CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naïve and Treatment-Experienced Korean and Taiwanese Subjects with Chronic Genotype 1 HCV Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
IND Number:	Not Applicable
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	To be determined
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-337-0131
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
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IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	Not applicable Not applicable To be determined
Study Centers Planned:	Approximately 14 sites in Korea Approximately 10 sites in Taiwan
Objectives:	The primary objectives of this study are: • To determine the antiviral efficacy of treatment with sofosbuvir (SOF)/ledipasvir (LDV) fixed-dose combination (FDC) as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12, defined as HCV RNA < lower limit of quantification [LLOQ] 12 weeks post treatment) • To evaluate the safety and tolerability of SOF/LDV FDC as assessed by review of the accumulated safety data The secondary objectives of this study are: • To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24) • To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation • To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

	The exploratory objectives of this study are: 
Study Design:	International (Korea and Taiwan), multicenter, open-label study in treatment-naïve and treatment-experienced adults with chronic genotype 1 HCV infection. Approximately 80 treatment-naïve and 80 treatment-experienced subjects will receive treatment with SOF 400 mg/LDV 90 mg fixed dose combination (FDC) tablet for 12 weeks. It is estimated that approximately 80 subjects will be enrolled in Korea and 80 subjects in Taiwan. Within each country approximately 50% (i.e., n~40) of subjects will be treatment-naïve and 50% will be treatment-experienced (i.e., n~40). Treatment-naïve is defined as having never received treatment for HCV with any interferon (IFN), ribavirin (RBV), or other approved or experimental HCV-specific direct acting antivirals. Treatment-experienced is defined as: a) IFN intolerant b) Non-response c) Relapse/Breakthrough *Note: For treatment-experienced subjects, prior exposure to HCV NS3/NS4A protease inhibitors is permitted.* Up to 20% of subjects enrolled in the study may have compensated cirrhosis at Screening.
Number of Subjects Planned:	Approximately 160 subjects
Target Population:	Treatment-naïve and treatment-experienced, chronic genotype 1 HCV infected adults
Duration of Treatment:	12 weeks

Diagnosis and Main Eligibility Criteria:	Chronic genotype 1, HCV infected, male and non-pregnant/non-lactating female subjects, ages 20 years and older, treatment-naïve or treatment-experienced, of whom approximately 20% may have compensated cirrhosis, may be eligible for the study. Reference Section 4.2 and 4.3 for detailed Inclusion and Exclusion criteria.
Study Procedures/ Frequency:	Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. The screening window can be extended to 42 days for subjects requiring liver biopsy or additional HCV genotyping. Study visits will occur at Screening, Baseline/Day 1, and on-treatment at the end of Weeks 1, 2, 4, 6, 8, 10, and 12. Following the last dose of study medication, all subjects will complete 4-Week and 12-Week Post-Treatment Visits. Subjects with HCV RNA < LLOQ at the 12-Week Post-Treatment Visit will also complete a 24-Week Post-Treatment Visit unless confirmed viral relapse occurs. Administration of interferon or any HCV-directed treatment, other than the study drug, is prohibited from 12 weeks prior to Screening until completion of the final post-treatment follow-up visit. Screening assessments include physical examination, height, weight, vital signs, 12-lead electrocardiogram (ECG), medical history, adverse events (AEs), concomitant medications, safety laboratory tests (hematology, chemistry, coagulation, urinalysis), HCV RNA, serology (HIV, HCV, HBV), hemoglobin A1c (HbA_{1c}), assessment of the presence or absence of cirrhosis, liver imaging for HCC (cirrhotics only), serum β-hCG (females of child bearing potential only), thyroid stimulating hormone (TSH), HCV genotyping, IL28B genotyping. On-treatment assessments include adverse events (AEs), concomitant medications, review of study drug adherence, physical examinations, vital signs, safety laboratory tests, HCV RNA, pharmacokinetic samples, and urine pregnancy tests (females of child bearing potential only). Single 12-lead ECGs will be collected at Screening, Baseline/Day 1 (prior to study drug administration) and on-treatment visits at the end of Weeks 1 and Week 12. Weight will be measured at Screening, Baseline/Day 1, on-treatment visit at the end of Week 12, and post-treatment Weeks 12 and 24 visits (as applicable).

Health Related Quality of Life (HRQoL) Survey will be conducted at Baseline/Day 1, on-treatment visits at the end of Weeks 2, 4, 8, and 12, and Post-Treatment Week 4 and 12 visits.

Pregnancy prevention counseling will be addressed with the subject at Baseline/Day 1, on-treatment visit at the end of Week 12, and post-treatment Week 4 visits.

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

Samples for viral RNA sequencing/phenotyping will be collected at Baseline/Day 1 and every visit thereafter. PPD Two archive plasma samples will be collected, one at Baseline/Day 1 and the second at the end of treatment visit for potential future biomarker testing. Subjects will have the opportunity to opt out of the archive sample collection. For subjects who provide their additional and specific consent, a blood sample will be collected at the Baseline/Day 1 visit for human pharmacogenomic testing (this sample may be drawn after Baseline/Day 1, if necessary).

Optional Substudies:

PPD

	PPD [redacted]
Test Product, Dose, and Mode of Administration:	SOF/LDV is manufactured as a FDC tablet, consisting of 400 mg SOF and 90 mg LDV, for oral administration. Subjects will take 1 tablet daily with or without food.
Reference Therapy, Dose, and Mode of Administration:	None.
Criteria for Evaluation:	
Safety:	AEs and safety laboratory tests will be collected throughout the study (through the 4-Week Post-Treatment Visit).
Efficacy:	Efficacy will be evaluated using scheduled assessments of HCV RNA performed using COBAS® TaqMan® HCV Test, v2.0 for use with the High Pure System.
Pharmacokinetics:	A single PK blood sample will be collected at each on-treatment visit for all subjects. PPD [redacted] If conducted, a target of ~10-15 subjects may be enrolled from each country. Serial PK samples would be collected over 24 hours post-dose. The PK of SOF (and its metabolites GS-566500 and GS-331007) and LDV would be assessed.
Statistical Methods:	The primary efficacy endpoint is SVR12 in all enrolled and treated subjects with chronic genotype-1 HCV infection. No statistical hypothesis testing will be performed. For each region (Korea and Taiwan) and overall, a point-estimate with two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) will be constructed for the SVR12 rate by treatment-naïve and treatment-experienced subjects. With a sample size of 80 subjects in the treatment-naïve and in the treatment-experienced group, a two-sided 95% exact confidence interval will extend at most 23% in length. Secondary efficacy endpoints include the proportion of subjects with SVR4, SVR24, breakthrough and relapse; and HCV RNA

	change from baseline. All continuous endpoints (except safety endpoints) will be summarized using an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) by treatment-naïve and treatment-experienced subjects for each region and overall. All categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition. Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
β-hCG	β-human chorionic gonadotropin
AE	adverse event
ALT	alanine aminotransferase (also SGPT)
ANC	absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (also SGOT)
AUC	area under the curve
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BID	twice a day
BLQ	below the lower limit of quantification
BMI	body mass index
BT	breakthrough
BW	body weight
CFR	Code of Federal Regulations
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
dL	Deciliter
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
ECIRB/IEC	Ethics Committee Institutional Review Board/ Independent Ethics Committee
eCRF	Electronic case report form(s)
E_{max}	Maximal effect
ESA	Erythropoiesis stimulating agent
eSAE	electronic Serious Adverse Event (system)
ESLD	End Stage Liver Disease
ET	early termination
EU	European Union
FAS	full analysis set

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

FDA	(United States) Food and Drug Administration
FDC	Fixed Dose Combination
FEV_1	forced expiratory volume in one second
GCP	Good Clinical Practice (Guidelines)
GCSF	Granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GMRs	geometric-least squares means ratios
GSI	Gilead Sciences, Inc.
GT	Genotype (viral)
Hb	Hemoglobin
HbA_{1c}	Hemoglobin A_{1c}
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HDPE	high-density polyethylene
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
HRQoL	Health Related Quality of Life (Survey)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL28B	IL28B gene
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IU	International Units
IUD	Intrauterine Device
IV	Intravenous
IVDA	Intravenous drug abuse
IWRS	Interactive Web Response System
kg	Kilogram
L	Liter
LDV	Ledipasvir
LLN	lower limit of the normal range

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

LLOQ	Lower limit of quantification
LLT	Lower-Level Term
LTFU	Lost to follow up
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
mmHg	millimeters mercury
NS (3/4A/5A/5B)	Non-structural Protein
PBMC	peripheral blood mononuclear cell(s)
Peg-IFNα	pegylated interferon
PG	Pharmacogenomic
P-gp	P-glycoprotein
PI	Protease inhibitor
PK	Pharmacokinetic
PT	Preferred Term
QA	Quality Assurance
QD	once daily (use only in tables)
QTcF	QT interval corrected using Fridericia' formula
RBC	Red blood cell count
RBV	Ribavirin
RNA	ribonucleic acid
RVR	rapid virologic response
SAE	serious adverse event
SD	Standard deviation
SF-36	Short-Form-36
SOC	Standard of Care or System Organ Class
SOF	Sofosbuvir
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
TE	Treatment-Experienced
TN	Treatment-Naïve
TGV	Tegobuvir
TND	Target not detected
TPO	thrombopoietin
TSH	Thyroid stimulating hormone
t½	An estimate of the terinal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate contstant (λz)

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

ULN	upper limit of the normal range
US	United States
WBC	white blood cell count

1. INTRODUCTION

1.1. Background

1.1.1. HCV Infection

Infection with the hepatitis C virus (HCV) is a serious, progressive, and often life-threatening disease affecting approximately 180 million adults worldwide {21360}. The infection, if untreated, can result in progressive liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC) and end stage liver disease (ESLD). Transmission of HCV infection is parenteral with the majority of infections occurring through administration of contaminated blood products, unsafe medical procedures, intravenous drug use or sexual transmission {8076}. The hepatitis C virus is classified into six major genotypes (GT), i.e., 1-6, with further division to a subtype level (e.g., a, b, c) {21479}. Virologic response rates to currently available therapies vary according to host IL28B genotype, baseline levels of HCV RNA and HCV genotype. The distribution of HCV genotypes and subtypes varies according to geographic region with the most common HCV genotypes in the United States and Europe being GT-1, GT-2 and GT-3. In Korea and Taiwan it is estimated that approximately 50% of infections are associated GT-1b and 50% with GT-2a {24218}, {24242}, {24215}. Genotypes 4, 5 and 6 are most prevalent in the Middle East, South Africa and Southeast Asia respectively {22110}.

Following acute infection approximately 15-20% of patients are able to clear the virus without intervention, however around 80% of patients go on to establish chronic hepatitis C {8076}. Treatment of chronic infection is currently based upon weekly subcutaneous administration of pegylated interferon (Peg-IFNα) with orally administered ribavirin (RBV) for 24 to 48 weeks dependent upon genotype and virologic response. This treatment regimen affords sustained virologic response rates (SVR) on the order of 42-46% in treatment-naïve patients with GT-1 and 76-82% in patients with GT-2/3 infection {23342}, {23351}. Recently, first generation protease inhibitors (PI) (i.e., telaprevir (TVR) and boceprevir (BCV)) have been approved in certain countries for use in patients with GT-1 infection when combined with Peg-IFNα+RBV. The Peg-IFNα+RBV+PI regimens have incrementally improved SVR rates in GT-1 treatment-naïve patients to approximately 70% however they are not approved for use in GT-2 infection and are associated with significant safety and tolerability concerns {17996}, {17492}. Peg-IFNα+RBV+PI regimens are not currently available in Korea or Taiwan and consequently patients with GT-1 infection failing to respond to Peg-IFNα +RBV have no current treatment options with spontaneous clearance of HCV negligible in these patients.

1.1.2. HCV Infection in Korea

In Korea, chronic HCV infection is one of the leading causes of chronic liver disease and hepatocellular carcinoma (HCC) {24211}. The age-standardized prevalence of HCV antibody (HCV Ab) in patients greater than 40 years of age is reported to be on the order of 1.3% which equates to around 193,000 people {24215}. The prevalence of HCV infection increases

with age and peaks in those individuals aged 60 years and older {24211}. The majority of infections occurred via contaminated blood transfusions prior to the introduction of blood-donor HCV Ab screening in 1991 {24216}. Consequently the majority of patients with chronic hepatitis C in Korea are elderly {24215} and are more likely to have progressive liver disease. HCV infection is more closely associated with HCC in the elderly Korean patients than are HBV infection and alcoholism {24210}, {24208}. Since the decline of transfusion-related hepatitis C the majority of new infections are behavior-related. Of particular note is the practice of acupuncture for chronic illnesses including joint disease, pain, sequelae of trauma and other conditions non-responsive to conventional therapies. Shin et al reported results of a case study in which 34.1% of men and 62.9% of women in rural Korea reported multiple acupuncture procedures with the associated risk fraction for HCV infection being 38% for men and 55% for women {24214}. Intravenous drug abuse (IVDA) is not thought to be a major contributor to the overall prevalence of HCV infection in Korea however this route of infection may contribute in young adults and those living in harbor cities on the southern and western coasts {24209}, {24211}. The predominant HCV genotypes in Korea are GT-1b and GT-2a which are roughly present in equal proportions and combined account for around 80-90% of infections {24216}, {24215}, {24209}. Host IL28B genotype has been widely reported as a predictor of virologic response to interferon (IFN)-based therapies for chronic HCV infection {22075}. The IL28B-CC genotype which confers a favorable virologic outcome to IFN-based therapy predominates in Korea with approximately 80-90% of patients with this genotype {24212}, {24238}. Consequently the sustained virologic response rates in Korean clinical trials evaluating Peg-IFNα+RBV in treatment-naïve GT-1 infection are on the order of 55-70% following 48 weeks of therapy {24211}, {24595}, {24387}, {24385}, {24237}, {24404}, {24388} . Although relatively high rates of virologic response are achievable with Peg-IFNα+RBV in treatment-naïve Korean patients due to the high proportion of IL28B CC genotype, Heo et al {24236} recently reported a significant difference in SVR rate observed in a clinical trial cohort versus that observed in clinical practice based upon 'Intention To Treat' (ITT) analysis; 81% (21/26) versus 55% (58/106). Although no difference was observed in the SVR rates between the clinical trial cohort and the clinical practice cohort according to per protocol analysis, the ITT is important since it more likely reflects the observed SVR in clinical practice across the country. The authors attribute the lower ITT SVR rate in the clinical practice cohort to decreased adherence to assigned therapy including dose reduction for clinical and laboratory adverse events. As previously described, the highest prevalence rates for HCV Ab in Korean patients are in those individuals aged 60 years and older. These elderly patients are more likely to be treatment-experienced and have progressive liver disease. Comorbid conditions (e.g., diabetes and cardiovascular disease) are common in this population and pose significant challenges to the use of Peg-IFNα+RBV therapy. As this group of patients continues to age the proportion of patients with chronic hepatitis C who will develop complications, including liver cirrhosis, HCC and ESLD is significant; {22077}. In addition, it is important to consider the proportion of patients who are ineligible for, intolerant of, or unwilling to receive Peg-IFNα+RBV who have no currently available antiviral treatment options {21256}. This also applies to patients who have previously failed to respond to Peg-IFNα+RBV therapy. Although Peg-IFNα+RBV can achieve high rates of SVR in treatment-naïve patients with chronic HCV infection when assigned therapy is tolerated,

there is an unmet medical need for effective, safe, well-tolerated, all oral therapies that can be used in an aging patient population in Korea.

1.1.3. HCV Infection in Taiwan

Taiwan has one of the highest prevalence rates of chronic hepatitis C in North-East Asia. In a nationwide survey conducted between 1996 and 2005 involving over 164,000 participants in out-reach community-based hepatitis screening programs the HCV seroprevalence was estimated to be 4.4% {24235}. The study reported an approximately equal seroprevalence in males (4.5%) and females (4.3%). Importantly seroprevalence varied geographically with certain areas of hyperendemicity such as Miaoli and Chiayi Counties where the age-adjusted seroprevalence was reported to be 7.6% and 6.1% respectively. The proportion of subjects with HCV antibodies progressively increased after the age of 20 years. The predominant routes of transmission are thought to be iatrogenic in nature including history of blood transfusion, medical injections and acupuncture {24239}, {24396}. Historically, glucose supplements, vitamins, and treatments for minor medical conditions have often been administered by injection. Prior to 1980 reusable syringes were commonly used particularly in rural areas with poor sterilization techniques likely contributing to the spread of HCV infection. After 1980, the rate of HCV infection was likely reduced following the introduction of disposable syringes. This may in part explain the higher prevalence of HCV infection in the elderly population in Taiwan. It has also been postulated that inhabitants of communities with high rates of HCV infection may have been repeatedly exposed to a common reservoir of infection contributing to the establishment of hyperendemic areas {24239}.

As previously described for Korea, the predominant HCV genotypes in Taiwan are GT-1b and GT-2a which are present in similar proportions and account for around 80-90% of all infections {24596}, {24218}, {24242}. The IL28B-CC host genotype conferring favorable virologic outcome to IFN-based therapy predominates with approximately 80-90% of patients with this genotype {22075}, {24241}. As a consequence the SVR rates in Taiwanese clinical trials evaluating Peg-IFNα+RBV in GT-1 infection are approximately 49-56% and 76-80% in treatment-naïve patients receiving 24 weeks and 48 weeks of treatment respectively {24410}, {24382}. However, as previously described in Taiwan the seroprevalence of HCV antibodies increases with age with the highest rates observed in those 60 years and older {24235}. The use of currently available therapy is problematic in the elderly due to contraindications to IFN and RBV and comorbidities such as cardiovascular disease and diabetes. In Taiwan for treatment-naïve patients with GT-1 infection aged ≥65 years the SVR rate for Peg-IFNα+RBV administered for 48 weeks has been reported to be 51.9% {24390}. The elderly patient population is more likely to have progressive liver disease and be at higher risk for the development of HCC and ESLD. For GT-1 infection the SVR rates for Taiwanese age-matched patients with HCC (post-curative management) and cirrhosis are reported to be 33% and 55% respectively {24240}. The safety, tolerability and efficacy of IFN+RBV therapy is suboptimal in this population. Finally, there are no currently available treatment options for those patients who are ineligible for, intolerant of, or who have previously failed to respond to IFN+RBV therapy.

There is a need for early intervention and eradication of HCV infection to reduce the burden of progressive liver disease including of HCC and ESLD. While early introduction of effective antiviral therapy is critical in order to reduce the potential future burden of advanced liver disease, safe and effective antiviral therapies that can be used in elderly patients with advanced disease is of paramount importance today. Gilead Sciences is developing the all-oral, interferon- and ribavirin-free SOF/LDV FDC regimen to address this need in Korean and Taiwanese patients with chronic genotype-1 HCV infection.

1.2. Sofosbuvir (formerly GS-7977) and Ledipasvir (formerly, GS-5885) Fixed Dose Combination

Sofosbuvir/ Ledipasvir Fixed Dose Combination (FDC) combines two HCV specific DAA agents into a single tablet for the treatment of chronic HCV infection. More than 1200 subjects have received treatment with this combination tablet to date.

Sofosbuvir (SOF), formerly GS-7977, is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed HCV replication. Over 2,000 subjects have received SOF containing regimens to date, from single doses up to repeat dosing for 24 weeks.

Ledipasvir (LDV), formerly GS-5885, is a novel HCV NS5A inhibitor that has demonstrated potent anti-HCV activity against genotype (1a and 1b) HCV infection. More than 1000 HCV infected subjects have been dosed with LDV in ongoing Phase 2 clinical studies, and over 700 subjects have been dosed with LDV for over 12 weeks.

1.2.1. General Information

For further information on SOF/LDV FDC, refer to the Investigator's Brochure (IB) for Sofosbuvir/GS-5885 Fixed Dose Combination including:

- In Vitro Anti-HCV Activity
- Nonclinical Pharmacokinetics and In Vitro Metabolism
- Nonclinical Pharmacology and Toxicology
- Clinical Experience

1.2.2. Summary of Additional Clinical Experience with Sofosbuvir

1.2.2.1. Clinical Pharmacology Studies with Sofosbuvir

A number of Phase 1 studies have been conducted with SOF and are summarized in the investigator brochure including: a relative bioavailability study (P7977-0111) to compare human exposure after administration of PSI-7851 (diastereomeric mixture of SOF and GS-491241; Investigator Brochure) to SOF, a human mass balance study (P7977-0312) to evaluate routes of elimination for SOF and metabolites, a methadone interaction study (P7977-0814) which demonstrated no interaction between SOF and methadone; and a

thorough QTc study (P7977-0613) demonstrating no effect of SOF upon the QT interval in humans.

A Phase I ethnic bridging study has also been conducted to compare the pharmacokinetics of single dose administration of SOF and SOF/LDV FDC in healthy Japanese and Caucasian subjects. This study which supports the global development program is described in Section 1.2.3.1.1 below.

1.2.2.2. Phase 2 Studies with Sofosbuvir

1.2.2.2.1. Study AI444-040 (Bristol-Myers Squibb IND 79,599)

AI444-040 {20485} was designed to evaluate the potential to achieve SVR with an oral, pan-genotypic, once-daily treatment regimen combining the investigational agents SOF and a NS5A inhibitor, daclatasvir (DCV), with or without RBV, in treatment naïve subjects chronically infected with genotypes 1, 2, or 3 HCV {24592}. In the initial phase of this study, subjects were randomized into six groups, evaluating three different dosing schedules in subjects with either genotype 1 HCV (n=44) or genotype 2/3 HCV (n=44). The groups were:

- SOF 400 mg QD for 7 days then DCV 60 mg QD + SOF 400 mg QD for 23 weeks
- SOF 400 mg QD + DCV 60 mg QD for 24 weeks
- SOF 400 mg QD + DCV 60 mg QD + RBV for 24 weeks

The primary endpoint of the study was SVR12. An interim analysis for safety and antiviral activity was conducted at 12 weeks on-treatment.

The study was subsequently expanded to evaluate SOF + DCV ± RBV for 24 weeks in genotype 1 HCV infected subjects who have previously failed telaprevir or boceprevir treatment and for 12 weeks in treatment-naïve genotype 1 HCV subjects. Preliminary data on the 12 and 24 week arms are available.

1.2.2.2.1.1. Study AI444-040 Preliminary Safety

Preliminary safety data have been reported. The most frequent (greater than or equal to 15% overall) adverse events (AEs) on treatment were fatigue, headache and nausea. Adverse events were generally mild to moderate intensity and did not lead to treatment discontinuation. Grade 3-4 laboratory abnormalities included anemia in subjects receiving RBV. Two subjects discontinued treatment for non-drug related AEs and both achieved SVR4. No subjects discontinued therapy due to treatment-related AEs.

1.2.2.2.1.2. Study AI444-040 Preliminary Efficacy

Preliminary efficacy data are tabulated in Table 1-1 below.

Table 1-1 The Proportions of Subjects Achieving Viral Load Below the Lower Limit of Quantification (HCV RNA <25 IU/mL) in Study AI444-040

	Genotype 1					Genotype 2 or 3		
Time (Week)	SOF(LI) +DCV [b] 24 weeks (Group A) (N = 15) n (%)	SOF +DCV 24 weeks (Group C) (N = 14) n (%)	SOF+ DCV+ RBV 24 weeks (Group E) (N = 15) n (%)	SOF +DCV 12 weeks (Group G) (N = 41) n (%)	SOF +DCV +RBV 12 weeks (Group H) (N = 41) n (%)	SOF(LI)+ DCV 24 weeks (Group B) (N = 16) n (%)	SOF+ DCV 24 weeks (Group D) (N = 14) n (%)	SOF +DCV +RBV 24 weeks (Group F) (N = 14) n (%)
4	15 (100)	14 (100)	15 (100)	39 (95)	41 (100)	16 (100)	14 (100)	14 (100)
EOT [a]	15 (100)	14 (100)	15 (100)	41 (100)	41 (100)	15 (94)	14 (100)	14 (100)
SVR4	15 (100)	14 (100)	15 (100)	40 (98)	39 (95)	14 (88)	14 (100)	12 (86)
SVR12	15 (100)	14 (100)	15 (100)	Pending[c]	Pending[c]	14 (88)	14 (100)	12 (86)

a EOT, End of Treatment

a LI, lead in; DCV, daclatasvir

b Pending, data collection ongoing

Preliminary HCV RNA data is also available on the SOF+DCV±RBV regimen administered for 24 weeks in GT-1 non-cirrhotics who had previously failed telaprevir or boceprevir containing regimens {24592}. Most of the subjects enrolled were HCV GT-1a (83%), IL28B non-CC (98%) and had estimated METAVIR stage ≥F2. The mean baseline HCV RNA was ≥6 log IU/mL. All subjects receiving SOF+DCV either with or without concomitant RBV, achieved rapid virologic suppression with HCV RNA <25 IU/mL by the on-treatment Week 4 visit. Early virologic suppression was maintained through the end of treatment (Week 24) with 100% (41/41) of subjects going on to achieve SVR4.

Table 1-2. Study AI444-040 HCV RNA <25 IU/mL during and post-treatment.

	GT1a/1b, prior Telaprevir or Boceprevir failure	
HCV RNA <25 IU/mL	DCV+SOF, 24 Weeks (n=21)	DCV+SOF+RBV, 24 Weeks (n=20)
On treatment Week 4	21 (100)	19 (95)[a]
End of Treatment (Week 24)	21 (100)	20 (100)
SVR4	21 (100)	20 (100)

Notes: [a]1 missing

1.2.2.2.2. NIAID Study 11-I-0258 (IND 112,681)

Study 11-I-0258 is a randomized controlled open-label study to assess safety, tolerability and efficacy of SOF 400 mg QD in combination with RBV in a total of 60 treatment-naïve HCV genotype 1 mono-infected individuals. The NIAID is the sponsor of the study under IND 112,681. Subjects were enrolled into 2 phases to evaluate both treatment duration as well as RBV dose. Phase 1 enrolled 10 subjects who were dosed with SOF 400 mg QD in combination with weight based RBV (1000 mg for participants weighing < 75 kg and 1200 mg for participants weighing ≥ 75kg) for 24 weeks; all subjects had ≤ stage 2 fibrosis. Upon completion of an interim safety review of these subjects at Week 12 of treatment, Phase 2 was initiated in 50 subjects with any stage of fibrosis. Phase 2 subjects were randomized in a 1:1 ratio to receive 24 weeks of SOF QD in combination with weight-based RBV (1000 mg or 1200 mg daily) or 24 weeks of SOF 400 mg QD with low dose RBV (600mg). All subjects have completed therapy in both phases of the study.

1.2.2.2.2.1. NIAID Study 11-I-0258 (IND 112,681) Preliminary Safety Data

The population was predominantly African American, genotype 1a, with a median baseline HCV RNA $\log_{10}$ ≥ 6.05. All subjects in Phase 1 were ≤ Stage 2 fibrosis while, in Phase 2, 24% of those receiving full-dose RBV and 28% of those receiving low-dose RBV had advanced fibrosis. The interim safety analysis is completed and SOF was assessed as being safe and well-tolerated. There were no SAEs and the safety profile was consistent with that expected for RBV.

1.2.2.2.2.2. NIAID Study 11-I-0258 (IND 112,681) Preliminary Efficacy Data

Preliminary HCV RNA data for both study phases are presented in Table 1-3.

Table 1-3. NIAID Study 11-1-0258: Percentage of Subjects with HCV RNA Achieving SVR

Time (Week)	Part 1	Part 2	
	SOF+Weight-based RBV 24 Weeks N=10 n (%)	**SOF+Weight-based RBV 24 Weeks N=25 n (%)**	**SOF+600 mg RBV 24 weeks (N = 25) n (%)**
4	9/10 (90%) [b]	24/25 (96%) [b]	24/25 (100%)
EOT [a]	9/10 (90%)	24/25 (96%) [b]	22/25 (88%) [c]
SVR4	9/10 (90%)	18/25 (72%) [b]	14/25 (56%)
SVR12	9/10 (90%)	17/25 (68%)	12/25 (48%)

a EOT, End of Treatment

b One subject discontinued therapy at Week 3

c 3 subjects dropped out before Week 8

1.2.2.3. Phase 3 Studies with Sofosbuvir

The SOF Phase 3 program includes 4 clinical studies: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), and GS-US-334-0110 (NEUTRINO).

Studies P7977-1231, GS-US-334-0107, and GS-US-334-0108 evaluated the efficacy and safety of SOF+RBV in different genotype 2 and 3 HCV patient populations. Study GS-US-334-0110 evaluated the efficacy and safety of SOF+Peg-IFNα+RBV for 12 weeks for treatment-naive subjects with genotype 1, 4, 5, and 6 HCV infection. Preliminary safety and efficacy data for each study are summarized below.

1.2.2.3.1. P7977-1231 (FISSION)

This Phase 3, randomized, multicenter, open-label, active-controlled study evaluated SVR12 rates of treatment-naïve, genotype 2 or 3 HCV-infected subjects randomized 1:1 to receive either 12 weeks of treatment with SOF (400 mg once daily) +RBV (1000 or 1200 mg per day in divided [BID] doses, as determined by subject's weight) or 24 weeks of treatment with Peg-IFNα (180 μg/week) +RBV (800 mg/day).

1.2.2.3.1.1. P7977-1231 (FISSION) Preliminary Safety Data

Treatment with SOF+RBV was well tolerated in this study, and the overall safety profile of SOF+RBV was favorable to that of Peg-IFNα +RBV. Specifically, the SOF+RBV group had lower rates of AEs (SOF+RBV 86%; Peg-IFNα+RBV 96%); Grade 3 or higher AEs (SOF+RBV 7%; Peg-IFNα +RBV 19%); Grade 2 or higher AEs (SOF+RBV 40%; Peg-IFNα +RBV 69%); treatment-related AEs (SOF+RBV 72%; Peg-IFNα +RBV 94%); AEs leading to permanent discontinuation of any of the study drugs (SOF+RBV 1%; Peg-IFNα +RBV 12%); and AEs leading to study drug interruption or dose modification (SOF+RBV 10%; Peg-IFNα+RBV 27%). The safety profile of SOF+RBV treatment was similar to the expected safety profile of RBV treatment.

Fatigue occurred with the highest AE incidence in both treatment groups, reported in 92 subjects (36%) in the SOF+RBV group and 134 subjects (55%) in the Peg-IFNα+RBV group. All of the other most common AEs (ie, those in ≥ 10% of subjects in either treatment group) were also reported in a lower percentage of subjects in the SOF+RBV group than the Peg-IFNα +RBV group. These AEs included events commonly associated with Peg-IFNα +RBV treatment, such as anemia, headache, nausea, insomnia, diarrhea, irritability, rash, myalgia, decreased appetite, pruritus, dizziness, influenza-like illness, arthralgia, chills, depression, pyrexia, pain, and neutropenia).

Serious AEs were infrequent in both treatment groups (SOF+RBV 3%, 7 subjects/8 events; Peg-IFNα+RBV 1%, 3 subjects/6 events). All individual SAE preferred terms were reported for only 1 subject, and no pattern was apparent in the types of events.

Most lab abnormalities in both groups were Grade 1 or 2 in severity.

1.2.2.3.1.2. P7977-1231 (FISSION) Preliminary Efficacy Data

Overall SVR12 rates were 67% (170/253) in the SOF+RBV group and 67% (162/243) in the Peg-IFNα+ RBV group. Since the lower bound of the 2-sided 95% confidence interval (CI) of the difference in the response rate (SOF+RBV − Peg-IFNα+ RBV) was greater than the prespecified 15% noninferiority margin, treatment with SOF+RBV for 12 weeks was determined to be noninferior to treatment with Peg-IFNα+ RBV for 24 weeks. The SVR12 rates for genotype 2 subjects were 97% versus 78% for those receiving SOF+RBV versus Peg-IFNα+ RBV, respectively, and for genotype 3 subjects were 56% versus 63% for those receiving SOF+RBV versus Peg-IFNα+ RBV, respectively. Among subjects with cirrhosis at baseline who received SOF+RBV, 47% achieved SVR12 compared with 38% of those who received Peg-IFNα+ RBV.

With the exception of one subject who was non-compliant (drug levels were undetectable), all subjects in the SOF+RBV arm became HCV negative on treatment and relapse accounted for the virologic failures.

1.2.2.3.2. GS-US-334-0107 (POSITRON)

Subjects (n=278) with genotype 2 and 3 HCV infection who were interferon intolerant or interferon ineligible or unwilling to take interferon were randomized (3:1) to receive 12 weeks of SOF (400 mg/day) plus RBV (1000 or 1200 mg/day) or matching placebo.

1.2.2.3.2.1. GS-US-334-0107 (POSITRON) Preliminary Safety Data

Treatment for 12 weeks with SOF+RBV was well tolerated in this study. The safety profile of SOF+RBV treatment was similar to the expected safety profile of RBV treatment.

The majority of subjects in both groups experienced at least 1 AE. The most frequently reported overall AEs and treatment-related AEs in both groups were fatigue, headache, and nausea. Most AEs were either Grade 1 (mild) or Grade 2 (moderate) in severity. Eight AEs leading to discontinuation of any study drug were reported in 5 (2%) SOF+RBV subjects and 4 AEs leading to discontinuation of any study drug were reported in 3 (4%) placebo subjects. No individual AE that led to discontinuation was experienced by more than 1 subject. No trends in SAE type or onset time were observed. Most laboratory abnormalities were Grade 1 or 2 in severity.

1.2.2.3.2.2. GS-US-334-0107 (POSITRON) Preliminary Efficacy Data

SVR12 was achieved by 78% (161/207) subjects receiving SOF+RBV compared with 0% (0/71) subjects receiving placebo ($p < 0.001$). Relapse accounted for all virologic failures in the SOF+RBV arm.

Subjects with genotype 2 HCV infection had a higher SVR12 rate than subjects with genotype 3 HCV infection (93% vs 61%). Overall 15% of subjects had cirrhosis at baseline; 61% of those receiving SOF+RBV achieved SVR12.

1.2.2.3.3. Study GS-US-334-0108 (FUSION)

This ongoing Phase 3, randomized, double-blind, multicenter study assessed the efficacy and safety of 12 or 16 weeks of SOF+RBV treatment in subjects with chronic genotype 2 or 3 HCV infection who had failed prior treatment with an interferon-based regimen. Eligible subjects were randomized in a 1:1 ratio to 12 or 16 weeks of treatment with SOF (400 mg/day) plus RBV (1000 to 1200 mg/day).

1.2.2.3.3.1. Study GS-US-334-0108 (FUSION) Preliminary Safety Data

Treatment with SOF+RBV for 12 or 16 weeks was generally well tolerated in this study, with no deaths, no discontinuations during SOF+RBV treatment, and few SAEs or Grade 3 or 4 AEs or laboratory abnormalities. Extending treatment duration to 16 weeks did not alter the safety profile of the regimen in terms of overall frequency or severity of AEs or laboratory abnormalities. The safety profile of SOF+RBV treatment was similar to the expected safety profile of RBV treatment.

The most frequently reported overall AEs in both treatment groups were fatigue, headache, nausea, and insomnia. Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity.

Most laboratory abnormalities were Grade 1 or Grade 2 in severity.

1.2.2.3.3.2. Study GS-US-334-0108 (FUSION) Preliminary Efficacy Data

A total of 50% of subjects (50/100) in the SOF+RBV 12-week group and 73% of subjects (69/95) in the SOF+RBV 16-week group achieved SVR12. The study met its primary endpoint of superiority over an historical control rate of 25% ($p < 0.001$). Treatment with SOF+RBV for 16 weeks resulted in higher SVR12 rates compared with the shorter treatment duration of 12 weeks. This difference was primarily a result of a lower response rate in subjects with genotype 3 HCV infection receiving 12 weeks of treatment. Among the 34% of FUSION participants who had compensated cirrhosis at baseline, 31% achieved SVR12 in the 12-week arm, and 66% achieved SVR12 in the 16-week arm.

Subjects with genotype 2 HCV infection had higher SVR12 rates than subjects with genotype 3 HCV infection in both the SOF+RBV 12-week group and the SOF+RBV 16-week group. Table 1-4 presents SVR12 by HCV genotype. In both treatment groups, relapse accounted for all virologic failures.

Table 1-4. GS-US-334-0108: Number (Percentage) of Subjects with SVR12 by Genotype (Full Analysis Set)

	SOF+RBV 12 Weeks + Placebo 4 Weeks Genotype 2 (N = 36)	SOF+RBV 16 Weeks Genotype 2 (N = 32)	SOF+RBV 12 Weeks + Placebo 4 Weeks Genotype 3 (N = 64)	SOF+RBV 16 Weeks Genotype 3 (N = 63)
SVR12	31/36 (86%)	30/32 (94%)	19/64 (30%)	39/63 (62%)

1.2.2.3.4. Study GS-US-334-0110 (NEUTRINO)

Treatment-naïve subjects with genotype 1, 4, 5, or 6 HCV infection (n= 327) were treated for 12 weeks with sofosbuvir (400 mg/day) plus RBV (1000 or 1200 mg/day) and Peg-IFNα (180 µg/week) in this Phase 3, open-label study.

1.2.2.3.4.1. Study GS-US-334-0110 (NEUTRINO) Preliminary Safety Results

Sofosbuvir was generally well tolerated in this study. The safety profile of SOF+Peg-IFNα+RBV treatment was similar to the expected safety profile of Peg-IFNα+RBV treatment. Five subjects (1.5%) had AEs that led to treatment discontinuation. Anemia was the only AE that led to discontinuation or all study treatment for more than 1 subject (2 subjects, 0.6%).

The most frequently reported AEs and treatment-related AEs were fatigue, headache and nausea. Most AEs were either Grade 1 or Grade 2 in severity. Approximately 15% of subjects experienced a Grade 3 AE; the most frequent Grade 3 AEs that occurred in ≥ 5 subjects were neutropenia, anemia, fatigue, and headache. No Grade 4 AEs were reported. SAEs were infrequently reported (1%) and no deaths occurred.

1.2.2.3.4.2. Study GS-US-334-0110 (NEUTRINO) Preliminary Efficacy Results

Twelve weeks of treatment with SOF+Peg-IFNα+RBV resulted in a high SVR12 rate of 90% in treatment-naive subjects with chronic genotype 1, 4, 5, or 6 HCV infections. Among genotype 1 subjects, 89% achieved SVR12. Of the 35 subjects with genotypes 4, 5, or 6, 97% achieved SVR12. Seventeen percent of subjects had compensated cirrhosis; 80% of these subjects achieved SVR12. The study met its primary endpoint of superiority over an historical SVR rate of 60% ($p < 0.001$). Relapse accounted for all virologic failures.

1.2.2.4. Safety Evaluation of SOF in Combination with RBV or Peg-IFNα and RBV

SOF 400 mg QD administered for up to 24 weeks has been well tolerated in studies to date with the observed AEs similar to those expected for the drugs with which it is coadministered - RBV or Peg-IFNα+RBV. As such, decreased hemoglobin is the most frequent laboratory abnormality when coadministered with RBV and with Peg-IFNα+RBV. Rates of decreased hemoglobin across the Phase 3 studies are described in Table 1-5.

Table 1-5. Pooled Phase 3 Studies: Subjects with Post-Baseline Hemoglobin < 10 g/dL and < 8.5 g/dL (Safety Analysis Set)

	Genotype 2, 3				Genotype 1, 4, 5, 6
	Placebo	SOF+RBV 12 weeks	SOF+RBV 16 weeks	Peg-IFNα+RBV 24 weeks	SOF+Peg-IFNα+RBV 12 weeks
	US-GS-334-0107 (N=71)	P7977-1231 US-GS-334-0107 US-334-0108 (N=566)	US-GS-334-0108 (N=98)	P7977-1231 (N=243)	US-GS-334-0110 (N=327)
Number of subjects with any post-baseline Hb value	71	563	98	242	327
Number (%) of subjects with any post-baseline Hb value < 10 g/dL	0	48 (9%)	5 (5%)	35 (15%)	74 (23%)
Number (%) of subjects with any post-baseline Hb value < 8.5 g/dL	0	5 (1%)	0	4 (2%)	8 (2%)

1.2.3. Summary of Additional Clinical Experience with Sofosbuvir and Ledipasvir

1.2.3.1. Clinical Pharmacology Studies

1.2.3.1.1. GS-US-334-0111 Pharmacokinetic Bridging Study in Japanese Subjects

To support the conduct of clinical studies in Japan a PK bridging study was conducted in accordance with ICHE5 to compare the safety, tolerability and PK profile in Japanese and Caucasian subjects following single-dose administration of SOF at the 200 mg, 400 mg (the intended therapeutic dose) and 800 mg dose levels. This study also evaluated the pharmacokinetic parameters of the 400 mg dose of SOF and the 90 mg dose of LDV administered as a single dose of the SOF/LDV FDC. This study was conducted in the United States.

1.2.3.1.1.1. GS-US-334-0111 Study Design

The study enrolled Japanese and Caucasian subjects with an approximately even distribution of healthy males and healthy, non-pregnant, non-lactating females between 18–45 years, inclusive, with a body mass index (BMI) $18 \leq BMI \leq 30$, who had either a normal 12-lead electrocardiogram (ECG) or one with abnormalities that were considered clinically

insignificant by the Investigator, normal renal function, no significant medical history, and were in good general health as determined by the investigator at screening. Japanese subjects had to be of first generation. Subjects must have been born in Japan, not lived outside Japan > 10 years, and could trace maternal and paternal Japanese ancestry of parents and grandparents. Lifestyle, including diet, has not significantly changed since leaving Japan. To be enrolled in the study Caucasian subjects must not have been of Japanese or Asian descent; those with parents or grandparents born in Japan or in any Asian country were excluded. Following completion of screening and baseline procedures, eligible subjects received one dose of study treatment on Day 1 corresponding to their assigned group. Each group comprised of 8 Japanese and 8 Caucasian subjects and received SOF at either the 200 mg, 400 mg or 800 mg dose levels (Groups 1-3), or 400 mg SOF + 90 mg LDV administered as a single dose of the SOF/LDV FDC (Group 4). Vital signs (heart rate, blood pressure) and a 12-lead ECG were performed at Screening, Day 0, Day 1 to 5 (Groups 1-3) or Day 7 (Group 4), or Early Termination visit (if applicable). Vital signs were also performed at the follow up visit. Assessment of adverse events and concomitant medications occurred at screening and daily throughout the study. Plasma and urine samples were collected at selected time points to assess the PK of SOF, GS-566500, GS-331007, and LDV.

1.2.3.1.1.2. GS-US-334-0111 Study Results

Preliminary pharmacokinetic (plasma and urine) results are available for all subjects in Table 1-6**.** As seen below, the geometric-least squares means ratios (GMRs) and associated 90% confidence intervals (CIs) for SOF, GS-566500, GS-331007, and LDV exposure parameters (AUC_{inf}, AUC_{last}, and C_{max}) are similar in the Caucasian and Japanese subjects.

Table 1-6. GS-US-334-0111 Geometric Least-Squares Mean Ratios (90% Confidence Intervals) for Sofosbuvir, GS-566500, GS-331007, and Ledipasvir Primary PK Parameters in Japanese versus Caucasian Subjects

	SOF 200 mg % GLSM Ratio (90% CI)	SOF 400 mg % GLSM Ratio (90% CI)	SOF 800 mg % GLSM Ratio (90% CI)	SOF/LDV FDC (400 mg/90 mg) % GLSM Ratio (90% CI)
SOF PK Parameter				
AUC_{last} (ng•h/mL)	97.02 (63.62, 147.96)	122.62 (92.54, 162.47)	106.20 (82.63, 136.49)	90.52 (54.44, 150.50)
AUC_{inf} (ng•h/mL)	97.30 (64.77, 146.16)	121.98 (92.30, 161.20)	106.27 (82.84, 136.33)	90.77 (54.90, 150.07)
C_{max} (ng/mL)	101.56 (62.88, 164.02)	107.05 (76.31, 150.18)	96.37 (62.23, 149.23)	93.82 (64.53, 136.42)
GS-566500 PK Parameter				
AUC_{last} (ng•h/mL)	158.37 (119.80, 209.34)	149.64 (117.13, 191.17)	125.17 (103.74, 151.03)	114.13 (78.15, 166.67)
AUC_{inf} (ng•h/mL)	153.51 (117.65, 200.30)	147.47 (116.45, 186.74)	124.39 (103.30, 149.79)	113.27 (78.24, 163.98)
C_{max} (ng/mL)	154.48 (116.12, 205.51)	138.62 (108.12, 177.72)	117.59 (98.72, 140.06)	130.16 (93.88, 180.44)
GS-331007 PK Parameter				
AUC_{last} (ng•h/mL)	80.29 (64.62, 99.77)	94.44 (78.30, 113.90)	82.32 (71.98, 94.16)	85.63 (63.56, 115.36)
AUC_{inf} (ng•h/mL)	82.37 (67.59, 100.36)	95.93 (80.14, 114.82)	83.68 (74.25, 94.30)	85.40 (64.04, 113.89)
C_{max} (ng/mL)	72.72 (57.86, 91.40)	113.48 (91.12, 141.32)	102.44 (73.52, 142.73)	94.34 (68.03, 130.82)
LDV PK Parameter				
AUC_{last} (ng•h/mL)	—	—	—	106.07 (68.95, 163.18)
AUC_{inf} (ng•h/mL)	—	—	—	106.66 (69.13, 164.59)
C_{max} (ng/mL)	—	—	—	125.63 (83.83, 188.26)

1.2.3.1.1.3. GS-US-334-0111 Study Conclusions

SOF and SOF/LDV FDC were well tolerated in this study. No clinically significant differences in the PK of SOF, its metabolites GS-566500 and GS-331007, or LDV were observed between Japanese and Caucasian subjects, supporting the use of SOF 400 mg or SOF/LDV FDC (400 mg/90 mg) in Japanese and non-Japanese subjects.

1.2.3.2. Phase 2 Studies with SOF+LDV and SOF/LDV FDC

1.2.3.2.1. Study P7977-0523 ELECTRON

ELECTRON is an ongoing 6-part, Phase 2 study comprising 22 treatment arms. Of particular importance to the efficacy and/or safety of the SOF/LDV FDC regimen the proposed for use in GS-US-337-0131 in Korea and Taiwan are treatment Arms 12-13 (Part 4) exploring SOF+LDV+RBV and Arms 16-21 (Part 6), exploring SOF/LDV±RBV in various patient populations:

- Arm 12: GT1, prior null responder, non-cirrhotics (12 weeks SOF+LDV+RBV; n=9)
- Arm 13: GT1, treatment-naïve, non-cirrhotics (12 weeks SOF+LDV+RBV; n=25)
- Arm 16: GT1, prior null responder, F4 cirrhotics (12 weeks SOF/LDV FDC; n=10)
- Arm 17: GT1, prior null responder, F4 cirrhotics (12 weeks SOF/LDV FDC+RBV; n=10)
- Arm 18: GT2/3: treatment-naïve, non-cirrhotics (12 weeks SOF/LDV FDC; n=10)
- Arm 20: GT1: Hemophiliacs (12 weeks SOF/LDV FDC+RBV =13)
- Arm 21: GT1, treatment-naïve, non-cirrhotic (6 weeks SOF/LDV FDC+RBV; n=25)

1.2.3.2.1.1. P7977-0523 (ELECTRON) Preliminary Safety

SOF+LDV+RBV and SOF/LDV ± RBV are generally well tolerated. One subject in the SOF+LDV+RBV groups discontinued treatment early due to a serious adverse event (colonic fistula) considered by the investigator not to be related to study drugs. No other serious adverse events have been reported. To date, no subjects receiving SOF/LDV ± RBV have discontinued treatment early. The most common adverse events were headache (44%), fatigue (23%), and nausea (22%), when safety data from Arms 12, 13, and 16-21 were pooled. No safety signal associated with treatment with SOF or LDV either separately or as a FDC has been identified.

1.2.3.2.1.2. P7977-0523 (ELECTRON) Preliminary Pharmacokinetic Data

An intensive PK substudy was conducted at Week 2 to examine the PK of SOF, GS-566500, GS-331007 and LDV in subjects receiving SOF+LDV+RBV (all subjects in Arms 12 and

13), and SOF/LDV FDC ± RBV who do not have hemophilia (target: up to 10 subjects in Arms 16-19, each, and up to 15 subjects in Arms 21-22).

Preliminary PK data are available for all subjects in Arms 12 (N = 9) and 13 (N = 25), and 21 (N = 15), and for the majority of subjects in Arms 16-17 (SOF: N = 11 out of 14, LDV: N = 12 out of 14). Preliminary PK data are shown in Table 1-7.

Similar plasma exposures of SOF, GS-566500, GS-331007 and LDV were achieved in all treatment groups, irrespective of presence or absence of cirrhosis.

Table 1-7. Study P7977-0523 (ELECTRON): SOF, GS-566500, GS-331007 and LDV PK Parameters Following Administration of SOF 400 mg + LDV 90 mg + RBV or SOF 400 mg/LDV 90 mg FDC ± RBV (Preliminary Data)

PK Parameter Mean (%CV)	Arm 12 GT1 SOF+LDV+RBV Prior Nulls	Arm 13 GT1 TN SOF+LDV+RBV	Arms 16-17 GT 1 FDC± RBV F4 cirrhotic (pooled)	Arm 21 GT 1 TN FDC
SOF	**N=9**	**N=25**	**N = 11**	**N = 15**
AUC_{tau} (hr·ng/mL)	1990 (66.0)	2220 (55.3)	2300 (28.8)*	1860 (48.5)**
C_{max} (ng/mL)	1040 (108)	1100 (70.7)	1120 (64.5)	1190 (53.0)
C_{tau} (ng/mL)	BLQ	BLQ	BLQ	BLQ
GS-566500	**N=9**	**N=25**	**N = 11**	**N = 15**
AUC_{tau} (hr·ng/mL)	2400 (22.2)	2690 (28.0)	3370 (23.7)	2530 (37.3)
C_{max} (ng/mL)	488 (25.0)	569 (29.1)	680 (21.5)	519 (42.8)
C_{tau} (ng/mL)	BLQ	BLQ	BLQ	BLQ
GS-331007	**N=9**	**N=25**	**N = 11**	**N = 15**
AUC_{tau} (hr·ng/mL)	8110 (16.1)	11200 (28.3)	11200 (36.0)	10500 (17.2)
C_{max} (ng/mL)	630 (17.9)	757 (21.9)	805 (31.1)	768 (19.0)
C_{tau} (ng/mL)	201 (16.6)	306 (34.4)	284 (44.6)	286 (26.2)
LDV	**N=9**	**N=25**	**N=12**	**N = 15**
AUC_{tau} (hr·ng/mL)	6420 (44.1)	7030 (41.6)	8190 (58.7)	7910 (45.4)
C_{max} (ng/mL)	367 (37.3)	386 (38.1)	437 (54.7)	434 (42.0)
C_{tau} (ng/mL)	188 (54.7)	216 (46.4)	261 (59.0)	252 (51.7)

Preliminary data reported to 3 significant figures; * N = 10; **N=14; BLQ: below the limit of quantitation

1.2.3.2.1.3. P7977-0523 (ELECTRON) Preliminary Efficacy

Virologic response data for all genotype 1 HCV-infected subjects from ELECTRON Arm 12 (SOF+LDV+RBV for 12 weeks in null responders; n=9) and Arm 13 (SOF+LDV+RBV for 12 weeks in GT1 treatment-naive subjects; n = 25) are presented in Table 1-8.

All subjects (100%) in Arms 12 and 13, irrespective of HCV genotype (1A or 1B) and IL28B allele (CC, CT, or TT) had HCV RNA < LLOQ at post treatment Weeks 2, 4, 8, and 12; no relapses were reported.

This contrasts with ELECTRON Arm 7 (SOF+RBV for 12 weeks in genotype 1 HCV-infected null responders) and Arm 8 (SOF+RBV for 12 weeks in genotype 1 treatment-naive subjects), where 10% and 88% of subjects, respectively, achieved SVR12. The addition of LDV increased the SVR12 rate in these populations to 100%, demonstrating the contribution of LDV to a SOF-containing regimen.

Table 1-8. Study P7977-0523 (ELECTRON): Arm 12 and Arm 13: SVR Data

Arm No.	Duration	N (GT-1)	RVR % (n)	SVR4 % (n)	SVR8 % (n)	SVR12 % (n)	Relapse % (n)	BT % (n)	LTFU % (n)
Arm 12 Nulls	12 wks	9 (9/9)	88.9 (8/9)	100 (9/9)	100 (9/9)	100 (9/9)	0 (0/9)	0 (0)	0 (0)
Arm 13 TN	12 wks	25 (25/25)	100 (25/25)	100 (25/25)	100 (25/25)	100 (25/25)	0 (0/25)	0 (0)	0 (0)

BT: breakthrough; LTFU: lost to follow up; TN = treatment-naïve

Available SVR data for all subjects enrolled in ELECTRON Arm 21 [SOF/LDV FDC tablet once daily + weight-based RBV for 6 weeks in treatment-naive genotype 1 HCV-infected subjects; n = 25] are tabulated below (Table 1-9). Twenty of 25 subjects achieved SVR8, while 5 subjects relapsed.

Table 1-9. Study P7977-0523 (ELECTRON): Arm 21 (FDC+RBV): Available SVR Data

Arm No.	Duration	N (GT1)	RVR % (n)	SVR4 % (n)	SVR8 % (n)	SVR12 % (n)	Relapse % (n)	BT % (n)	LTFU % (n)
Arm 21 GT1 TN	6 wks	25 (25/25)	100 (25/25)	88 (22/25)	76 (19/25)	67 (16/24)*	32 (8/25)	0 (0)	0 (0)

BT: breakthrough; LTFU: lost to follow up
*Data are presented as observed; data for one subject is pending

The full-length NS5A region was analyzed at baseline for all 34 subjects enrolled in Arms 12 and 13 (27 genotype 1a and 7 genotype 1b) by standard population sequencing. Overall, 4/34 (11%) subjects had LDV RAVs present at baseline (Table 1-10). 3/4 subjects with baseline NS5A RAVs were genotype 1a with M28T, Q30H, or L31M variants detected. A single genotype 1b subject had a detectable LDV RAV (L31M) at baseline. Previous in vitro data demonstrates that these NS5A variants individually confer moderate to high level reductions in susceptibility to LDV in vitro (25- to 140-fold). No virologic breakthrough or relapse was observed in these subjects or any other subjects in these treatment arms, as all achieved SVR12. This indicates that the presence of observed NS5A RAVs does not preclude the ability of subjects to achieve SVR12 on SOF+ LDV+RBV treatment. Resistance analysis of other arms containing SOF and LDV is pending.

Table 1-10. Study P7977-0523 (ELECTRON): Subjects with Baseline Ledipasvir RAVs in NS5A in Arms 12 and 13

Subject ID	Genotype	Treatment Group	NS5A RAV	NS5A Single Mutant Fold-change in LDV EC50	SVR 4 Result	SVR 8 Result	SVR 12 Result
PPD	1b	Arm 13: 12 W SOF+LDV+RBV (GT1 TN)	L31M	L31M: 140	SVR	SVR	SVR
PPD	1a	Arm 13: 12 W SOF+LDV+RBV (GT1 TN)	Q30H	Q30H: 73	SVR	SVR	SVR
PPD	1a	Arm 13: 12 W SOF+LDV+RBV (GT1 TN)	M28T	M28T: 25	SVR	SVR	SVR
PPD	1a	Arm 12: 12 W SOF+LDV+RBV (GT1 Nulls)	L31L/M	L31M: 140	SVR	SVR	SVR

1.2.3.2.2. Study GS-US-337-0118 LONESTAR

LONESTAR is a single center Phase 2 study evaluating SOF/LDV±RBV in treatment-naive and treatment-experienced genotype 1 HCV-infected subjects. In summary, subjects were enrolled into 2 cohorts as follows:

- Cohort 1: Treatment-naive, non-cirrhotic subjects received SOF/LDV±RBV for 8 weeks or SOF/LDV for 12 weeks (Groups 1, 2 and 3; n ~ 20/group)
  - Group 1 (n=20): SOF/LDV FDC once daily for 8 weeks

— Group 2 (n=20): SOF/LDV FDC once daily + RBV (1000 or 1200 mg/day divided BID) for 8 weeks

— Group 3 (n=20): SOF/LDV FDC once daily for 12 weeks

- Cohort 2: Treatment-experienced, PI-failure subjects, of whom 50% were cirrhotic, received SOF/LDV±RBV for 12 weeks (Groups 4 and 5; n ~ 20/group)

— Group 4 (n=20): SOF/LDV FDC once daily for 12 weeks

— Group 5 (n=20): SOF/LDV FDC once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

In Cohort 1, (Groups 1-3) randomization was stratified by genotype (1a or 1b). In Cohort 2 (Groups 4-5) randomization was stratified by genotype (1a or 1b) and the presence or absence of cirrhosis.

All subjects in this study have completed treatment in Groups 1 to 5. Preliminary safety, PK, and efficacy data are presented below.

1.2.3.2.2.1. Study GS-US-337-0118 (LONESTAR): Preliminary Safety

Based on a preliminary review of the data, SOF/LDV FDC was well tolerated in this study. Adverse events were generally mild or moderate. Three SAEs were reported, none of which was considered related to the study drugs. There were no discontinuations due to adverse events. The most frequent adverse events were nausea (n = 8, 8%), anemia (n = 6, 6%), and headache (n = 6, 6%). To date, no safety signal associated with SOF/LDV FDC has been identified.

1.2.3.2.2.2. Study GS-US-337-0118 (LONESTAR): Preliminary Pharmacokinetic Data

PPD

Preliminary pharmacokinetic data are shown in Table 1-11.

Preliminary PK data showed similar SOF, GS-566500 and GS-331007 systemic exposures in subjects who were treatment-naive and those who were PI failures with or without cirrhosis. LDV mean exposure parameters (AUC_{tau}, C_{max} and C_{tau}) were similar in PI failure subjects with or without cirrhosis and overall modestly (~ 30-40%) lower than LDV plasma exposures in non-cirrhotic treatment-naive subjects.

Table 1-11. Study GS-US-337-0118 (LONESTAR): SOF, GS-566500, GS-331007 and LDV PK Parameters Following Administration of SOF/LDV (400 mg/90 mg) ± RBV (Preliminary Data)

PK Parameter Mean (%CV)	Groups 1-3 GT1 TN FDC± RBV (pooled)	Groups 4-5 GT1 PI Failure FDC± RBV without Cirrhosis (pooled)	Groups 4-5 GT1 PI Failures FDC± RBV with Cirrhosis (pooled)
SOF	**N=48**	**N=14**	**N=21**
AUC_{tau} (hr·ng/mL)	2260 (47.8)†	2460 (42.6)*	2440 (39.3)
C_{max} (ng/mL)	1280 (60.1)	1310 (48.5)	1520 (46.4)
C_{tau} (ng/mL)	BLQ	BLQ	BLQ
GS-566500	**N=47**	**N=14**	**N=21**
AUC_{tau} (hr·ng/mL)	3420 (27.5)	4110 (37.4)	4240 (31.8)
C_{max} (ng/mL)	689 (34.2)	734 (37.1)	846 (33.2)
C_{tau} (ng/mL)	15.1 (30.5) ††	13.5 (29.5)**	13.3 (25.5)**
GS-331007	**N=47**	**N=14**	**N=14**
AUC_{tau} (hr·ng/mL)	12600 (34.6)	11600 (39.3)	11900 (36.6)
C_{max} (ng/mL)	937 (34.8)	801 (36.2)	885 (35.0)
C_{tau} (ng/mL)	336 (46.7)	327 (48.3)	301 (45.2)
LDV	**N=47**	**N= 14**	**N= 21**
AUC_{tau} (hr·ng/mL)	9470 (51.8)	6210 (44.9)	6510 (65.1)
C_{max} (ng/mL)	504 (43.9)	356 (37.4)	364 (52.7)
C_{tau} (ng/mL)	344 (63.1)	202 (57.8)	220 (72.8)

Preliminary data reported to 3 significant figures; † N =45; †† N=4; *N=13; ** N=3; BLQ: below the limit of quantitation

1.2.3.2.2.3. Study GS-US-337-0118 (LONESTAR): Preliminary Efficacy

Virologic response data for all subjects enrolled in LONESTAR is presented in Table 1-12.

All subjects in Groups 1-3 were treatment-naive and non-cirrhotic. In Group 1 (SOF/LDV FDC for 8 weeks), 95% of subjects, irrespective of HCV genotype (1A or 1B) and IL28B allele (CC, CT, or TT), had HCV RNA < LLOQ at post-treatment Week 12. A single subject relapsed at the post-treatment Week 8 assessment. In Group 2, all subjects (100%) had HCV RNA < LLOQ at post-treatment Weeks 4, 8, and 12. In Group 2, SVR4 and SVR8, were initially reported as 95%, due to Subject PPD then being unavailable for these visits. Subsequently, this subject was found to be < LLOQ, target not detected (TND) at post-treatment week 12 (SVR12), and therefore SVR4 and SVR8 data has been imputed. In Group 3, all subjects (100%) had HCV RNA < LLOQ at post-treatment Week 8. Of note,

2 subjects with missing data at post-treatment Week 4, had HCV RNA < LLOQ at post-treatment week 8, and thus SVR4 data was imputed for these subjects.

All subjects in Groups 4 and 5 previously failed treatment with a PI+ Peg-IFNα+RBV regimen; in each group, approximately 50% of subjects have cirrhosis. In Group 4, 95% were HCV RNA < LLOQ at post-treatment Week 4. In Group 5, 95% were HCV RNA < LLOQ at post-treatment Week 4 (one subject in Group 5 experienced SAEs of anemia and suicidal ideation and has not yet returned during the post-treatment period).

Of the 22 cirrhotic subjects in Groups 4 and 5, one subject (Group 4) experienced virologic failure, and one subject (Group 5) has not yet returned for any post-treatment follow up visits.

Table 1-12. Study GS-US-337-0118 (LONESTAR): Groups 1, 2, 3, 4 and 5 SVR Data

Grp. No./ Population/ Regimen	Duration	N (GT1)	RVR % (n)	SVR4 % (n)	SVR8 % (n)	SVR12 % (n)	Relapse % (n)	BT % (n)	LTFU % (n)
1 GT1 TN SOF/LDV	8 wks	20 (20)	100 (20/20)	100 (20/20)	95 (19/20)	95 919/20)	5 (1/20)	0 (0)	0 (0)
2 GT1 TN SOF/LDV+RBV	8 wks	21 (21)	100 (21/21)	100 (21/21)*	100 (21/21)	100 (21/21)	0 (0/21)	0 (0)	0 (0)
3 GT1 TN SOF/LDV	12 wks	19 (19)	100 (19/19)	100 (19/19)	100 (19/19)	100 (16/16)**	0 (0/19)	0 (0)	0 (0)
4 GT1 PI Failures SOF/LDV	12 wks	19 (19)	100 (19/19)	95 (18/19)	TBD	TBD	5 (1/19)	0 (0)	0 (0)
5 GT1 TE SOF/LDV+RBV	12 wks	21 (21)	100 (21/21)	95 (20/21)***	TBD	TBD	0 (0/21)	0 (0)	0 (0)

BT = breakthrough; LTFU = lost to follow up; GT = genotype; TN = treatment-naive; TE = treatment-experienced

* Previously reported as 95%, due to Subject PPD being unavailable for these visits. Subsequently, this subject was found to be < LLOQ, TND at post-treatment week 12 (SVR12), and therefore SVR4 and SVR8 data has been imputed.

** Three subjects are pending at this time point. Data are presented as observed

*** Subject number PPD experienced SAEs of Anemia and Suicidal Ideation and has not yet returned during the post-treatment period.

1.2.3.2.2.4. Study GS-US-337-0118 (LONESTAR): Preliminary Resistance Analysis

The full-length NS5A region was analyzed at baseline for all 100 subjects (76 genotype 1a and 24 genotype 1b by LiPA) by deep sequencing. Baseline NS5A resistance associated variants (RAVs) were detected in a total of 9/100 (9%) subjects. Eight genotype 1a subjects and 1 genotype 1b subject had at least one LDV RAVs present at baseline, at levels ranging from 1.3% to 99.9%. Eight genotype 1a subjects with baseline NS5A RAVs had M28T, Q30L, Q30H, Q30R, L31M, Y93C, or Y93H variants detected while one genotype 1b subject had Y93H RAV. All these mutants, except Q30L, have been shown to confer significant reductions in susceptibility to LDV in vitro (Table 1-13). Of these 9 subjects, 2/9 subjects experienced virologic relapse. One subject (subject PPD had L31M present at 21.45% prior to treatment and experienced virologic relapse following 8 weeks of FDC treatment. Another subject (subject PPD had >99% Q30H and >99% of Y93H (double mutants Q30H+Y93H likely) at baseline and experienced virologic relapse following 12 weeks of FDC treatment. In contrast, the remaining 7 out of 9 subjects achieved SVR4, or SVR12 (n = 5 on FDC and n=2 on FDC+RBV) despite the presence of baseline RAVs that confer a high level of reduced susceptibility to LDV. These data indicate that the presence of NS5A RAVs at baseline do not preclude the ability of subjects treated with SOF+LDV or SOF+LDV+RBV regimens from achieving a sustained virologic response.

Table 1-13. Study GS-US-337-0118 (LONESTAR): Subjects with Baseline Ledipasvir RAVs

Subject ID	Genotype	Treatment Group	NS5A Mutant (%)	NS5A Single Mutant Fold-change in LDV EC50	SVR 4 Result	SVR 8 Result	SVR 12 Result
PPD	1a	Group 1	L31M (21.45%)	L31M: 140	Relapse		
PPD	1a	Group 1	L31M (91.54%), Q30H (3.28%)	L31M: 140 Q30H:73	SVR	SVR	SVR
PPD	1b	Group 2	Y93H (43.51%)	Y93H: 3310	SVR	SVR	SVR
PPD	1a	Group 3	Y93C (14.05%)	Y93C: 2531	SVR	SVR	N/A
PPD	1a	Group 3	Q30R (1.34%)	Q30R: 170	SVR	SVR	N/A
PPD	1a	Group 3	Q30H (95.00%)	Q30H: 73	SVR	SVR	N/A
PPD	1a	Group 4	Q30H (99.42%), Y93H (99.89%)	Q30H: 73 Y93H: 3029	Relapse		
PPD	1a	Group 5	M28T (53.84%), Q30R (96.65%)	M28T: 25 Q30R: 170	SVR	N/A	N/A
PPD	1a	Group 5	Q30L (98.83%), Y93H (99.56%)	Q30L: 4 Y93H: 3029	SVR	N/A	N/A

1.2.3.3. Phase 3 Studies with SOF/LDV FDC

1.2.3.3.1. GS-US-337-0102 (ION-1)

Study GS-US-337-0102 is a Phase 3, multicenter, randomized, open-label study investigating efficacy and safety of SOF/LDV ± RBV for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection. 207 subjects were enrolled in Part A. The study is ongoing.

1.2.3.3.2. GS-US-337-0109 (ION-2)

Study GS-US-337-0109 is a Phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of SOF/LDV FDC ± RBV for 12 and 24 weeks in treatment-experienced subjects with chronic genotype 1 HCV infection. Enrollment is complete.

1.2.3.3.3. GS-US-337-0108 (ION-3)

Study GS-US-337-0108 is a Phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of SOF/LDV FDC±RBV for 8 weeks and SOF/LDV FDC for 12 weeks in treatment-naive subjects with chronic genotype 1 HCV infection. Enrollment is ongoing.

1.2.4. Summary of Additional Clinical Experience with LDV

The adult safety database for LDV includes data for over 500 healthy volunteers and over 1000 chronic HCV infected subjects exposed to at least one dose of LDV in the 6 ongoing Phase 2 studies. Over 700 chronic HCV infected subjects have been exposed to ≥ 12 weeks of LDV containing regimens.

1.2.4.1. Ongoing Clinical Pharmacology Studies

1.2.4.1.1. Study GS-US-248-0117

GS-US-248-0117 was an open-label, Phase 1, multiple-dose, 2-cohort, pharmacokinetic (PK) study in subjects with Child-Pugh-Turcotte (CPT) B (moderate) hepatic impairment and matched healthy subjects. The PK safety and tolerability of dual or triple combination treatments of LDV 30 mg once daily plus GS-9451 (Gilead HCV NS3/4A protease inhibitor) 200 mg once daily (Cohort 1) and LDV 30 mg once daily plus GS-9451 200 mg once daily plus tegobuvir (TGV) 30 mg twice daily (Cohort 2), administered for 12 days each, were evaluated. Fifty subjects (n = 20 in Cohort 1; n = 30 Cohort 2) were enrolled and received study drugs.

Table 1-14 presents the steady state PK parameters and statistical comparisons of LDV following administration of LDV+GS-9451± TGV in subjects with moderate hepatic impairment and in subjects with normal hepatic function. Ledipasvir plasma PK parameters (AUC_{tau}, C_{max} and C_{tau}) were comparable in subjects with moderate hepatic impairment and matched controls who received a combination of LDV + GS-9451. Ledipasvir plasma exposure was modestly lower (~34-36%) in subjects with moderate hepatic impairment, as compared to matched controls upon administration of LDV + GS-9451 +TGV. These data indicate lack of an increase in LDV plasma exposure in subjects with moderate hepatic impairment relative to subjects with normal hepatic function.

The mean % free fraction for LDV, assessed at the time of maximum concentration (T_{max}) and at the end of the dosing interval (T_{last}), was similar in subjects with moderate hepatic impairment and those with normal hepatic function, demonstrating lack of an effect of hepatic impairment on protein binding (analysis done on Cohort 2).

Table 1-14. GS-US-248-0117: LDV Steady-State Pharmacokinetic Parameters and Statistical Comparisons in Subjects with Moderate Hepatic Impairment and Matched Controls with Normal Hepatic Function Following Administration of LDV+GS-9451±TGV

LDV PK Parameters Mean (%CV)	Reference Treatment: Normal Matched Control Group	Test Treatment: Moderate Hepatic Impairment Group	GLSM Ratio (%) (90% CI) Test/Reference
Cohort 1 (N = 9)			
AUC_{tau} (ng*hr/ml)	3405.0 (50.0)	3601.1 (52.9)	100.22 (63.42, 158.40)
C_{max} (ng/ml)	208.6 (46.1)	197.9 (47.3)	90.80 (59.30, 139.04)
C_{tau} (ng/ml)	120.6 (56.4)	138.4 (59.5)	105.39 (62.21, 178.53)
Cohort 2 (N = 14)			
AUC_{tau} (ng*hr/ml)	4756.0 (41.8)	2994.8 (42.4)	63.86 (47.36, 86.11)
C_{max} (ng/ml)	271.7 (41.8)	169.7 (39.9)	63.80 (47.09, 86.45)
C_{tau} (ng/ml)	177.7 (46.0)	113.5 (41.5)	66.10 (48.96, 89.26)

A review of the safety data showed LDV was generally well tolerated when co-administered with GS-9451 and with or without TGV to CPT B (moderate) hepatic impaired subjects and matched healthy subjects. No SAEs, Grade 3 or 4 AEs, deaths, or withdrawal due to AEs were reported in the study. The frequency of treatment-emergent AEs reported in the CPT B (moderate) hepatic impaired subjects were similar to those reported in matched healthy subjects. The most frequently reported AEs (in >2 subjects) overall were diarrhea, abdominal distension, fatigue, muscle tightness, headache, and eczema. Treatment-emergent AEs were mostly mild in severity except for a moderate AE of muscle tightness reported in 2 healthy subjects during LDV+GS-9451+TGV administration. A Grade 3 hyperbilirubinemia was noted in 2 moderately hepatic impaired subjects co-administered LDV and GS-9451, a result consistent with the known inhibition of bilirubin transporters by GS-9451. No other Grade 3 or 4 laboratory abnormality was reported in >1 subject.

Based on these data, dose adjustment of LDV in moderate or mild hepatic impairment is not warranted.

1.2.4.1.2. Study GS-US-248-0125

GS-US-248-0125 was an open-label, Phase 1, cross-over, multiple-dose, multi-cohort study that evaluated the effect and drug interaction potential of a triple combination of DAAs, LDV

90 mg QD +GS-9451 200 mg QD+TGV 30 mg BID, on OATP, BCRP, and Pgp substrates using phenotypic probes in healthy volunteers. In addition, the drug interaction potential of DAAs with Pgp inducers, Pgp inhibitors and mixed OATP/MRP2/Pgp inhibitors was assessed.

Effect of LDV+GS-9451+TGV on OATP, BCRP, Sodium-Taurocholate Cotransporting Polypeptide (NTCP), or Pgp Substrates Using Phenotypic Probes

Administration of LDV+GS-9451+TGV with an OATP substrate pravastatin resulted in a modest increase of ~ 2.7 to 2.8-fold in AUC and C_{max} of the probe drug, as compared to pravastatin administration alone. Pravastatin t1/2 remained similar in both treatments; suggestive of the effect of DAAs on the relative bioavailability and not the systemic clearance of the probe drug. The magnitude of this interaction is comparable to that observed with clarithromycin and is likely caused by the first-pass inhibition of hepatic drug transporters OATP by GS-9451, a moderate/potent inhibitor of OATP1B1/1B3 (AD-169-2275). In accordance with the prescribing information on the use of pravastatin with clarithromycin {18314}, pravastatin dose should be limited to 40 mg once daily with LDV+GS-9451+TGV. Monitoring for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis during co-administration of these agents is recommended.

Coadministration of rosuvastatin and LDV+GS-9451+TGV resulted in increases of ~8- to 9-fold in rosuvastatin AUC and ~18-fold increase in rosuvastatin C_{max}. Considering a substantial increase in rosuvastatin exposure relative to a more modest increase in pravastatin; this interaction is likely mediated by the inhibition of several drug transporters that mediate uptake or efflux of rosuvastatin (i.e. OATP, BCRP and NTCP). These results are also consistent with GS-9451 being is a moderate/potent inhibitor of OATP, a moderate inhibitor of NTCP (AD-169-2275) and BCRP drug transporters (AD-169-2249), and of LDV being a weak to moderate inhibitor of BCRP (AD-256-2109). There were no statistically significant differences in rosuvastatin t1/2 in the two treatments, indicative of the lack of effect of LDV+GS-9451+TGV on the systemic clearance of the probe drug. The magnitude of an increase in rosuvastatin exposure by DAAs in this study is also modestly higher than that observed upon co-administration of rosuvastatin with cyclosporine {21139}. Concurrent administration of rosuvastatin and cyclosporine resulted in ~ 7-fold increase in rosuvastatin AUC and ~11-fold increase in rosuvastatin C_{max}. As such, rosuvastatin should not be co-administered with LDV+GS-9451+TGV.

Modestly higher digoxin (AUC: ~1.3- to 1.6-fold higher; C_{max}: 1.2-fold higher) exposures were observed with DAAs, indicative of intestinal inhibition of Pgp transporters by GS-9451 and/or LDV, consistent with in vitro data that show that both GS-9451 and LDV are weak Pgp inhibitors. These results from this study do not preclude administration of triple DAA combination with Pgp substrates. However, owing to digoxin narrow therapeutic index, an increase in digoxin exposure is considered clinically relevant (exposure increase > 1.25-fold {15555}) and monitoring of subjects for the signs and symptoms of digoxin toxicity is warranted if administered with LDV+GS-9451+TGV.

Effect of Pgp Inducers, Pgp Inhibitors and Mixed OATP/MRP2/Pgp Inhibitors on LDV+GS-9451+TGV and the Effect of LDV+GS-9451+TGV on Cyclosporine

Substantial reductions in the exposure parameters of GS-9451, LDV and TGV were observed upon administration with a Pgp inducer rifampin. GS-9451 AUC and C_{max} were ~ 83% and 67% lower, respectively, with rifampin, as compared to DAAs administration alone. Similarly, LDV AUC was ~ 56% to 59% lower and C_{max} was ~ 35% lower, respectively, whereas TGV AUC was ~ 60% lower and C_{max} was ~25% lower. As such, these DAAs should not be administered with Pgp inducers.

Coadministration of LDV+GS-9451+TGV with verapamil resulted in ~ 2-fold higher AUC and ~ 1.6-fold higher C_{max} of GS-9451, ~ 1.5- 1.7-fold higher AUC of LDV, and 1.3- to 1.4-fold higher AUC of TGV. Ledipasvir and TGV C_{max} remained comparable in both treatments. These increases in DAAs exposure are likely mediated by inhibition of Pgp drug transporters by verapamil. Dose adjustment of GS-9451 when given with Pgp inhibitors is dependent on target clinical exposures. Considering only modest increase in LDV and TGV exposure upon administration with verapamil, these agents may be co-administered with Pgp inhibitors.

Coadministration of DAAs with cyclosporine resulted in ~ 2-fold higher AUC_{tau} and C_{tau}, and ~1.8-fold higher C_{max} of GS-9451. Dose adjustment of GS-9451 when given with cyclosporine is dependent on target clinical exposures. Ledipasvir and TGV primary exposure parameters AUC_{tau}, C_{max}, and C_{tau} and cyclosporine exposure parameters AUCinf, AUClast and C_{max} were comparable in both treatments. The geometric least-squares means ratios for the test versus reference treatments and their associated 90% confidence intervals remained within the predefined lack of interaction bounds of 70% to 143%. As such, LDV or TGV may be coadministered with a mixed OATP/MRP2/Pgp inhibitor cyclosporine.

The combination of LDV+GS-9451+TGV when administered alone or with probe drugs was generally well tolerated. A total of 70 treatment-emergent AEs were reported in 45 subjects. Of those 24, AEs were considered related to any study drug, which includes those considered related to probe drugs alone. The majority of treatment-emergent AEs reported were mild in severity with 12 moderate and 1 severe AE reported. The severe AE of interstitial pneumonitis was reported in a subject in Cohort 2 after completing 10 days of GS-9451+LDV+TGV treatment and 3 days after the subject was co-administered GS-9451+LDV+TGV + digoxin. The event was reported 2 days later as an SAE, when the subject was hospitalized for several days of fever, nausea, vomiting, and weakness. The subject's symptoms and CT scan findings were suggestive of atypical pneumonia. Upon admission to the hospital, the subject was administered broad spectrum antibiotics. The subject's symptoms improved and the subject was discharged from the hospital 12 days later. Due to the inability to identify a community acquired pathogen, the severe AE and SAE were reported as interstitial pneumonitis and considered by the investigator as possibly related to GS-9451, LDV, TGV, and digoxin.

Overall, no clinically significant laboratory abnormalities consistent with drug induced organ toxicity or changes in vital signs or electrocardiogram (ECG) findings reported during LDV+GS-9451+TGV administration alone and when co-administered with the probe drugs were identified. Two subjects in Cohort 4 were withdrawn due to abnormal ECG findings after administration of a single dose of verapamil alone. In the absence of the potential drug-drug interaction data between verapamil and LDV+GS-9451+TGV, the subjects were withdrawn prior to co--administration of verapamil and LDV+GS-9451+TGV. The abnormal ECG findings of atrioventricular block are consistent with the known adverse effects of verapamil administration.

1.2.4.1.3. Study GS-US-169-0105 (Cohort 4)

A single supratherapeutic dose of LDV 360 mg (conventional formulation) was administered to healthy subjects (n=15) under fasted conditions in Cohort 4 of GS-US-169-0105. Preliminary PK data showed that exposures achieved at 360 mg dose were similar to those observed with a 100 mg single dose, suggesting the absorption of LDV (conventional formulation) is solubility limited.

Overall, LDV 360 mg was generally well tolerated. No SAEs, Grade 3 or 4 AEs, deaths, or withdrawals due to AEs were reported during the study. The most frequently reported AE was constipation in two subjects. No clinically significant laboratory abnormalities were observed. No subject had notable changes in mean vital sign parameters during the study, and no vital sign result was recorded as an AE. No subjects had clinically significant ECG results during the study.

1.2.4.1.4. Study GS-US-256-0110 (Amendment 1, cohort 2)

The PK, safety and tolerability of LDV spray-dried solid dispersion formulation, administered at supratherapeutic dose of 120 mg BID for 11 days (21 doses) to healthy volunteers are being evaluated. Fourteen subjects comprised of male and non-pregnant, non-lactating female subjects aged between 18 to 45 years old were enrolled and received study drug. Serial blood samples were collected on Days 1 and 11. Time-matched ECG measurements were obtained in duplicate at Baseline (Day 0) and on Day 11. When LDV was administered at 120 mg BID for 11 days, supratherapeutic exposures were achieved. Consistent with a long LDV half-life ($T_{½}$), substantial LDV accumulation (AUC: AI 8.5, C_{max}: AI 6.2) was observed upon multiple BID dosing (Day 11) relative to the first dose (Day 1). Descriptive comparisons of LDV AUC and C_{max} values at 120 mg versus 30 mg revealed approximately dose proportional increases in exposure, suggestive of near linear PK of the spray-dried formulation over this dose range.

An exploratory PPD

PPD

Based on a preliminary safety data review, LDV was generally well tolerated in this cohort. No SAE, Grade 3 or 4 AEs, or deaths were reported. One subject discontinued treatment early due to streptococcal pharyngitis of moderate severity. No two subjects experienced the same AE. One Grade 3 laboratory abnormality, 3+ blood in the urine, was reported in a 35 year old female. Per the Principle Investigator, this result was non-clinically significant. No subjects had clinically significant ECG results during the study.

1.2.4.1.5. Study GS-US-334-0101

Study GS-US-334-0101 was a Phase 1 study evaluating the potential for drug-drug interaction between SOF and LDV. The study was an open-label fixed-sequence study in healthy volunteers, in which Cohort 1 subjects received single doses of SOF (400 mg, once daily) alone or in combination with multiple doses of LDV (90 mg, spray-dried dispersion, once daily), under fasted conditions.

Preliminary PK results for the combination of SOF with LDV (Cohort 1) are presented below Table 1-15, and demonstrate lack of a clinically significant interaction between SOF and LDV.

Table 1-15. Study GS-US-334-0101: Pharmacokinetic Data for SOF, Metabolites (GS-566500 and GS-331007) and LDV on Administration of Sofosbuvir (SOF) and LDV Alone or in Combination

SOF (n=17)			
Mean (%CV)	**SOF alone**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	794 (36.3)	1750 (27.8)	229 (191, 276)
AUC_{last} (ng hr/mL)	787 (36.6)	1740 (27.8)	230 (191, 277)
C_{max} (ng/mL)	929 (52.3)	1870 (27.9)	221 (176, 278)
GS-566500 (n=17)			
Mean (%CV)	**SOF alone**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	1110 (31.6)	1950 (22.8)	179 (155, 207)
AUC_{last} (ng hr/mL)	1060 (32.7)	1890 (22.8)	182 (157, 210)
C_{max} (ng/mL)	312 (38.7)	553 (26.6)	182 (154, 216)
GS-331007 (n=17)			
Mean (%CV)	**SOF alone**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	10900 (17.5)	13000 (16.7)	119 (113, 126)
AUC_{last} (ng hr/mL)	10200 (17.9)	12100 (15.5)	119 (113, 125)
C_{max} (ng/mL)	1060 (17.3)	864 (20.1)	81.2 (76.9, 85.8)
LDV (n=17)			
Mean (%CV)	**LDV alone**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{tau} (ng.hr/mL)	11900 (26.2)	11400 (27.1)	95.8 (92.1, 99.5)
C_{max} (ng/mL)	756 (24.7)	735 (27.0)	96.5 (89.9, 104)
C_{tau} (ng/mL)	375 (28.8)	360 (31.2)	95.5 (91.9, 99.1)

Data presented as 3 significant figures.

Sofosbuvir plasma exposure was increased by ~ 2.3-fold by LDV. The effect of LDV on SOF is likely due to inhibition of intestinal P-gp and/or BCRP, of which SOF is a known substrate. GS-331007 (predominant, circulating metabolite of SOF) exposure was unaffected by LDV. The increase in SOF (SOF, top panel) is not considered clinically significant due to its very low and transient exposure relative to total drug related material (DRM) exposure (DRM, calculated as the sum of the AUCs for each of the analytes, corrected for molecular weight). Based on this calculation, the AUC of SOF with LDV is only ~ 5.7% of DRM AUC. A drug interaction study (P7977-1819) of SOF with cyclosporine (potent multi-drug transporter inhibitor) demonstrated a 4-fold increase in systemic SOF exposure on administration with cyclosporine; the AUC of SOF increased from ~3 % (SOF alone) to

~11% (SOF with cyclosporine) of DRM AUC. Safety margins for all analytes of SOF on administration with cyclosporine continue to remain adequate (AUC safety margin ranges from 1.9 to 16.0) compared to exposures obtained in toxicology studies and dose modification of SOF is not warranted.

Ledipasvir PK was not altered on co-administration with SOF. Accordingly, SOF and LDV may be co-administered without dose adjustment.

No treatment-emergent AEs were reported in Cohort 1, based on a review of preliminary data. Two Grade 3 laboratory abnormalities were observed: an unconfirmed neutrophil count of 700 µL in an African-American subject with an otherwise normal white blood cell count; and an unconfirmed 3+ blood in urine in an adult menstruating female. No Grade 4 laboratory abnormalities were observed.

1.2.4.1.6. Study GS-US-337-0101

Study GS-US-337-0101 is an ongoing, single-center, Phase 1, single-dose, cross-over study evaluating the relative bioavailability and the effect of food on the PK of SOF 400 mg/LDV 90 mg FDC in healthy volunteers.

In Cohort 1, the PK of SOF 400 mg/LDV 90 mg FDC was evaluated relative to that of SOF 400 mg + LDV 90 mg, coadministered as individual components. The effect of food (moderate-fat or high calorie/high-fat meals) on the PK of SOF/LDV FDC was evaluated in Cohort 2.

Preliminary PK data from Cohorts 1 and 2 are presented in Table 1-16 and Table 1-17, respectively.

Table 1-16. Study GS-US-337-0101: Preliminary Pharmacokinetic Data for SOF, Metabolites (GS-566500 and GS-331007) and LDV on Administration of SOF/LDV FDC and SOF+LDV as Individual Components

SOF (n=28)			
Mean (%CV)	**SOF/LDV FDC**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	1350 (37.7)	1560 (39.4)	87.2 (77.8, 97.6)
AUC_{last} (ng hr/mL)	1340 (37.9)	1560 (39.6)	87.2 (77.7, 97.7)
C_{max} (ng/mL)	1320 (68.3)	1550 (46.1)	82.3 (71.2, 95.2)
GS-566500 (n=28)			
Mean (%CV)	**SOF/LDV FDC**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	1690 (30.0)	2000 (27.8)	85.4 (76.2, 95.8)
AUC_{last} (ng hr/mL)	1650 (30.8)	1950 (28.5)	85.4 (75.6, 96.4)
C_{max} (ng/mL)	429 (33.2)	509 (28.7)	86.0 (74.8, 98.9)
GS-331007 (n=28)			
Mean (%CV)	**SOF/LDV FDC**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	11900 (23.5)	12500 (23.1)	95.4 (89.9, 101)
AUC_{last} (ng hr/mL)	11200 (24.4)	11800 (23.6)	95.3 (89.5, 101)
C_{max} (ng/mL)	784 (36.2)	764 (27.3)	100 (91.2, 110)
LDV (n=28)			
Mean (%CV)	**SOF/LDV FDC**	**SOF + LDV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	9570 (46.6)	9620 (45.6)	95.7 (79.1, 116)
AUC_{last} (ng hr/mL)	7950 (41.6)	8040 (40.0)	95.3 (79.0, 115)
C_{max} (ng/mL)	314 (45.2)	314 (40.5)	98.2 (82.1, 118)

Data presented as 3 significant figures.

Similar plasma exposures of SOF, its metabolites GS-566500 and GS-331007, and LDV were achieved upon administration of SOF/LDV FDC and SOF+LDV, co-administered as individual components. The lower bounds of the 90% confidence intervals (CIs) for the primary PK parameters (AUC and C_{max}) of SOF, GS-566500 and LDV were greater than 70%. The GMR% and 90% CIs for GS-331007 primary PK parameters were contained within bioequivalence bounds of 80-125%. Based on these data, this SOF/LDV FDC tablet formulation has been selected for Phase 3 clinical development.

Table 1-17. Study GS-US-337-0101: Preliminary Pharmacokinetic Data for SOF, Metabolites (GS-566500 and GS-331007) and LDV on Administration of SOF/LDV FDC Fasted or with a Moderate-Fat Meal or with A High-Calorie/High Fat Meal

SOF (n=29)			
Mean (%CV)	**SOF/LDV FDC Fasted**	**SOF/LDV FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1530 (39.2)	2880 (33.6)	194 (176, 214)
AUC_{last} (ng hr/mL)	1520 (39.6)	2870 (33.8)	195 (1767, 215)
C_{max} (ng/mL)	1240 (49.6)	1540 (39.4)	126 (109, 147)
	SOF/LDV FDC Fasted	**SOF/LDV FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1530 (39.2)	2590 (34.1)	178 (161, 197)
AUC_{last} (ng hr/mL)	1520 (39.6)	2580 (34.4)	178 (161, 197)
C_{max} (ng/mL)	1240 (49.6)	1380 (40.6)	115 (99.0, 134)
GS-566500 (n=29)			
Mean (%CV)	**SOF/LDV FDC Fasted**	**SOF/LDV FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1520 (41.3)	2490 (21.1)	175 (161, 189)
AUC_{last} (ng hr/mL)	1470 (43.3)	2440 (21.5)	180 (164, 196)
C_{max} (ng/mL)	352 (42.7)	489 (21.8)	151 (136, 167)
	SOF/LDV FDC Fasted	**SOF/LDV FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1520 (41.3)	2550 (22.6)	179 (165, 194)
AUC_{last} (ng hr/mL)	1470 (43.3)	2500 (23.0)	184 (168, 201)
C_{max} (ng/mL)	352 (42.7)	507 (26.1)	154 (139, 171)
GS-331007 (n=29)			
Mean (%CV)	**SOF/LDV FDC Fasted**	**SOF/LDV FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	11800 (23.0)	13800 (17.9)	117 (112, 123)
AUC_{last} (ng hr/mL)	11300 (23.4)	12800 (18.3)	114 (108, 121)
C_{max} (ng/mL)	865 (26.6)	696 (19.7)	82.0 (76.0, 88.0)
	SOF/LDV FDC Fasted	**SOF/LDV FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	11800 (23.0)	12900 (19.0)	112 (107, 118)
AUC_{last} (ng hr/mL)	11300 (23.4)	12200 (19.4)	110 (103, 116)
C_{max} (ng/mL)	865 (26.6)	597 (23.3)	70.0 (65.0, 76.0)

LDV (n=27)			
Mean (%CV)	**SOF/LDV FDC Fasted**	**SOF/LDV FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	9610 (52.3)	10100 (33.8)	120 (103, 141)
AUC_{last} (ng hr/mL)	7940 (51.0)	8220 (30.0)	118 (101, 139)
C_{max} (ng/mL)	310 (45.4)	313 (26.0)	112 (96.0, 131)
	SOF/LDV FDC Fasted	**SOF/LDV FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	9610 (52.3)	8740 (34.0)	107 (92.0, 126)
AUC_{last} (ng hr/mL)	7940 (51.0)	7350 (31.3)	107 (91.0, 126)
C_{max} (ng/mL)	310 (45.4)	254 (27.5)	92.0 (79.0, 108)

Data presented as 3 significant figures.

Food slowed the rate of absorption of SOF (median T_{max}: 1.00 versus 2.00 hours) with only modest alteration in the bioavailability, as evidenced by increases of 2-fold or less in SOF and GS-566500 plasma exposure. For GS-331007, an approximately 20-30% lower C_{max} was observed upon SOF administration with food with no change in AUC. The %GMR and associated 90% CI (fed/fasted treatments) for AUC of GS-331007 were within the equivalence bounds of 70% to 143%. Since the decrease in GS-331007 C_{max} was modest and the AUC parameters met the equivalence criteria, the effect of food on GS-331007 PK was not considered clinically significant. These results are consistent with the data from previous Phase 1 studies (P7977-1318 and P7977-0111), which demonstrated that SOF could be administered without regard to food.

Similar LDV plasma exposures (AUC and C_{max}) are achieved upon administration of LDV as the FDC under fasted or fed conditions. The %GMR and associated 90% CIs (fed/fasted treatments) were within the equivalence bounds of 70-143%. While a "negative" food effect was previously observed on LDV (single agent administered as conventional formulation), the PK of LDV (spray dried formulation) administered within the SOF/LDV FDC does not appear to be altered by food.

As such, SOF/LDV FDC may be administered without regard to food.

Based on a preliminary safety data review of Cohorts 1 and 2, SOF/LDV FDC was generally well tolerated. Fifty-eight subjects were enrolled and 56 completed the study as planned. Two subjects withdrew consent in Cohort 2 for reasons not associated with an AE. The most frequently reported AEs in >1 subject were vessel puncture site pain (n=5), headache (n=5), abdominal pain (n=3), menstrual cramps (n=3), and constipation (n=3). AEs were transient and mostly mild in severity. A pregnancy was reported during the end of study follow-up visit in a 36 year old, PPD female, that later resulted in a SAE of spontaneous abortion (first trimester). No other SAEs, ≥ Grade 2 AEs, or clinically significant laboratory abnormalities were reported.

1.2.4.2. Other Ongoing Phase 2 Studies

Study GS-US-248-0120 is an ongoing all oral Phase 2 study that will examine the safety, tolerability and antiviral efficacy of LDV administered with GS-9451, TGV and RBV in treatment naïve, genotype 1 HCV infected subjects. Dosing is complete.

Study GS-US-248-0121 is an ongoing Phase 2 study that will examine the efficacy, safety, and tolerability of response guided therapy of combinations LDV + GS-9451 + Peg-IFNα/RBV for 6 or 12 weeks, compared to Peg-IFNα/RBV for 24 weeks in genotype 1 HCV infected, IL28B CC subjects. Dosing is complete.

Study GS-US-248-0131 is an ongoing all oral Phase 2 study that will examine the safety, tolerability and antiviral efficacy of LDV, GS-9451, TGV and RBV compared with LDV, GS-9451 with TGV or RBV in treatment-experienced subjects with chronic genotype (1a or 1b) HCV infection. Dosing is complete.

Study GS-US-248-0132 is an ongoing all oral Phase 2 study that will examine the safety, tolerability and antiviral efficacy of LDV, GS-9451, TGV and RBV; LDV, GS-9451 and TGV; LDV, GS-9451 and RBV in IFN ineligible or intolerant subjects with chronic genotype (1a or 1b) HCV infection. Dosing is complete.

Study GS-US-256-0148 is an ongoing Phase 2b study that will examine the efficacy, safety, and tolerability of response guided therapy with LDV, Peg-IFNα and RBV with or without GS-9451 in genotype 1 HCV infected, treatment-naïve subjects. Dosing is complete.

Study GS-US-256-0124 is an ongoing Phase 2b study that will examine the efficacy, safety, and tolerability of response guided therapy of combinations of oral antivirals (LDV, TGV, and/or GS-9451) with Peg-IFNα and RBV in treatment experienced subjects with chronic genotype 1 HCV infection. Dosing is complete.

1.2.4.2.1. Adverse Events in Ongoing Phase 2 Studies

The treatment-emergent AEs reported through September 2012 for all subjects enrolled in the GS-US-248-0120, GS-US-248-0131, GS-US-248-0132, GS-US-248-0121 (Arm 1), GS-US-256-0124, GS-US-256-0148, aggregated by treatment regimen, is shown in Table 1-18.

Table 1-18. Treatment-Emergent Adverse Events Experienced by ≥10% of Subjects in Any Interferon-Free Regimen

Preferred Terms	LDV IFN-free regimens (N=469)	LDV + GS-9451 + TGV (N=109)	LDV + GS-9451 + TGV + RBV (N=251)	LDV + GS-9451 + RBV (N=109)	LDV IFN-containing regimens (N=622)	LDV + GS-9451 + Peg-IFNα+ RBV (N=506)	LDV + Peg-IFNα+ RBV (N=116)
Subjects experiencing any AE with ≥10% incidence	85%	81%	88%	83%	96%	96%	98%
Fatigue	29%	27%	30%	27%	45%	45%	46%
Headache	28%	31%	26%	28%	37%	38%	35%
Nausea	17%	18%	16%	18%	28%	27%	34%
Rash	10%	6%	13%	9%	24%	24%	22%
Insomnia	12%	11%	12%	13%	22%	22%	22%
Pruritus	13%	10%	14%	12%	19%	18%	22%
Cough	9%	6%	10%	11%	18%	18%	17%
Diarrhea	9%	6%	11%	6%	16%	16%	15%
Anaemia	6%	0	6%	11%	16%	16%	16%
Dizziness	7%	12%	7%	3%	12%	12%	10%

1.3. Rationale for This Study

This Phase 3b study is designed to evaluate the efficacy and safety of the SOF/LDV FDC tablet administered for 12 weeks in treatment-naïve and treatment-experienced subjects with chronic genotype 1 HCV infection. Up to 20% of subjects enrolled in the study may have compensated cirrhosis at screening.

As previously described in Sections 1.1.2 and 1.1.3 in there is a significant unmet medical need in Korea and Taiwan for simple, well-tolerated, IFN-free, all-oral antiviral regimens for the treatment of chronic HCV infection. The current standard of care (Peg-IFNα+RBV) for these patients in Korea and Taiwan is associated with significant toxicity, with many patients unwilling to be treated with these regimens. There also exists substantial numbers of patients who cannot receive Peg-IFNα due to relative or absolute contraindications {20450}, {17893}, {17893}, {15573}, {17892}, {3291}.

Gilead has developed an FDC consisting of SOF with LDV, 2 well-tolerated, potent, once-daily antiviral agents in late phase clinical development. Based on Phase 2 data, the

SOF/LDV FDC has the potential to be a simple and highly effective all-oral, once daily treatment regimen for chronic genotype 1 HCV infection, after 12 weeks of treatment.

Initial proof of concept for the efficacy of SOF administered in combination with a HCV NS5A inhibitor came from the AI444-040 study (Section 1.2.2.2.1). In this study 12 weeks of SOF+DCV resulted in SVR4 rates of 95% and 98% when administered with RBV and without RBV respectively. In addition 100% (41/41) SVR4 was achieved when SOF+DCV±RBV was administered for 24 weeks in subjects who had failed to respond to Peg-IFNα+RBV+PI therapy.

Subsequently, proof of concept for the efficacy of the SOF+LDV combination came from ELECTRON Arm 13 (n=25), in which 100% of the treatment-naïve patients who received SOF+LDV+RBV for 12 weeks achieved SVR12 (Section 1.2.3.2.1). Proof of concept for the efficacy of this same regimen in the most difficult-to-treat treatment-experienced patients (null responders) also came from ELECTRON Arm 12 (n=9), in which 100% of these patients achieved SVR12 after 12 weeks of therapy (Section 1.2.3.2.1).

Finally demonstration that concurrent administration of RBV was not required with the SOF+LDV regimen to attain high rates of viral cure comes from the GS-US-337-0118 (LONESTAR) study. Recent data from this ongoing study reports SVR8 rates of 95% (19/20) and 100% (21/21) in GT-1 treatment-naïve subjects for SOF/LDV FDC administered for 8 weeks, both with and without concomitant RBV respectively (Section 1.2.3.2.2). Following administration of SOF/LDV FDC for 12 weeks in GT-1 treatment-naïve subjects, 100% (19/19) achieved SVR4. In GT-1 protease-inhibitor failures SOF/LDV FDC administered for 12 weeks achieved an SVR4 rate of 95% (18/19). Finally SOF/LDV FDC +RBV administered for 12 weeks in GT-1 treatment-experienced subjects achieved an SVR4 rate of 95% (20/21); the final subject in this cohort is yet to return to the clinic in the post-treatment period (Section 1.2.3.2.2).

The ongoing, blinded GS-US-337-0102 (ION-1) Phase 3 study (Section 1.2.3.3.1) is evaluating the same SOF/LDV FDC regimen proposed for the study in Korea and Taiwan. The Data Monitoring Committee met on 25 March 2013 to evaluate the safety and predefined interim futility criteria, and indicated the study was safe to proceed unchanged. Neither Group 3 (SOF/LDV FDC, 12 weeks) nor Group 4 (SOF/LDV FDC + RBV, 12 weeks) met protocol defined futility criteria.

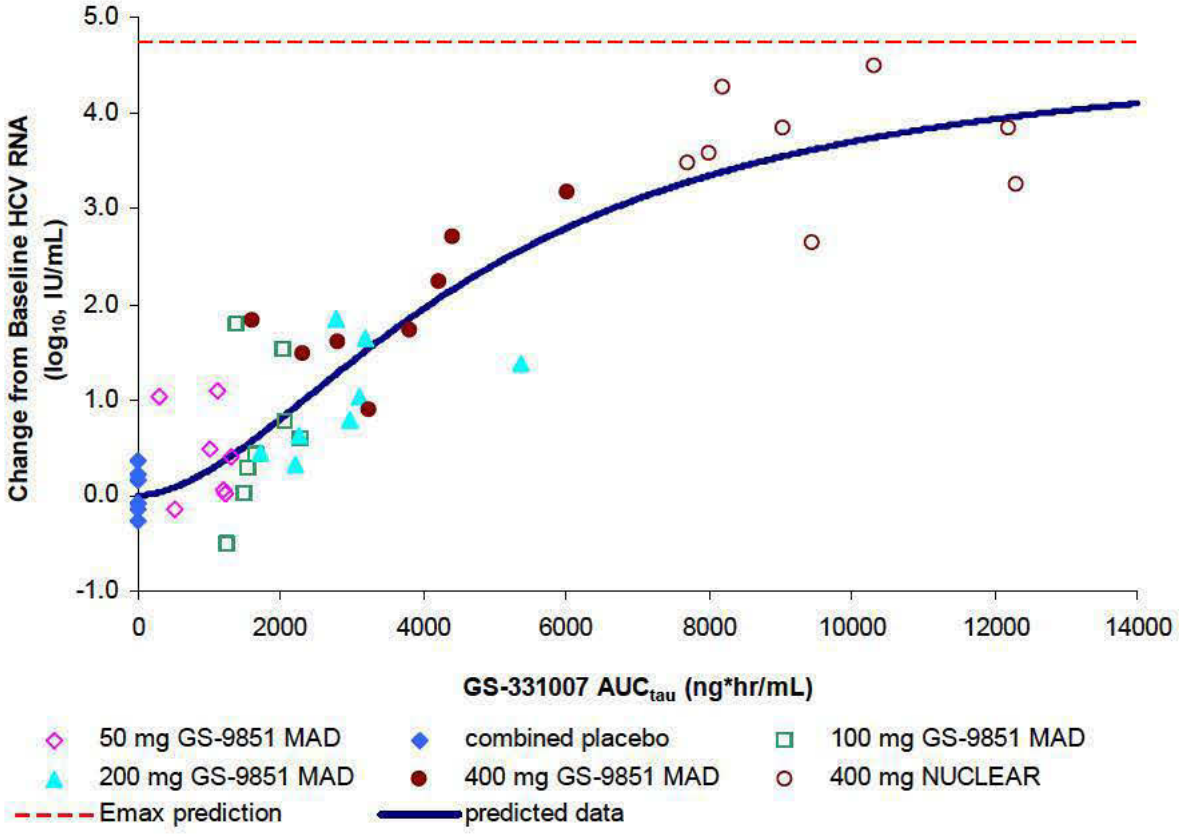
Current data for the SOF/LDV FDC indicates the regimen to be safe, well-tolerated and associated high degrees of antiviral efficacy supporting the conduct of the proposed Phase 3 study in Korean and Taiwanese subjects with GT-1 chronic hepatitis C.

1.4. Rationale for Dose Selection of SOF

The SOF dose selected for further development in Phase 3 studies is 400 mg once daily. Selection of the 400 mg dose is based on E_{max} modeling with early virologic and human exposure data and on efficacy and safety results from phase 2 trials.

Standard pharmacodynamic models were fit to examine the relationship between change from baseline in HCV RNA and steady-state pharmacokinetic parameters for GS-331007 (major plasma metabolite of GS-9851 and of SOF) after 3 days of monotherapy with GS-9851 (diastomeric mixture of SOF and its enantiomer) or SOF. The mean GS-331007 AUC_{tau} for the 400 mg dose is associated with approximately 77% of the maximal HCV RNA change from baseline achievable as determined by this model, a value on the inflection point of the exposure-response sigmoidal curve. Furthermore, a relatively linear exposure-response relationship in the 20 to 80% maximal effect range is observed. Sofosbuvir exhibits dose-proportional increases in exposure (up to 1200 mg), thus, doses below 400 mg are expected to yield considerable reductions in the magnitude of HCV RNA change from baseline. Similarly, substantial increases in exposure (and hence dose) would be required to improve on the efficacy prediction of 77% in the plateau of the exposure-response curve and to observe an appreciable increase in antiviral effect (see model prediction in Figure 1-1).

Figure 1-1. Day 3 Change from Baseline HCV RNA vs GS-331007 AUC_{tau} during SOF or GS-9851 Monotherapy



GS-9851 MAD = GS-9851 data from multiple ascending dose study; NUCLEAR = SOF data from Study P7851-1102

In a study evaluating the efficacy of 200 mg and 400 mg doses of SOF in combination with Peg-IFNα+RBV for 12 weeks followed by Peg-IFNα+RBV for 12 weeks (Study P7977-0422 [PROTON]), the 400 mg dose level was associated with higher SVR rates and lower occurrence of viral breakthroughs during the Peg-IFNα+RBV dosing phase, after completion of SOF+PEG-IFNα+RBV, in treatment-naïve subjects with genotype 1 HCV infection. Progression of the 400 mg SOF dose is further supported by preliminary efficacy results in other phase 2 studies.

The safety profile of SOF also supports selection of 400 mg for continued development. SOF 400 mg whether given as monotherapy, +RBV, or +Peg-IFNα+RBV has been well tolerated in studies to date. The safety and tolerability profile of the SOF 400 mg dose level was similar to that of the 200 mg dose level in Study P7977-0422. The AE profile observed in studies evaluating the combination SOF+RBV was similar to the AE profile of that expected following treatment with RBV alone.

1.5. Rationale for Dose Selection of LDV

Ledipasvir dose of 90 mg has been selected for co-formulation with SOF and evaluation in this study based on the multiple-dose safety and antiviral activity data (studies GS-US-256-0102 and GS-US-248-0120) and PK data (studies GS-US-256-0101 and GS-US-256-0110 formulation study). The Phase 1 multiple-ascending dose study GS-US-256-0102 established the anti-HCV activity of LDV. In this study, the maximum median HCV RNA $\log_{10}$ reduction was 3 or greater for all cohorts dosed with ≥ 3 mg of LDV. An E_{max} PK/PD model indicates that the exposures achieved following administration of the 30 mg dose provides > 95% of maximal antiviral response in genotype 1a HCV infected subjects. It was also observed that 30 mg or greater of LDV likely provided coverage of some drug related mutations that doses less than 30 mg did not, based on an analysis of NS5A mutants that arose in response to exposure to LDV. Therefore, 30 mg and 90 mg of LDV were selected for further clinical evaluation.

In IFN-free Study GS-US-248-0120, 30 mg of LDV (Arm 1) is being compared to 90 mg of LDV (Arm 2), administered with a background of 3 other antiviral agents, GS-9451, TGV, and RBV. When comparing these 2 arms, it is notable that the breakthrough (BT) rate (number of subjects with HCV RNA > lower limit of quantification (LLOQ) after having achieved vRVR/total number of subjects who achieved vRVR), is higher in Arm 1 (BT = 33%, 11/33; 30 mg LDV), than Arm 2 (BT = 12%, 9/74; 90 mg LDV). Therefore, the 90 mg dose of LDV may confer a greater antiviral coverage that prevents viral breakthrough. For this reason, a 90 mg dose has been selected as for further clinical testing in Phase 3 studies. More than 400 subjects have been dosed with 90 mg of LDV for over 12 weeks.

In study GS-US-256-0110, an optimized spray-dried formulation of LDV showed an ~25% increase in LDV exposure, as assessed by AUC and C_{max} and a modestly lower variability in exposure compared to the original formulation; as such an spray dried formulation has been selected for clinical development and co-formulation with SOF into the FDC tablet.

1.6. Overall Risk/Benefit Assessment

The SOF/LDV FDC product combines a potent HCV nucleotide NS5B inhibitor and a potent HCV NS5A inhibitor.

The potential benefits of SOF/LDV FDC for the treatment of chronic HCV are:

- Greater antiviral efficacy (i.e., rapid and durable eradication of HCV) compared to the current standard of care (Peg-IFNα +RBV)
- A reduction in the AEs currently associated with the use of Peg-IFNα+RBV
- A simple, well-tolerated regimen to replace the current complex, response-guided Peg-IFNα +RBV regimens.
- The potential benefit of a shortened SOF/LDV FDC therapy of 12 weeks is a decrease in the burden of treatment for both patients and physicians, through a reduction in the overall number of patient visits.

The safety profile of SOF includes approximately 1600 chronic HCV-infected subjects that have been administered over 12 weeks of SOF in combination with a DAA, Peg-IFNα, with or without RBV. No clinical safety issues related to SOF have been identified to date. The safety profile of LDV includes over 1000 chronic HCV-infected subjects, of whom over 700 have been administered more than 12 weeks of LDV, which was given in combination with other DAAs, Peg-IFNα, with or without RBV. No clinical safety issues related to LDV have been identified to date.

Furthermore, there is no expectation of significant overlapping or new, unexpected toxicities upon administration of SOF/LDV together as an FDC. To date, the SOF/LDV FDC ± RBV has been administered to over 1200 HCV infected subjects in ongoing phase 2/3 trials. No clinical safety issues related to the SOF/LDV FDC have been identified to date.

During the conduct of the study the Sponsor will perform ongoing safety data review.

In summary, there is no currently approved all-oral treatment available for HCV-infected patients. This study will support the registration of the SOF/LDV FDC in treatment-naïve and treatment-experienced Korean and Taiwanese subjects with chronic genotype 1 HCV infection including those with compensated cirrhosis.

1.7. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To determine the antiviral efficacy of treatment with sofosbuvir (SOF)/ledipasvir (LDV) fixed-dose combination (FDC) as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12, defined as HCV RNA < lower limit of quantitation [LLOQ] 12 weeks post treatment)

- To evaluate the safety and tolerability of SOF/LDV FDC as assessed by review of the accumulated safety data

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)

- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation

- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

The exploratory objectives of this study are:

PPD

3. STUDY DESIGN

3.1. Endpoints

The primary endpoints of this study are:

- The primary efficacy endpoint is SVR12 (HCV RNA <LLOQ 12 weeks after discontinuation of therapy) in the Full Analysis Set (FAS) population.
- The primary safety endpoint is any AE leading to permanent discontinuation of study drug.

Secondary endpoints of this study include:

- Secondary efficacy endpoints include the proportion of subjects with: HCV RNA < LLOQ at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24); viral breakthrough; relapse; and HCV RNA change from baseline.

3.2. Study Design

This will be an international (Korea and Taiwan), multicenter, open-label study in treatment-naïve and treatment-experienced adults with chronic genotype 1 HCV infection.

It is estimated that approximately 80 subjects will be enrolled in Korea and 80 subjects in Taiwan for a total of 160 enrolled subjects. Within each country approximately 50% (i.e., n~40) of subjects will be treatment-naïve and 50% will be treatment-experienced (i.e., n~40).

Up to 20% of subjects enrolled in the study may have compensated cirrhosis at Screening.

3.3. Study Treatment

Approximately 80 treatment-naïve and 80 treatment-experienced subjects will receive treatment with SOF 400 mg/LDV 90 mg fixed dose combination (FDC) tablet for 12 weeks.

3.4. Duration of Treatment

All subjects will complete screening, on-treatment, and post-treatment assessments. Screening assessments will be completed within 28 days of the Baseline/Day 1 visit or within 42 days if a liver biopsy or additional HCV genotyping is required. All subjects will receive treatment for 12 weeks. All subjects will complete a 4-week and 12-week Post-Treatment visit. Subjects with HCV RNA < LLOQ at the 12-Week Post-Treatment visit will also complete a 24-Week Post-Treatment visit unless confirmed viral relapse occurs.

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

3.5. Discontinuation Criteria

When medically feasible, the Medical Monitor must be consulted prior to the premature discontinuation of treatment in a given subject.

Study drug 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 to not be in the subject's best interest
- Pregnancy of female subject

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 in HCV RNA from nadir
- HCV RNA ≥ LLOQ through 8 weeks of treatment

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

All subjects will complete the 4-Week and 12-Week Post-treatment visits. Subjects with HCV RNA < LLOQ at the 12-week Post-treatment visit will return for the 24-week Post-treatment visit, unless confirmed viral relapse occurs. Study drug may be discontinued in the following instances:

- Significant protocol violation
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason
- Discontinuation of the study at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

If a subject meets discontinuation criteria during treatment, an Early Termination (ET) visit will be required (Section 6.4.9). Following completion of the Early Termination visit, all subjects must complete the 4-week and 12-week Post-Treatment visits. All patients with HCV RNA < LLOQ at the 12-week Post-Treatment visit must return to the clinic for 24-week Post Treatment assessments, unless confirmed viral relapse occurs.

3.6. Source Data

A Health Related Quality of Life survey, Short-Form-36 (SF-36) will be completed by subjects at various timepoints during the study and be used as source data. The subject should read the questionnaire by himself/herself and write/mark answers directly onto the questionnaire.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 160 subjects will be enrolled in this study with approximately 80 treatment-naïve subjects and approximately 80 treatment-experienced subjects. Up to 20% of subjects enrolled in the study 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 ≥ 20 years

3) Body weight ≥ 40 kg

4) HCV RNA ≥ 10^4 IU/mL at Screening

5) HCV treatment-naïve, as defined as no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent; OR HCV treatment-experienced with medical records that include sufficient detail of prior treatment with IFN to allow for categorization of prior response as either:

    a) IFN Intolerant: Subject completed ≤ 12 weeks of treatment (ending ≥ 3 months prior to Screening) with IFN and discontinued treatment due to development or significant worsening of at least one of the following conditions:

        - Significant local or systemic adverse reaction to IFN (e.g., hypersensitivity, injection site reactions)
        - Psychiatric disease necessitating hospitalization or period of disability or psychosis, schizophrenia, bipolar disorder, depression, schizoaffective disorder, suicidal ideation, or suicide attempt
        - Significant cognitive impairment
        - Neuropathy
        - Disabling flu-like symptoms (arthralgias, fatigue, pyrexia, myalgia)

- Gastrointestinal toxicity with nausea, vomiting or diarrhea
- Thrombocytopenia (platelets < 25,000/μL)
- Neutropenia (ANC < 500/μL)
- Development of colitis, non-alcoholic pancreatitis or ophthalmologic disorders
- Autoimmune disorder including but not limited to: myositis, hepatitis, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, immune (idiopathic) thrombocytopenic purpura, psoriasis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, thyroiditis.
- AE related to IFN that is not listed after consultation with the Medical Monitor

b) Non-Response: Subject did not achieve undetectable HCV RNA levels while on treatment

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

6) Genotype 1 HCV at Screening as determined by the Central Laboratory. Any non-definitive results will exclude the subject from study participation

7) Confirmation of chronic HCV infection documented by either:

a) A positive anti-HCV antibody test or positive HCV RNA or positive HCV genotyping test at least 6 months prior to the Baseline/Day 1 visit, or

b) A liver biopsy performed prior to the Baseline/Day 1 visit with evidence of chronic HCV infection

8) Cirrhosis determination [up to 20% of subjects enrolled in the study may have compensated 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) Fibroscan indicative of cirrhosis as evidenced by a result > 12.5 kPa

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

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

ii) Fibroscan within 6 months of Baseline/Day 1 with a result of ≤ 12.5 kPa

c) In the absence of a definitive diagnosis of the presence or absence of cirrhosis by the above criteria, a liver biopsy is required; liver biopsy results will supersede any imaging studies or blood test results and be considered definitive.

9) Liver imaging within 6 months of Baseline/Day 1 to exclude hepatocellular carcinoma (HCC) is required in patients with cirrhosis

10) Screening ECG without clinically significant abnormalities

11) Subjects must have 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) HbA_{1c} ≤ 8.5%

f) Creatinine clearance (CL_{cr}) ≥ 50 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 ≥ 3g/dL

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

12) 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 Baseline/Day 1 prior to randomization.

13) 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.

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

15) 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 12 months prior to Baseline/Day 1 or has not required medication in the last 12 months may be enrolled.

    h) Malignancy within the 5 years prior to screening, with the exception of specific cancers that are 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) If treatment-naïve, prior exposure to approved or experimental HCV-specific direct-acting antiviral agent(s). If treatment-experienced, prior exposure to approved or experimental HCV-specific direct-acting antiviral agent(s) other than NS3/4A protease inhibitors is prohibited.

3) Pregnant or nursing females.

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

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

6) Donation or loss of more than 400 mL blood within 2 months prior to Baseline/Day 1

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

8) Administration of interferon or any HCV-directed treatment, other than the study drug, is prohibited from 12 weeks prior to Screening until completion of the final post-treatment follow-up visit.

9) Chronic use of systemically administered immunosuppressive agents (e.g., prednisone equivalent > 10 mg/day), azathioprine or monoclonal antibodies such as infliximab.

10) Known hypersensitivity to SOF, LDV, or formulation excipients.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization and Treatment Codes

This is an open-label, non-randomized study. Every subject will receive SOF/LDV FDC tablet for 12 weeks. An Interactive Web Response System (IWRS) will be employed to manage subject enrollment and study drug dispensation.

5.2. Description and Handling of Sofosbuvir/Ledipasvir Fixed-Dose Combination

5.2.1. Formulation

Sofosbuvir (SOF)/ledipasvir (LDV) fixed-dose combination (FDC) tablets are orange, diamond-shaped, film-coated tablets containing 400 mg of SOF and 90 mg of LDV. The tablets are debossed with "GSI" on one side and "7985" on the other side. The SOF/LDV FDC tablets contain the following inactive ingredients: lactose monohydrate, copovidone, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol, FD&C yellow # 6 /sunset yellow FCF aluminum lake.

5.2.2. Packaging and Labeling

Sofosbuvir (SOF)/ledipasvir (LDV) fixed-dose combination (FDC) tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and a silica gel desiccant canister or sachet and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

All labels for SOF/LDV FDC bottles to be distributed to study centers in participating countries shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA) and local regulations as applicable.

Sufficient quantities of SOF/LDV FDC tablets to complete the entire study will be shipped to the investigator or qualified designee from Gilead Sciences Materials & Logistics (or its designee).

5.2.3. Storage and Handling

Sofosbuvir (SOF)/ledipasvir (LDV) FDC bottles should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25 °C; excursions are permitted between 15 °C and 30 °C.

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the Investigational Medicinal Product (IMP) 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/LDV FDC.

5.3. Dosage and Administration of Sofosbuvir/Ledipasvir FDC

Sofosbuvir/Ledipasvir FDC 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 IMP doses. In order to maintain compliance with the treatment regimen, SOF/LDV FDC should be administered at approximately the same time each day.

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

5.4. Prior and Concomitant Medications

Concomitant medications taken within 30 days prior to Screening, up to and including the date of the visit four weeks after discontinuation of study treatment need to be recorded in the source documents and electronic case report form(s) (eCRFs).

Administration of interferon or any HCV-directed treatment, other than the study drug, is prohibited from 12 weeks prior to Screening until completion of the final post-treatment follow-up visit.

The following medications are prohibited during the screening period and for a minimum of 30 days prior to the Baseline/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 use of 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 (inhibitors or inducers of drug transporters ie, P-gp) with study drug may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug.

Examples of representative medications which are prohibited from 30 days prior to Baseline/Day 1 through the end of treatment are listed below:

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

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

a The 30 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 daily dose of 20 mg of famotidine or equivalent. Antacids that directly neutralize stomach pH (i.e. Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/LDV FDC administration.

b May result in an increase in the concentration of study drugs and/or concomitant medications

c May result in a decrease in the concentrations of study drugs.

d Use with study drugs may result in an increase in the concentration of the HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

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

5.5. Accountability for SOF/LDV FDC

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

SOF/LDV FDC accountability records will be provided to each study site to:

- Record the date received and quantity of IMP kits.
- Record the date, subject number, subject initials, the IMP kit number dispensed.
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

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

Study medication will be reconciled using medication pill counts at every post-baseline visit by the investigator or designee (e.g., pharmacist, study coordinator) in order to monitor the subject's adherence with the medication regimen.

5.5.1. Investigational Medicinal Product Return or Disposal

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

6. STUDY PROCEDURES

Study visits will occur at Screening, Baseline/Day 1, and on-treatment at the end of Weeks 1, 2, 4, 6, 8, 10, and 12. All subjects will complete 4-week and 12-week Post-Treatment visits. In addition, all subjects with HCV RNA < LLOQ at the 12-week Post-Treatment visit will complete a 24-week Post-Treatment visit unless confirmed viral relapse occurs. The end of study will occur at the 12-week or 24-week Post-Treatment visit according to virologic response.

Administration of interferon or any HCV-directed treatment, other than the study drug, is prohibited from 12 weeks prior to Screening until completion of the final post-treatment follow-up visit.

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

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

Information on the specific laboratory parameters to be measured and clinical assessments to be performed are provided below.

6.1. Subject Enrollment and Treatment Assignment

6.2. Pretreatment Assessments

6.2.1. Screening Visit (Day -28 to Day -1)

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

Subjects will be screened to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain signed informed consent
  - — A separate informed consent will be required from subjects participating in the intensive pharmacokinetic and/or pharmacogenomic sub-studies.
- Determine inclusion eligibility (Reference Section 4.2 and 4.3)

  - If the 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)

- Obtain medical history (Reference Section 6.6.2.)
- 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 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 and subtype of HCV infection
  - HCV antibody, HIV 1/2 antibody, and HBV surface antigen (HBsAg)
  - HbA1c
  - TSH
- Obtain urine sample for:
  - Urinalysis

Record any adverse events occurring after signing of the consent form.

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

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any

non-serious adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Randomization

This is a non-randomized study. An Interactive Web Response System (IWRS) will be employed to manage subject enrollment and study drug dispensation.

6.4. Treatment Assessments

6.4.1. Baseline/Day 1 Visit

The following baseline tests and procedures must be completed prior to dosing/dispensing:

- Confirm eligibility
- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - — Hematology & Chemistry
  - — Coagulation tests
  - — HCV RNA
  - — Viral RNA Sequencing / Phenotyping Sample
  - — Archive Sample (for subjects that have not opted out)
  - — Pharmacogenomic testing (for subjects who have consented to participate in the Pharmacogenomic Substudy)

- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Drug Administration
  - Dispense study drugs as directed by the IWRS
  - Instruct the subject on the packaging, storage and administration of study drug
  - Instruct the subject on how to complete the subject diary
  - Observe the subject taking the first dose of study drugs and record the time of first dose.

6.4.2. Week 1 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 1.

- Obtain vital signs
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Single PK Sample
  - Viral RNA Sequencing / Phenotyping Sample
- Complete medication pill count and review patient diary data with subject

6.4.3. Week 2 (± 3 days)

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

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Subject completes Health Related Quality of Life Survey, SF-36

- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Single PK Sample
  - Viral RNA Sequencing / Phenotyping Sample
  - If applicable at Week 2, collect serial PK substudy samples (for subjects who have consented to participate in the PK substudy)
- Complete medication pill count and review dosing diary data with subject

6.4.4. Week 4 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 4:

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Subject completes Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Single PK Sample
  - Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
  - If applicable at Week 4, collect serial PK substudy samples (for subjects who have consented to participate in the PK substudy)
- Complete medication pill count and review patient diary data with subject
- Dispense study drugs as directed by the IWRS

6.4.5. Week 6 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 6.

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Single PK Sample
  - Viral RNA Sequencing / Phenotyping Sample
- Complete medication pill count and review patient diary data with subject

6.4.6. Week 8 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 8:

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Subject completes Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Single PK Sample
  - Viral RNA Sequencing / Phenotyping Sample
- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Complete medication pill count and review patient diary data with subject
- Dispense study drugs as directed by the IWRS

6.4.7. Week 10 (± 3 days)

The following procedures/assessments are to be completed at the end of Week 10.

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology & Chemistry
  - HCV RNA
  - Single PK Sample
  - Viral RNA Sequencing / Phenotyping Sample

Complete medication pill count and review patient diary data with subject

6.4.8. Week 12 (± 3 days)

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

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Perform 12-lead ECG
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - Hematology & Chemistry
  - Coagulation tests
  - HCV RNA
  - Single PK Sample
  - Viral RNA Sequencing / Phenotyping Sample
  - Archive Sample (for subjects that have not opted out)
- Obtain urine sample for:

- β-hCG pregnancy test for females of childbearing potential only

- Complete medication pill count and review patient diary data with subject

6.4.9. Early Termination (ET)/Unscheduled Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments at the unscheduled visits 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.

The Sponsor (e.g. Medical Monitor and Clinical Program Manager)/ PAREXEL must be informed, as soon as possible, when a subject prematurely discontinues treatment. The primary reason for premature treatment discontinuation must be provided to the Sponsor/ PAREXEL.

If a subject discontinues treatment early for any reason then 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
- Pregnancy prevention counseling
- Subject completes a Health Related Quality of Life Survey, SF-36
- Obtain blood samples for:
  - Hematology & Chemistry
  - Coagulation tests
  - HCV RNA
  - Single PK Sample
  - Viral RNA Sequencing / Phenotyping Sample
  - Archive Sample (for subjects that have not opted out)

- Obtain urine sample for:
  - β-hCG pregnancy test for females of childbearing potential only
- Complete medication pill count and review dosing diary data with subject

6.5. Post-Treatment Assessments

All subjects must complete the Post-Treatment Week 4 and Week 12 visits. For subjects who have completed an ET visit, the post-treatment Week 4 and Week 12 follow-up visits will be scheduled at 4 and 12 weeks after the last dose of study drug. All subjects with HCV RNA < LLOQ at the 12-week Post-Treatment visit will also complete the 24-week Post-Treatment visit, unless viral relapse is determined.

6.5.1. Post Treatment Week 4 (± 5 days)

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

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes a Health Related Quality of Life 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

All subjects, including those who prematurely discontinue study drug, must return for Post Treatment Visit at Week 12.

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

The following procedures/assessments are to be completed for the Post-treatment Week 12 and 24 Visits:

- Obtain body weight
- Obtain vital signs
- Subject completes a Health Related Quality of Life Survey, SF-36 (Post treatment Week 12 only)
- Obtain blood samples for:
  - HCV RNA
  - Viral RNA Sequencing / Phenotyping Sample

Subjects with HCV RNA < LLOQ at the Post-Treatment Week 12 Visit will return at the post-treatment Week 24 Visit.

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 MCV.

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

Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatinine, Total Bilirubin (reflex to Direct Bilirubin), Direct Bilirubin at Screening only, Glucose, Lipase, Potassium, Sodium; Gamma-glutamyl transferase (GGT) at Baseline 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 the High Pure System. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. Gilead reserves the right to use alternate assays for HCV RNA and HCV genotype should the above assays become unavailable or are not definitive.

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

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

Additional Tests: Hemoglobin A1c (HbA1c), and TSH (reflex free T4).

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 will be collected on all subjects during screening. Additionally, for treatment naïve subjects, any relative or absolute contraindications to interferon treatment ("IFN ineligible") should be identified. Information related to HCV infection will also be collected.

For treatment-experienced subjects, obtain HCV treatment history, in order to categorize the patient as either IFN-intolerant, non-responder or relapse/breakthrough, defined as:

- IFN-intolerant: Subjects considered to be IFN-intolerant must (according to investigator judgment) have sufficiently recovered from IFN-related clinical adverse events and/or laboratory abnormalities prior to Screening. In addition, all other protocol eligibility criteria must be met.

- Non-Responder: Subject did not achieve undetectable HCV RNA levels (HCV RNA ≥ LLOQ) while on treatment. For Peg-IFNα/IFN/RBV non-responders, subjects should be further defined as Null or Partial Responders:

  — Null Responders: HCV RNA < 2 Log_{10} reduction during the first 12 weeks of treatment.

  — Partial Responders: HCV RNA ≥ 2 Log_{10} reduction during the first 12 weeks of treatment.

- Relapse/Breakthrough: Subject achieved undetectable HCV RNA levels (HCV RNA < LLOQ) during treatment or within 4 weeks of end of treatment, but did not achieve a sustained virologic response (SVR).

6.6.3. Complete Physical Examination

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

6.6.4. 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 Baseline as part of routine safety monitoring.

6.6.7. Viral RNA Sequencing / Phenotyping Sample

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

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

6.6.8. Archive Sample

A plasma sample will be obtained from all subjects at the Baseline/Day 1 visit and at the end of treatment (i.e., Week 12) or Early Termination visit for future research use. Unlike the

other samples drawn from subjects, this protocol does not define the type of research that may be conducted using this sample. This research could involve the use of the sample for HCV genotyping/phenotyping assays (as applicable) or their development, for retesting the amount of HCV in the blood, for measurement of antiviral drug levels in the blood, for future testing to learn more about how the study drug has worked against HCV or for clinical laboratory testing to provide additional clinical data. No human genetic testing will be performed. This plasma sample will be stored for up to 10 years after the study closure. Subjects enrolled in the study will have the opportunity to withdraw consent from storage and use of the Archive sample for future research.

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

6.6.9. Single Pharmacokinetic (PK) Sample

Single PK blood samples will be collected for all subjects at each on-treatment visit after Baseline/Day 1 and archived for PK analysis of SOF (and its metabolites GS-566500 and GS-331007) and LDV.

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

6.6.10. Intensive Pharmacokinetic (PK) Substudy

PPD

6.6.11. Pharmacogenomic (PG) Substudy

PPD

6.6.12. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period and for a minimum of 1 month following the last dose of study drug. In the event of a positive urine pregnancy test result, subjects will be instructed to stop study drugs immediately and return to the clinic as soon as possible for a confirmatory serum pregnancy test.

6.6.13. Health Related Quality of Life Survey

A health related quality of life survey, SF-36 will be completed by patients at Baseline/Day 1, On-treatment Weeks 2, 4, 8, 12, Post-treatment Weeks 4 and 12, and Early Termination (if applicable). The subject should read the questionnaire by himself/herself and write/mark answers directly onto the questionnaire.

6.7. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.4.9). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

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

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

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

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

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

All AEs, regardless of causal relationship, that occur from initiation of study medication until 4 weeks after last administration of study IMP must be 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 post-treatment follow up period.

Investigators are not obligated to actively seek SAEs after post treatment follow-up. However, if the investigator learns of any SAEs that occur after study participation has concluded, i.e., after the 12-week or 24-week post treatment visit (as applicable) and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

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

- At the time of study start, SAEs may be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

<u>Serious Adverse Event Paper Reporting Process</u>

- All SAEs will be recorded on the serious adverse event report form and submitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of the designated PAREXEL Pharmacovigilance Representative.

<u>Electronic Serious Adverse Event (eSAE) Reporting Process</u>

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

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

PAREXEL and Gilead Sciences Pharmacovigilance Representative contact information is as follows:

PAREXEL Pharmacovigilance Representative:	SAE Hotline:	+ 65 6221 8582
	Korea:	+ 00308 13 2766
	Taiwan:	+ 00801 10 4423
	E-mail:	medical_singapore@parexel.com
PAREXEL Medical Monitor:	Name:	Nino Kurtsikidze
	Phone:	PPD
	Fax:	PPD
	E-mail:	PPD
Gilead Sciences Medical Monitor (Back-Up):	Name:	Phil Pang, MD, PhD
	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.

7.4. Gilead Reporting Requirements

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

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

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

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

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

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

7.6. Subject Stopping Rules

The Medical Monitor must be consulted prior to dose discontinuation of SOF/LDV FDC unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject.

Due to a clinical or laboratory event, administration of study drug may be discontinued. There is no option for SOF/LDV FDC dose reduction. If SOF/LDV FDC is stopped due to

toxicity, it must not be restarted; if SOF/LDV FDC is discontinued, the subject must complete an ET visit. Post-treatment 4-Week and 12-Week visits must also be scheduled, 4 and 12 weeks from the last dose of study drug. Subjects with HCV RNA < LLOQ at the 12-week Post-Treatment visit will complete the 24-week Post-Treatment visit, unless viral relapse is determined.

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 > 3 x Baseline/Day 1 *and* total bilirubin > 2 x ULN, confirmed by immediate repeat testing
- Elevation of ALT > 15 x ULN, confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 adverse event or laboratory abnormality assessed as related to SOF/LDV FDC

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

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

A pregnancy report is used to report any pregnancy following maternal or paternal exposure to the medicinal product.

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. In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess

dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report all pregnancies that are identified after the subject first consents to participate in the study (ie, signs the informed consent) and throughout the study, including the post study drug follow-up period, to the PAREXEL Pharmacovigilance Representative/ PAREXEL Safety Department using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in the Serious Adverse Events section (Section 7.3). Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to the PAREXEL Pharmacovigilance Representative.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to the PAREXEL Pharmacovigilance Representative 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 study drugs must also be reported and relevant information should be submitted to the PAREXEL Representative using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject's partner should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com.

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

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to the PAREXEL Pharmacovigilance Representative within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP, but do not apply to concomitant medications. Except for situations that result in AEs, special situations involving concomitant medications will not be reported. Any inappropriate use of medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

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.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary analysis objectives of this study are:

- To determine the antiviral efficacy of combination treatment with sofosbuvir (SOF)/ledipasvir (LDV) fixed-dose combination (FDC) as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of therapy (SVR12, defined as HCV RNA < lower limit of quantitation [LLOQ] 12 weeks post treatment).

- To evaluate the safety and tolerability of SOF/LDV FDC as assessed by review of the accumulated safety data

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)

- To evaluate the kinetics of circulating HCV RNA during treatment and after treatment discontinuation

- To evaluate the emergence of viral resistance to SOF and LDV during treatment and after treatment discontinuation

The exploratory objectives of this study are:

PPD

[redacted]

8.1.2. Primary Endpoint

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

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

8.1.3. Secondary Endpoint

Secondary efficacy endpoints include the proportion of subjects with: HCV RNA < LLOQ at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24); viral breakthrough; relapse; and HCV RNA change from baseline.

8.1.4. Other Endpoints of Interest

Additional efficacy evaluations may include ALT normalization; and the health related quality of life endpoints.

8.2. Analysis Conventions

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

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

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The analysis set for antiviral activity analyses will be the Full Analysis Set (FAS) which includes subjects who were enrolled and received at least one dose of study drug and have chronic genotype (1a, 1b, or mixed 1a/1b) HCV infection.

8.2.1.2. Safety

The primary analysis set for safety analyses is defined as subjects who were enrolled and 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 the last dose of study drug plus 30 days.

8.2.1.3. Pharmacokinetics

The PK analysis set will include all subjects who are enrolled and have received at least one dose of study drug and for whom concentration data of analytes [SOF, LDV, and metabolite(s), as appropriate] are available. The PK analysis set will be used for analyses of general PK.

8.3. Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. In general, 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 immediately 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 will be considered a failure at the time points on, or following, the date of 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 baseline result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the baseline 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 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).

PK concentration values below the lower limit of quantitation (BLQ) will be treated as zero for determination of summary and order statistics. Individual values that are BLQ will be presented as “BLQ” in the concentration data listing. For the presentation of summary and order statistics, if at least 1 subject has a concentration value BLQ for the time point, then the minimum value will be displayed as “BLQ”. If more than 50% of the subjects have a concentration data value BLQ for the time point, then the minimum and median values will be displayed as “BLQ”. If all subjects have concentration data values BLQ for the time point, then all order statistics (minimum, first quartile [Q1], median, third quartile [Q3], maximum) will be displayed as “BLQ”.

Exposure parameters that are selected for statistical analysis will be natural log-transformed. Concentration values that are BLQ will be excluded for any ratio or natural log-transformed statistical analysis.

8.3.1. Interim Analysis

No formal interim analyses are planned for this study.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by treatment-naive and treatment-experienced subjects.

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

Baseline characteristic data will include a summary of body mass index, HCV RNA level (log_{10} IU/mL), HCV genotype (1a or 1b, or mixed 1a/1b), IL28B genotype, presence/absence of cirrhosis, baseline ALT level, and additional endpoints as necessary.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

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

A point estimate with a two-sided 95% exact confidence interval using the binomial distribution (Clopper-Pearson method) {20839} will be constructed for the SVR12 rate by treatment-naïve and treatment-experienced subjects.

8.5.2. Secondary Analysis

The proportion of subjects with HCV RNA below LLOQ over time (including SVR12) will be presented by treatment-naive and treatment-experienced subjects in tabular and graphical form.

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

Exploratory analyses may be performed to assess PPD

PPD

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

8.6. Safety Analysis

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

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug will be summarized. Safety endpoints will be summarized as the number (proportion) of subjects with events or abnormalities for categorical data or as an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data.

8.6.1. Extent of Exposure

A subject's extent of exposure to IMP data will be generated from the IMP administration data. Exposure data will be summarized.

8.6.2. Adverse Events

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

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any new or worsening adverse event that begins on or after the date of first dose of IMP up to the date of last dose of IMP plus 30 days.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, (HLT,) and PT) will be provided:

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

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

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

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the laboratory toxicity grading scheme defined in Appendix 3 of this protocol. The incidence of treatment-emergent laboratory abnormalities, defined as values that increase by at least one toxicity grade from baseline at any time post-baseline up to the date of last dose of study drug plus 30 days will be summarized. If baseline data are missing, then any post-baseline graded abnormality (i.e., at least Grade 1) will be considered treatment emergent.

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

8.7. Pharmacokinetic Analysis

Plasma concentrations of the study drug and metabolite(s) over time, if analyzed, will be summarized using descriptive statistics. Details of the analysis plan will be provided in the pharmacokinetic reporting and analysis plan.

8.8. Sample Size

With a sample size of 80 subjects in the treatment-naïve and in the treatment-experienced group, a two-sided 95% exact confidence interval will extend at most 23% in length.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

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

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."

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

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved informed consent form (ICF) for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements. PPD The Pharmacogenomic consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB [or] IEC and governmental approval with correspondence, informed consent, drug

records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will used his/her log in credentials to confirm that the forms have been reviewed, and that the entries required per the protocol scheduled of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

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

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

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

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

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

9.3.2. Access to Information for Auditing or Inspections

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

9.3.3. 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 and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naïve and Treatment-Experienced Korean and Taiwanese Subjects with Chronic Genotype 1 HCV Infection

GS-US-337-0131, Original, 28 May 2013

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

Phillip S. Pang

Phil Pang, MD, PhD (Printed)
Medical Monitor

PPD

5/28/2013

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed) _____ Signature _____

Date _____ Site Number _____

Appendix 2. Study Procedures Table

Appendix Table 1. Screening and On-Treatment Study Visits

Clinical Assessments	Screening[a]	On Treatment Period								
	Day -28 to Day -1	Baseline/ Day 1[b]	Week 1 (±3 days)	Week 2 (±3 days)	Week 4 (±3 days)	Week 6 (±3 days)	Week 8 (±3 days)	Week 10 (±3 days)	Week 12 (±3 days)	ET
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X							X	X
Liver Imaging (Cirrhotics Only)	X									
Height	X									
Weight	X	X							X	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X
12-lead ECG[d]	X	X	X						X	X
Adverse Events	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		X		X	X		X		X	X
Hematology & Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X							X	X
Serum HCV RNA	X	X	X	X	X	X	X	X	X	X

Clinical Assessments	Screening[a]	On Treatment Period								
	Day -28 to Day -1	Baseline/ Day 1[b]	Week 1 (±3 days)	Week 2 (±3 days)	Week 4 (±3 days)	Week 6 (±3 days)	Week 8 (±3 days)	Week 10 (±3 days)	Week 12 (±3 days)	ET
Single PK Sample			X	X	X	X	X	X	X	X
Viral RNA Sequencing /Phenotyping Sample (Plasma)[e]		X	X	X	X	X	X	X	X	X
Archive Sample[j]		X							X	X
Serum or Urine Pregnancy Test	X	X			X		X		X	X
Urinalysis	X									
IL28B Genotype, HCV Genotype	X									
HCV Ab, HIV Ab and HBsAg	X									
Hemoglobin A1c, TSH	X									
PK Substudy Collection[f]				X	X					
Single Pharmacogenomic Sample[g]		X								
Review of Study Drug Adherence and Drug Accountability[h]			X	X	X	X	X	X	X	X
Study Drug Dispensing[i]		X			X		X			

a The screening window can be extended to 42 days for subjects requiring liver biopsy or additional HCV genotype testing.

b Baseline/Day 1 assessments must be performed prior to dosing.

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

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

e Serum samples will be collected and stored for potential HCV sequencing and other virology studies.

f Subjects that consent to the optional PK substudy will have serial PK samples drawn at Week 2 or Week 4 visit.

g 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.

h Study medication and dosing diary, will be reconciled at every post-baseline visit by the investigator or designee in order to monitor the subject's adherence with the medication regimen.

i Study Drug will be dispensed per IWRS directions. Subjects must be instructed to bring back all bottles of study medication(s) in the original container at every post baseline study visits through the end of treatment.

j Archive plasma samples will be collected at the Baseline/Day 1 visit and at the end of treatment for subjects who have not opted out of sample collection

Appendix Table 2. Post Treatment Study Visits

Clinical Assessments	Post Treatment Period[a]		
	Post Treatment Week 4 (±5 days)	**Post Treatment Week 12 (±5 days)**	**Post Treatment Week 24 (±5 days)**
Weight		X	X
Vital Signs[b]	X	X	X
Adverse Events	X		
Concomitant Medications	X		
Pregnancy Prevention Counseling	X		
Health Related Quality of Life	X	X	
Hematology & Chemistry	X		
Serum HCV RNA	X	X	X
Viral Sequencing Sample (Plasma)[c]	X	X	X
Serum or Urine Pregnancy Test	X		

a All subjects will complete both 4-week and 12-week Post-Treatment visits regardless of the treatment duration. Subjects with HCV RNA < LLOQ at their 12-week Post-Treatment visit will complete a 24-week Post-Treatment visit, unless viral relapse is determined. The end of study will occur at the 24-week Post-Treatment visit.

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

c Plasma samples will be collected and stored for potential HCV sequencing 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 **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE) **Infant, 22–35 Days** (HIV POSITIVE OR NEGATIVE) **Infant, 1–21 Days** (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L 9.5 to 10.5 g/dL 95 to 105 g/L 12.0 to 13.0 g/dL 120 to 130 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L 8.0 to < 9.5 g/dL 80 to < 95 g/L 10.0 to < 12.0 g/dL 100 to < 120 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L 7.0 to < 8.0 g/dL 70 to < 80 g/L 9.0 to < 10.0 g/dL 90 to < 100 g/L	< 6.0 g/dL < 60 g/L < 7.0 g/dL < 70 g/L < 9.0 g/dL < 90 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC)	1000 to 1300/mm^3	750 to < 1000/mm^3	500 to < 750/mm^3	< 500/mm^3
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/mm^3	1000 to < 1250/mm^3	750 to < 1000/mm^3	< 750/mm^3
	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/mm^3	3000 to < 4000/mm^3	1500 to < 3000/mm^3	< 1500/mm^3
	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/mm^3	200 to < 300/mm^3	100 to < 200/mm^3	< 100/mm^3
	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/mm^3	500 to < 600/mm^3	350 to < 500/mm^3	< 350/mm^3
	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/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

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
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA

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

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

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	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.

With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

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

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

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

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

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

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year** **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
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

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

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss **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 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **Necrosis (involving dermis and deeper tissue)**
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

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

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

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

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc

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

1. Background

Non-clinical toxicity studies of sofosbuvir and ledipasvir demonstrated no adverse effect on embryo-fetal development. However, there are no clinical studies of sofosbuvir or ledipasvir in pregnant women. 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 Baseline/Day 1 visit prior to randomization. They must also agree to one of the following from 3 weeks prior to Baseline/Day 1 until 30 days after last dose of study drug.

- 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 last dose of study drug:
  - intrauterine device (IUD) with a failure rate of < 1% per year
  - female barrier method: cervical cap or diaphragm with spermicidal agent
  - 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 the date of Screening until 90 days after the last dose of study drug. If their female partner is of child bearing 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 study drug.

Male subjects must agree to refrain from sperm donation for at least 90 days after the last dose of study drug.

4. Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they (or their partner) become pregnant at any time during the study, or if they become pregnant within 30 days (90 days for partners of male subjects) of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.