Classification as treatment naïve or treatment experienced (approximately 20% of subjects may be treatment experienced):
    a) Treatment naïve is defined as having never been exposed to approved or experimental HCV-specific direct-acting antiviral agents or prior treatment of HCV with interferon or ribavirin
    b) Treatment experienced is defined as prior treatment failure to a regimen containing interferon either with or without RBV that was completed at least 8 weeks prior to Day 1. **Subject must not have discontinued the prior regimen that resulted in virologic failure due to an adverse event.**
        i) The subject's medical records must include sufficient detail of prior virologic failure to allow for categorization of prior response (Reference Section 6.2.1), as either:
            (1) Non-Responder: Subject did not achieve undetectable HCV RNA levels while on treatment, or
            (2) Relapse/Breakthrough: Subject achieved undetectable HCV RNA levels during treatment or within 4 weeks of the end of treatment but did not achieve SVR

8) Cirrhosis Determination (approximately 20% of subjects may have cirrhosis)

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

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

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

      iii) Fibroscan® with a result of >12.5 kPa

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

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

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

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

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

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

10) Females of childbearing potential (as defined in Appendix 4) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to enrollment

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

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

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

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

4.3. Exclusion Criteria

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

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

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

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

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

   d) Clinical hepatic decompensation (i.e., ascites, encephalopathy or variceal hemorrhage).

   e) Solid organ transplantation.

   f) Significant pulmonary disease, significant cardiac disease or porphyria.

   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 6 months prior to Day 1 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) Significant drug allergy (such as anaphylaxis or hepatotoxicity).

2) Screening ECG with clinically significant abnormalities

3) Subjects has the following laboratory parameters at screening:

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

   b) AST > 10 × ULN

   c) Direct bilirubin > 1.5 × ULN

   d) Platelets < 50,000/μL

e) HbA1c > 8.5%

f) Creatinine clearance (CL_{cr}) < 60 mL /min as calculated by the Cockcroft-Gault equation {2202}

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

h) Albumin < 3 g/dL

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

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

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

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

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

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

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

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

11) Known hypersensitivity to GS-5816, SOF, or formulation excipients.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

An Interactive Web Response System (IWRS) will be employed to manage subject enrollment and study drug re-supply. Eligible subjects will be enrolled and assigned to the open-label treatment. Every subject will receive SOF/GS-5816 tablet for 12 weeks.

5.2. Description and Handling of SOF/GS-5816 FDC

5.2.1. Formulation

The SOF/GS-5816 (400 mg/100 mg) tablets are pink, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side. In addition to the active ingredients, the SOF/GS-5816 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/GS-5816 (400 mg/100 mg) tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

SOF/GS-5816 bottles to be distributed to study centers shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA) and/or other local regulations as applicable.

5.2.3. Storage and Handling

SOF/GS-5816 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/GS-5816.

Sufficient quantities of SOF/GS-5816 tablets to complete the entire study will be shipped to the investigator or qualified designee from Gilead Sciences Clinical Supply Management (or its designee).

5.2.4. Dosage and Administration of Sofosbuvir/GS-5816 FDC

SOF/GS-5816 (400 mg/100 mg) 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(s) of study medication as soon as possible during the same day. Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

5.3. Study Drug Adherence and Drug Accountability

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

Study medication will be reconciled using medication pill count at all on treatment visits by the investigator or designee (i.e. pharmacist) in order to monitor the subject's adherence with the medication regimen.

5.4. Concomitant Medications

Concomitant medications taken within 30 days prior to Screening, approximately and including 30 days after the last dose of study drug need to be recorded in the source documents and electronic case report forms (eCRFs).

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

- Hematologic stimulating agents (e.g. 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 (e.g., infliximab)

- Investigational agents or devices for any indication

Concomitant use of certain medications or herbal/natural supplements (e.g., substrates, inhibitors or inducers of drug transporters or metabolizing enzymes [e.g., P-gp or CYP3A]) with study drug(s) may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug(s) or these medications. The use of the following agents is prohibited from **21 days prior to Day 1** through the end of treatment.

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

Table 5-1. List of Disallowed 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]		Diltiazem, Verapamil, Amiodarone, Dronedarone, Quinidine, Ranolazine, Bosentan, Olmesartan, Valsartan, Digoxin[d]
Herbal/Natural Supplements[b]	St. John's Wort, Echinaccea. Milk thistle (i.e. silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[e]		Rosuvastatin (≤10 mg/day), Atorvastatin, Simvastatin, Pravastatin, Pitavastatin, Fluvastatin, Lovastatin
Other	Modafinil [b], Sulfasalazine[c], Methotrexate[c]	

a The 21 day washout period does not apply to PPIs, which can be taken up to 7 days before baseline Day 1. H2-receptor antagonists must not exceed a dose of 20 mg famotidine or equivalent and can be taken simultaneously with SOF/GS-5816 and/or staggered by 12 hours. Antacids that directly neutralize stomach acid (i.e. Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/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 symptoms of digoxin toxicity.
e Use with SOF/GS-5816 may result in an increase in the concentration of HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

Medications for disease conditions **excluded** from the protocol (e.g., HIV-1 infection, active cancer, transplantation) are not listed under this Concomitant Medication section and are disallowed in the study.

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

5.5. Investigational Medicinal Product Return or Disposal

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

6. STUDY PROCEDURES

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

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

6.1. Subject Enrollment

Study visits will occur at Screening, Day 1, and on-treatment at the end of Weeks 1, 2, 4, 6, 8, 10, and 12. Post treatment Visits will occur at Weeks 4, 12, and 24 (if applicable) following the last dose of study medications.

All subjects will complete post treatment Week 4 regardless of treatment duration. Subjects with HCV RNA < LLOQ at the post treatment Week 4 and/or Week 12 visits will complete the subsequent post treatment visits, unless viral relapse is determined. The end of study will occur at the post treatment Week 24 visit.

Information on the specific laboratory parameters to be measured and clinical assessments to be performed are provided in (Section 6.6.1).

6.2. Screening Assessments

6.2.1. Screening Visit

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

The following will be performed and documented at screening:

- Obtain signed informed consent
  - PPD
- Determine inclusion eligibility (Reference Section 4.2 and 4.3)
  - If the presence of cirrhosis is determined, then appropriate diagnostic imaging (CT or Ultrasound) should be performed to exclude the presence of hepatocellular carcinoma (HCC)

- Obtain medical history
  - If treatment experienced, record the duration of the prior treatment and the type of interferon and/or ribavirin or DAA administered
  - Record whether the subject had a Non-response or Relapse/Breakthrough during prior treatment
    - Non-Response: Subject did not achieve undetectable HCV RNA while on treatment.
    - Relapse/Breakthrough: Subject achieved undetectable HCV RNA during treatment or within 4 weeks of the end of treatment, but did not achieve SVR
- Perform complete physical examination
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Perform 12-lead ECG
- Assessment of adverse events (AEs) and concomitant medications
- Obtain blood samples for tests:
  - Hematology & Chemistry
  - Coagulation tests
  - HCV RNA
  - Serum β-hCG pregnancy test for females of childbearing potential only
  - IL28B genotype
  - Determination of genotype of HCV infection
  - HCV antibody, HIV 1/2 antibody, and HBV surface antigen (HBsAg)
  - HbA_{1c}
  - Fibrotest
- Obtain urine sample for:
  - Urinalysis
  - Drug screen

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic after screening for the Day 1 visit assessments and enrollment into the study.

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

6.3. Treatment Assessments

Treatment procedures/assessments will occur at Day 1, at the end of Weeks 1, 2, 4, 6, 8, 10, and 12.

6.3.1. Day 1 Visit

Day 1 tests and procedures must be completed prior to enrollment and dosing/dispensing of study drug.

At the Day 1 visit, the following procedures/assessments are to be completed according to the Study Procedures Table in Appendix 2.

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Subject completes Health Related Quality of Life (HRQoL) Survey, SF-36
- Obtain blood samples for tests:
  - Hematology & Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Pregnancy prevention counseling

- PPD
- PPD
- Confirm Eligibility
- Drug Administration
  - Dispense study drug as directed by IWRS
  - Instruct the subject on the packaging, storage, and administration of study drug
  - Observe the subject taking the first dose of study drug

6.3.2. Week 1, 2, 4, 6, 8, and 12 Visits (± 3 days)

The following procedures/assessments are to be completed at the end of Weeks 1, 2, 4, 6, 8, 10, and 12 according to the Study Procedures Table in Appendix 2.

- Perform complete physical examination (Week 12 only)
- Obtain body weight (Week 12 only)
- Obtain vital signs
- Perform 12-lead ECG (Weeks 1 and 12 only)
- Assessment of AEs and concomitant medications
- Subject completes Health Related Quality of Life (HRQoL) Survey, SF-36 (Week 12 only)
- Obtain blood samples for tests:
  - Hematology & Chemistry
  - Coagulation tests (Week 12 only)
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only (Weeks 4, 8, and 12 only)
- Pregnancy prevention counseling (Week 12 only)

- PPD
- Complete medication dosage unit counts
- Drug Administration:
  - Dispense study drug as directed by IWRS (Weeks 4 and 8 only)

6.4. Early Termination (ET)/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 virologic failure, a Viral RNA Sequencing / Phenotyping Sample must be collected.

For subjects who have completed an ET visit, the post treatment Week 4, and, if applicable, Weeks 12 and 24 follow-up visits will be scheduled after last dose of the study drug.

If the subject discontinues treatment early, for any reason, the following assessments for the early termination (ET) visit must be performed:

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Subject completes Health Related Quality of Life (HRQoL) Survey, SF-36, if available
- Obtain blood samples for tests:
  - Hematology & Chemistry
  - Coagulation tests
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only (Weeks 4, 8, and 12 only)

- Pregnancy prevention counseling
- PPD
- Complete medication dosage unit counts

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

6.5. Post Treatment Assessments

The post treatment Week 4, 12, and 24 visits should be timed from the date of last administration of study drugs. All subjects must complete the post treatment Week 4 visit. Subjects with HCV RNA < LLOQ at the post treatment Week 4 and/or Week 12 visits will complete the subsequent post treatment visits, unless viral relapse is determined.

6.5.1. Post Treatment Week 4 (± 5 days)

The following procedures/assessments are to be completed at the post treatment Week 4 visit according to the Study Procedures Table in Appendix 2.

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes Health Related Quality of Life (HRQoL) Survey, SF-36
- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only

6.5.2. Post Treatment Weeks 12 and 24, if applicable (± 5 days)

The following procedures/assessments are to be completed at the post treatment Week 12 and 24, visits according to the Study Procedures Table in Appendix 2.

- Obtain body weight
- Obtain vital signs

- Subject completes Health Related Quality of Life (HRQoL) Survey, SF-36 (Post Treatment Week 12 only)

- Obtain blood samples for:

  — HCV RNA

  — Viral RNA Sequencing / Phenotyping Sample

6.6. Procedures and Specifications

6.6.1. Clinical Laboratory Analytes

Hematology: hematocrit, hemoglobin (Hb), platelet count, red blood cell count (RBC), white blood cell count (WBC) with differential (absolute and percentage) including lymphocytes, monocytes, neutrophils, eosinophils, basophils, reticulocyte count and mean corpuscular volume (MCV).

Coagulation: international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT).

Chemistry: Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), albumin, alkaline phosphatase, creatine kinase, creatinine, total Bilirubin (reflex to direct bilirubin), glucose, lipase, potassium, sodium; Fibrotest/APRI calculation and direct bilirubin at Screening only.

Urinalysis: appearance, blood, color, glucose, leukocyte esterase, pH, protein, urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal.

Virological Tests: Serologies for HCV, HBV and HIV. HCV RNA will be measured using the COBAS TaqMan HCV Test, v2.0 for Use with Ampliprep. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay (reflex to Trugene). Gilead reserves the right to use alternate assays for HCV RNA and HCV genotype should the above assays become unavailable.

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

Pregnancy Tests: Serum β-hCG or Urine β-hCG

Additional Tests: Urine Drug screen (for amphetamines, cocaine, methadone, opiates) and hemoglobin A1c (HbA1c)

6.6.2. 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 (only applicable for treatment experienced subjects), will be collected on all subjects during screening.

If treatment experienced, record the duration of the prior treatment and the type of interferon and/or ribavirin and, if applicable, protease inhibitor administered

6.6.3. Complete Physical Examination

A complete physical examination should be in keeping with a complete physical examination performed as part a new patient evaluation and 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.

6.6.4. 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.

6.6.5. Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation {2202} 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)

6.6.6. 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 Day 1 as part of routine safety monitoring.

6.6.7. Viral RNA Sequencing / Phenotyping Sample

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

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

6.6.8. PPD

6.6.9. PPD

manual.

6.6.10. 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 study drug.

If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

6.6.11. Health Related Quality of Life Survey (HRQoL)

A Health Related Quality of Life survey (HRQoL) SF-36 will be completed by subjects, provided a validated translation in the subject's primary language is available, at Day 1, On-Treatment visits at Week 12 and post treatment Weeks 4 and 12 visits (if applicable), and Early Termination (if applicable). The subject should read the questionnaire by himself/herself and write/mark answers directly onto the questionnaire.

7. TOXICITY MANAGEMENT

7.1. Subject Stopping Rules

Administration of study medication may be discontinued in the event of a clinical or laboratory event. The Gilead Medical Monitor must be consulted prior to dose discontinuation of SOF/GS-5816 unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject.

There is no option for dose reduction of SOF/GS-5816.

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

- Elevation of ALT and/or AST > 5x Baseline/Day 1 or nadir, confirmed by immediate repeat testing
- Abnormal elevation of ALT > 3x Baseline/Day 1 and total bilirubin > 2x ULN, confirmed by immediate repeat testing
- Elevation of ALT > 15x ULN, confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 adverse event or laboratory abnormality assessed (and confirmed by immediate repeat testing) as related to SOF/GS-5816

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 8.5.1)
- 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 (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., 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 (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

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 (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

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

The relationship to study procedures (e.g., 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, (e.g., 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 (CRF/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, until 4 weeks after last administration of study drug must be collected/reported to the CRF/eCRF database as instructed.

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

Serious Adverse Events

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

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

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

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

Electronic Serious Adverse Event (eSAE) Reporting Process

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

- If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit as described above.

  — 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.

Contact information is as follows:

Gilead DSPH: Fax: +44 (0) 208 587 2386

Email: safety_FC@gilead.com

Gilead Sciences Medical Monitor:	Name:	Anu Osinusi, MD
	Phone:	PPD
	Mobile:	PPD
	Fax:	PPD
	E-mail:	PPD

- 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 CRF/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 drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

8.5. Special Situations Reports

8.5.1. Definitions of Special Situations

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

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

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

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

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

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

8.5.2. Instructions for Reporting Special Situations

8.5.2.1. Instructions for Reporting Pregnancies

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

Refer to Section 8.3 and the CRF/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 (e.g., 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. Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

8.5.2.2. Reporting Other Special Situations

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

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

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

Refer to Section 8.3 and the CRF/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 CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Objectives and Endpoints

9.1.1. Analysis Objectives

The primary objectives of this study are:

- To evaluate the efficacy of treatment with SOF/GS-5816 for 12 weeks in subjects with chronic HCV infection as measured by the proportion of subjects with SVR12
- To evaluate the safety and tolerability of treatment with SOF/GS-5816 for 12 weeks

The secondary objectives of this study are:

- To determine the proportion of subjects with SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF and GS-5816 during treatment and after cessation of treatment

The exploratory objectives of this study are:

P
P
D

9.1.2. Primary Endpoint

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

9.1.3. Secondary Endpoint

Secondary endpoints include the following:

- The proportion of subjects with: HCV RNA < LLOQ at 4 and 24 weeks after cessation of therapy (SVR4 and SVR24)
- The proportion of subjects with HCV RNA < LLOQ on treatment

- HCV RNA change from Day 1
- The proportion of subjects with virologic failure

9.1.4. Safety Endpoints

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

9.1.5. Other Endpoints of Interest

PPD

9.2. Analysis Conventions

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

The study drug in this study includes SOF/GS-5816. Last dose of study drug refers to the last dose of SOF/GS-5816 and will be used in the definition of treatment-emergent AEs and laboratory abnormalities as well as the efficacy endpoints of SVR at various post treatment time points.

9.2.1. Analysis Sets

9.2.1.1. Efficacy

The analysis set for antiviral activity analyses will be the Full Analysis Set (FAS) which includes subjects who were enrolled into the study and received at least one dose of study drugs.

9.2.1.2. Safety

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

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

9.2.2. Data Handling Conventions

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

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

Any subject with missing data due to premature discontinuation of the study medication will be considered a failure at the date of premature discontinuation and all time points subsequent to the date of premature discontinuation. If no HCV RNA values are obtained after the last dose of study medication, the subject will be considered a treatment failure for the SVR endpoints.

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

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

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

Values for missing safety laboratory data will not be imputed; however, a missing Day 1 result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the 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).

9.2.3. Interim Analysis

An interim analysis may be performed as appropriate for Region 2 or a specific country in Region 2 after all subjects enrolled in the relevant countries have been followed through 12 weeks post treatment or discontinued from the study.

9.3. Demographic Data and Baseline Characteristics

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

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

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

9.4. Efficacy Analysis

9.4.1. Primary Analysis

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

In the primary efficacy analysis, the SVR12 rate in Region 1 will be compared to the pre-specified performance goal of 85% by using a two-sided exact one-sample binomial test at the 0.05 significance level. The null (H0) and alternative (H1) hypotheses used to assess superiority of SOF/5816 in Region 1 relative to the performance goal of 85% are:

- H0: SVR12 rate = 85%
- H1: SVR12 rate ≠ 85%

It is difficult to characterize a single historical control rate for all genotypes included in this study given the different standards of care of each genotype (some of which include interferon), and the lack of historical data for genotype 4, 5, and 6 participants. Given these difficulties, rather than use a historical control rate as the basis for assessing the primary endpoint, a pre-specified performance goal is defined as a benchmark against which the efficacy of SOF/GS-5816 will be tested. The benchmark sets a high bar of 85%. The basis for this benchmark includes the overall trend toward increasing SVR rates in recent years, the higher SVR rates observed with Peg-IFN + RBV treatment in Chinese and other Asian subjects {24218} compared with other races, and the general appeal of using a fixed clinically relevant threshold as a measure of treatment benefit {28509} of SOF/GS-5816.

A confidence interval approach will be used to estimate the SVR12 rates for Region 2 and for the overall population (ie, combined Region 1 and Region 2).

The point-estimate with the 2-sided 95% exact confidence interval (CI) using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rates by region and the overall population, and may be for individual countries as appropriate.

9.4.2. Secondary Analysis

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

Descriptive summaries and listings will be provided for additional efficacy evaluations of the proportion of subjects who experience virologic failure, serum HCV RNA actual values and change from baseline, other endpoints of interest including ALT normalization and Health Related Quality of Life (HRQoL) endpoints.

PPD [redacted]

9.5. Safety Analysis

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

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

9.5.1. Extent of Exposure

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

9.5.2. Adverse Events

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

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

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

- All AEs,
- All study drug-related AEs,
- Combined Grade 2, 3 and 4 AEs,
- Combined Grade 3 and 4 AEs,
- Combined Grade 2, 3 and 4 study drug-related AEs,

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

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

9.5.3. Laboratory Evaluations

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

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

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.

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

9.5.4. Other Safety Evaluations

Individual data for 12-lead ECG, vital signs measurements will be listed by subject and summarized by region and overall by incidence of events/abnormalities or descriptive statistical summaries (n, mean, SD, median, Q1, Q3, minimum, and maximum), as appropriate. In comparison to pre-treatment (either Screening or pre-dose on Day 1) values, vital signs measurements and 12-lead ECG findings will additionally be summarized using pre-determined, clinically relevant thresholds.

9.6. Sample Size

The sample size justification is based on the Region 1 population. A sample size of 260 subjects in Region 1 will provide more than 80% power to detect an improvement of at least 6 percentage points in SVR12 rate from the performance goal of 85% by using a two-sided exact one-sample binomial test at the significance level of 0.05.

In addition, a confidence interval approach will be used to estimate the SVR12 rates for Region 2 and for the overall population (ie, combined Region 1 and Region 2). With 100 subjects from Region 2, and 360 subjects from the overall population, the 2-sided 95% exact CIs for different observed SVR12 rates are presented in the table below.

Region	Observed SVR12 rate	2-sided 95% exact CI
Region 2 (n=100)	80% (80 out of 100)	71% - 87%
	90% (90 out of 100)	82% - 95%
Overall (n=360)	80% (288 out of 360)	75% - 84%
	90% (324 out of 360)	86% - 93%

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States IND, the investigator will ensure that the basic principles of *"Good Clinical Practice,"* as outlined in 21 CFR 312, subpart D, *"Responsibilities of Sponsors and Investigators,"* 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/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.

This study is also subject to and will be conducted in accordance with 21 CFR, part 320, 1993, *"Retention of Bioavailability and Bioequivalence Testing Samples."*

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

This protocol 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) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained **before** starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

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 utilize an IRB or IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

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, (where local regulations allow) and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from Gilead Sciences, including but not limited to the Investigator Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of Gilead Sciences 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 Sciences. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Files and Retention of Records

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

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

The required source data are listed in the Source Data verification Plan, and should include sequential notes containing at least the following information for each subject:

- subject identification (name, date of birth, gender);
- documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- participation in trial (including trial number);
- trial 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 trial medication (preferably drug dispensing and return should be documented as well);
- record of all adverse events and other safety parameters (start and end date, and preferably including causality and intensity);
- concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated 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 required by applicable regulatory requirements, by local regulations, or by an agreement with Gilead Sciences. The investigator must notify Gilead Sciences 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 Sciences must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead Sciences to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 10 years for purposes of this study.

10.1.6. Electronic Case Report Forms (eCRF)

For each subject enrolled, an eCRF must be completed and signed by the principal investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This also applies to records for those subjects who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.7. Drug Accountability

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Gilead Sciences and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with Gilead Sciences requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet Gilead Sciences' requirements for disposal, arrangements will be made between the site and Gilead Sciences or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences or its representatives, to IRBs or IECs, 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 Sciences. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

10.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies).
Gilead Sciences 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.

After conclusion of the study and without prior written approval from Gilead Sciences, 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 Sciences in an abstract, manuscript, or presentation form; or
- the study has been completed at all study sites for at least 2 years.

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

The investigator will submit 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. The investigator will comply with Gilead Sciences' 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. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice (ICH GCP) guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs 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 CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead Sciences 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 Sciences medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead Sciences access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead Sciences 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

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404
STUDY ACKNOWLEDGEMENT

A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks in Subjects with Chronic HCV

GS-US-342-1518, Original Protocol, 16 January 2015

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

Anu Osinusi

Anu Osinusi, MD (Printed)
Medical Monitor

PPD

Signature

Jan 19, 2015

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table
Study Visits

			On-treatment Study Week (± 3 days)							Post treatment Study Week (± 5 days)[i]		
	Screening	Day 1	1	2	4	6	8	10	12/ET	4	12	24
Clinical Assessments												
Informed Consent	X											
Determine Eligibility	X	X										
Medical History	X											
Physical Examination	X	X							X			
Height	X											
Weight	X	X							X		X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[c]	X	X	X						X			
AEs	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X		
Pregnancy Prevention Counseling		X							X	X		
Health Related Quality of Life Survey, SF-36		X							X	X	X	
Review of Study Medication Compliance[g]			X	X	X	X	X	X	X			
Study Drug Dispensing[a]		X			X		X					

	Screening	Day 1	On-treatment Study Week (± 3 days)							Post treatment Study Week (± 5 days)[i]		
			1	2	4	6	8	10	12/ET	4	12	24
Laboratory Assessments												
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X		
Coagulation Tests	X	X							X			
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X
Viral RNA Sequencing / Phenotyping Sample[j]		X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing[d]	X	X			X		X		X	X		
Urinalysis, Urine Drug Screen	X											
HCV Genotyping, IL28B	X											
HCV, HIV, HBV Serology	X											
HbA1c, Fibrotest®	X											
PPD												
Pharmacogenomic Sample[e]		X										
Imaging for Hepatocellular Carcinoma (HCC)[f]	X											

a Day 1 assessments must be performed prior to dosing.

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

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

d Females of childbearing potential only. Serum β-hCG pregnancy test performed at screening and confirmation of positive urine pregnancy test. All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period. If urine is positive, confirm immediately with serum β-hCG.

e Only for subjects who have provided consent for this sample and testing. This sample can be obtained at a subsequent visit if not obtained at Day 1.

f If presence of cirrhosis is determined, then appropriate diagnostic imaging (e.g., CT or ultrasound) should be performed to exclude the presence of hepatocellular carcinoma (HCC)

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

h PPD

i All subjects will complete Post treatment Week 4. Subjects with HCV RNA < LLOQ at the post treatment Week 4 and/or Week 12 visits will complete the subsequent post treatment visits, unless viral relapse is determined.

j Plasma samples will be collected for possible viral resistance and other Virology studies

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

Version: 18June2012

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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC)	1000 to 1300/mm3	750 to < 1000/mm3	500 to < 750/mm3	< 500/mm3
Adult and Pediatric, > 7 Days	1.00 to 1.30 GI/L	0.75 to < 1.00 GI/L	0.50 to < 0.75 GI/L	< 0.50 GI/L
Infant, 2 – ≤ 7 Days	1250 to 1500/mm3	1000 to < 1250/mm3	750 to < 1000/mm3	< 750/mm3
	1.25 to 1.50 GI/L	1.00 to < 1.25 GI/L	0.75 to < 1.00 GI/L	< 0.75 GI/L
Infant, 1 Day	4000 to 5000/mm3	3000 to < 4000/mm3	1500 to < 3000/mm3	< 1500/mm3
	4.00 to 5.00 GI/L	3.00 to < 4.00 GI/L	1.50 to < 3.00 GI/L	< 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm3	200 to < 300/mm3	100 to < 200/mm3	< 100/mm3
	300 to 400/µL	200 to < 300/µL	100 to < 200/µL	< 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm3	500 to < 600/mm3	350 to < 500/mm3	< 350/mm3
	0.60 to 0.65 GI/L	0.50 to < 0.60 GI/L	0.35 to < 0.50 GI/L	< 0.35 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Platelets	100,000 to < 125,000/mm3 100 to < 125 GI/L	50,000 to < 100,000/mm3 50 to < 100 GI/L	25,000 to < 50,000/mm3 25 to < 50 GI/L	< 25,000/mm3 < 25 GI/L
WBCs	2000/mm3 to 2500/mm3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm3 1.00 to < 1.50 GI/L	< 1000/mm3 < 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%

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	146 to 150 mEq/L 146 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	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 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	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
Hypoglycemia **Adult and Pediatric** **≥ 1 Month** **Infant, < 1 Month**	 55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	 40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	 30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	 < 30 mg/dL < 1.64 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** **≥ 7 Days** **Infant, < 7 Days**	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L 11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L > 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L > 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L > 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.14 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days** **Infant, ≤ 14 Days** (non-hemolytic) **Infant, ≤ 14 Days** (hemolytic)	> 1.0 to 1.5 × ULN NA NA	> 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	> 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL > 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 5.0 × ULN > 30.0 mg/dL > 513 µmol/L > 25.0 mg/dL > 428 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	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
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	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
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)	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
Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA 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

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	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** **Pediatric > 3 Mo to < 10 Years**	200 to 999 mg/24 h 201 to 499 mg/m2/24 h	>999 to 1999 mg/24 h >499 to 799 mg/m2/24 h	>1999 to 3500 mg/24 h >799 to 1000 mg/m2/24 h	> 3500 mg/24 h > 1000 mg/ m2/24 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

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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)

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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** **Pediatric < 1 Year**	 Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr Liquid stools (more unformed than usual) but usual number of stools	 Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs. Liquid stools with increased number of stools OR Mild dehydration	 Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated Liquid stools with moderate dehydration	 Life-threatening consequences (eg, hypotensive shock) Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock

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

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

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

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

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

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm2) Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm2) Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue) Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

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

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

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

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

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

1. Background

Non-clinical toxicity studies of SOF demonstrated no adverse effects on fertility or embryo-fetal development. Clinical data available at this time suggest that this drug does not have a drug-drug interaction (DDI) with hormones used for contraception.

Non-clinical toxicity studies of GS-5816 demonstrated no effects on fertility or embryo-fetal development. Preliminary clinical pharmacological data available at this time suggest that GS-5816 does not have a drug-drug interaction (DDI) with hormones used for contraception. Therefore SOF/GS-5816 can be administered with hormonal contraceptives.

However, the risks of treatment with SOF/GS-5816 during pregnancy in human have not been evaluated. Please refer to the latest version of the investigator's brochure for additional information.

2. Definition of Female of Childbearing Potential and Contraceptive Requirements for Female Subjects (and their male partners)

Women ≥ 54 years of age with cessation for ≥ 12 months of previously occurring menses, or women of any age who have had a hysterectomy, or have had both ovaries removed, or have had medically documented ovarian failure will be considered to be of non-childbearing potential.

Women < 54 years of age (including those with amenorrhea of any duration) who have not had a hysterectomy, and have not had both ovaries removed, and have not had medically documented ovarian failure will be considered to be of childbearing potential.

Women of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on the Day 1 visit prior to enrollment. They must also agree to one of the following from 3 weeks prior to Day 1 until 30 days after the last dose of SOF/GS-5816.

- Complete abstinence from intercourse. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) is not permitted.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom from the date of Screening until 30 days after the last dose of SOF/GS-5816:

  — intrauterine device (IUD) with a failure rate of < 1% per year

  — female barrier method: cervical cap or diaphragm with spermicidal agent (where available)

- tubal sterilization
- vasectomy in male partner
- hormone-containing contraceptive:
  - implants of levonorgestrel
  - injectable progesterone
  - oral contraceptives (either combined or progesterone only)
  - contraceptive vaginal ring
  - transdermal contraceptive patch

3. Contraceptive Requirements for Male Subjects (and their female partners)

All male study participants must agree to consistently and correctly use a condom from Baseline until 90 days after the last dose of SOF/GS-5816. 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 90 days after the last dose of SOF/GS-5816.

Male subjects must agree to refrain from sperm donation for at least 90 days after the last dose of SOF/GS-5816.

4. Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days (or 90 days for partners of male subjects) of the last dose of SOF/GS-5816. Subjects who become pregnant or who suspect that they are pregnant must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the investigator.

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