CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
IND No.:	106,739
EudraCT Number	Not Applicable
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-334-0123
Gilead Sciences Study Director and Medical Monitor:	Name: Stephen Rossi, PharmD Telephone: (650) 522-4212 Fax: (650) 522-1975 E-mail: stephen.rossi@gilead.com
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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

Study Title:	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects
IND Number:	106,739
EudraCT Number:	Not Applicable
Study Centers Planned:	Approximately 45 sites in North America
Objectives:	The primary objectives of this study are as follows: • To determine the efficacy of treatment with GS-7977 + ribavirin (RBV) by proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12) • To evaluate the safety and tolerability of GS-7977 + RBV 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 GS-7977 during treatment and after treatment discontinuation The exploratory objectives of this study are: • To identify or validate genetic markers that may predict the natural history of disease, response to therapy and/or the tolerability of medical therapies through genetic discovery research (e.g., pharmacogenomics), in subjects who provide their separate and specific consent. • To assess the effect of treatment on health related quality of life

Study Design:

Open-label study in subjects with chronic Genotype 1, 2 and 3 HCV-infection who are co-infected with HIV-1. A total of 230 (115 GT 2/3 and 115 GT1) subjects with HIV-1/HCV co-infection will be enrolled into one of 3 treatment regimens depending on their genotype and prior HCV treatment history. Subjects will be treated with oral GS-7977 plus weight based RBV for 12 or 24 weeks of treatment.

1. Genotype 2 and 3 Treatment Naive subjects will receive **12** weeks of treatment.
2. Genotype 2 and 3 Treatment Experienced subjects will receive **24** weeks of treatment.
3. Genotype 1 Treatment Naive subjects will receive **24** weeks of treatment.

Equal enrollment of Genotype 2 and 3 as well as treatment naive and treatment experienced subjects will be targeted. Approximately 20% of the subjects enrolled will have evidence of compensated cirrhosis at Screening.

Subjects will be maintained on similar timing of administration and dosing conditions for their ARV regimens during the study period as those prior to the study. Post-treatment follow-up visits will be performed for all subjects at 4 weeks following the last dose of study drug. Subjects with HCV RNA < lower limit of quantification (LLOQ) at post-treatment Week 4 will return at post-treatment Week 12 and Week 24 unless confirmed HCV relapse occurs. Subjects who experience HCV virologic breakthrough or whom do not achieve an HCV RNA <LLOQ will be enrolled into a separate Sequence Registry study. Safety assessments, including monitoring of HIV RNA and CD4 T-cell, counts will be performed at all study visits.

HCV RNA results will be blinded to the Investigator and Sponsor post Screening through SVR 24. Sponsor employees involved in the virologic analysis of samples from subjects that fail to respond to treatment (virologic failures) will have access to HCV RNA data in order to identify the appropriate subject samples for virologic analyses.

	Registry Studies **Sequence Registry Study** Subjects who do not achieve SVR, as well as those who achieve SVR and later become detectable, will be eligible for enrollment in the Sequence Registry Study. The purpose of the Sequence Registry Study will be to monitor the persistence of resistant mutations for up to 3 years after the last dose of study medication. The Sequence Registry Study is described in a separate protocol (GS-US-248-0123). **SVR Registry Study** Subjects who achieve SVR at 24-weeks post treatment will be eligible for enrollment in the SVR Registry Study. The purpose of the SVR Registry Study will be to evaluate durability of SVR for up to 3 years post-treatment. The SVR Registry Study is described in a separate protocol (GS-US-248-0122).
Number of Subjects Planned:	Approximately 230 (115 Genotype 1 and 115 Genotype 2/3)
Target Population:	HCV treatment naïve and treatment experienced (Genotype 2/3 only) subjects age ≥ 18 years with chronic genotypes 1, 2 and 3 HCV infection who are co-infected with HIV-1.
Duration of Treatment:	12 weeks for Genotype 2 and 3 HCV treatment naïve subjects; 24 weeks for Genotype 1 HCV treatment naïve and Genotype 2/3 HCV treatment experienced.

Diagnosis and Main Eligibility Criteria:	Subjects must meet the following eligibility criteria: • Age ≥ 18 years with chronic HCV and HIV-1 co-infection. • HCV RNA ≥ 1 x 10^4 IU/mL at Screening • HCV Genotype 1(treatment naïve only), 2 or 3 determined at Screening • HIV-1 infection confirmed with a positive ELISA and Western-blot at Screening (if necessary). • Adequate medical records to be categorized based on IFN eligibility or prior treatment with PEG/RBV into one of the following categories as defined in Section 6.4.2 of the protocol: o **Treatment Naïve - IFN-eligible** o **Treatment Naïve - IFN-ineligible** o **Treatment Experienced - IFN Intolerant (Genotype 2/3 only)** o **Treatment Experienced - Non-Response (Genotype 2/3 only)** o **Treatment Experienced - Relapse/Breakthrough (Genotype 2/3 only)** • Ability to determine the presence/absence of compensated cirrhosis o Up to 20% of study subjects may be cirrhotic • Cirrhosis is defined as any of the following: o Liver biopsy performed within 2 years of screening showing cirrhosis o A FibroTest® score of >0.75 AND an AST:platelet ratio index (APRI) of >2 performed during Screening • Absence of cirrhosis is defined as one of the following: o A liver biopsy performed within 2 years of screening showing absence of cirrhosis o A FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 performed during screening In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy is required during screening. If both a biopsy and FibroTest® plus APRI results are obtained, the biopsy results will supersede for the determination of cirrhosis. • HIV antiretroviral therapy (ARV) criteria of one of the following: • ARV untreated for ≥ 8 weeks preceding the Screening visit with a CD4 T-cell count >500 cells/mm^3 [up to 10% of study subjects may be ARV untreated], or

- On a stable, protocol-approved, ARV for >8 weeks prior to Screening with a CD4 T-cell count >200 cells/mm^3 and undetectable plasma HIV-1 RNA level by local assay for ≥ 8 weeks preceding the Screening visit. HIV-1 viral load results should be measured within 1 year of the Screening visit. Screening HIV RNA must be < 50 cp/mL as measured by the COBAS AMPLIPREP/COBAS TaqMan 2.0 HCV RNA assay.
  - Subjects who switched from atazanavir/ritonavir (boosted) to darunavir/ritonavir (boosted) prior to Amendment 2 will be exempt from the 8 week stable ARV regimen requirement as defined in Section 6.4.2.
- HIV antiretroviral medications allowed in this study include the following and should be administered per the prescribing information in the package insert:
  - emtricitabine/tenofovir plus:
    - atazanavir/ritonavir (boosted); or
    - darunavir/ritonavir (boosted); or
    - efavirenz; or
    - raltegravir; or
    - rilpivirine

Alternative combinations of the above listed medications may be allowed on a case by case basis. ARV regimens not on the above list are excluded from this study.

- Body mass index (BMI) ≥ 18 kg/m^2
- Subjects must have the following laboratory parameters at Screening:
  - ALT ≤ 10 × the upper limit of normal (ULN)
  - AST ≤ 10 × ULN
  - Hemoglobin ≥ 12 g/dL for male, ≥ 11 g/dL for female subjects
  - INR ≤1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR
  - Albumin ≥ 3 g/dL
  - Direct bilirubin ≤ 1.5 × ULN
    - For subjects receiving an atazanavir/ritonavir (boosted) regimen, a direct bilirubin > 1.5 x ULN will be allowed if <25% of the total bilirubin.

Diagnosis and Main Eligibility Criteria: (Continued)	○ HbA1c ≤ 10% ○ Creatinine clearance (CL_{cr}) ≥ 60 mL/min as determined by Cockroft-Gault {2202} • Agree to use two forms of highly effective contraception, as referenced in Section 4.2, for the duration of the study and for 6 months (7 months for males) after the last dose of study medication. Females of childbearing potential must have a negative pregnancy test at Screening and Baseline Subjects will be ineligible if they meet any of the following criteria: • Non-genotype 1/2/3 or mixed genotype at Screening • Genotype 1 subjects who have received prior HCV treatment • Poor control with ARV therapy requiring a modification of therapy within 1 month of GS-7977 dosing. • Prior exposure to a direct-acting antiviral targeting the HCV NS5B polymerase. Subjects participating in the Drug Interaction (part A) of P7977-1910 protocol are an exception to this criterion • Evidence or history of hepatic decompensation • Hematologic or biochemical parameters at screening outside the protocol-specified requirements • Screening ECG with clinically significant abnormalities as determined by the investigator • Chronic hepatitis B virus (HBV) infection • Hepatocellular carcinoma or other malignancy (with exception of certain resolved skin cancers) • Chronic use of systemic immunosuppressive agents or immunomodulatory agents • Active or recent history (≤ 1 year) of drug or alcohol abuse • A new AIDS-defining condition diagnosed within 30 days prior to screening • Active, serious infection (other than HIV-1 or HCV) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Baseline • History or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of the study, or interfere with the subject's

	participation for the full duration of the study, such that it is not in the best interest of the subject to participate See Sections 4.2 and 4.3 of the protocol for full inclusion/Exclusion criteria.
Study Procedures/ Frequency:	Study visits will occur at Screening, Baseline (Day 1) and at the end of Weeks 1, 2, 4, 6, 8, 10, and 12 for the Genotype 2 and 3 HCV treatment naïve subjects. Additional study visits occur at the end of Weeks 16, 20 and 24 for Genotype 1 HCV treatment naïve and HCV treatment-experienced Genotypes 2 and 3. Post-treatment follow-up visits will be performed for all subjects at 4 weeks following the last dose of study drug. Subjects with HCV RNA < lower limit of quantification (LLOQ) at post-treatment Week 4 will return at post-treatment Week 12 and Week 24. Screening assessments include physical examination, vital signs, concomitant medications, safety laboratory tests, HCV RNA, HIV-1 RNA, CD4 T-cell count and percent, serology (HIV, HCV, HBV), hemoglobin A1c (HbA1c), Fibrotest®/APRI, imaging for HCC (cirrhotics only), lipase, serum β-hCG (females of child bearing potential only), thyroid stimulating hormone (TSH), IL28B genotyping, urinalysis and urine drug screen. On-treatment assessments include adverse events (AEs), concomitant medications, physical examination, vital signs, safety laboratory tests, HCV RNA, HIV-1 RNA, CD4 T-cell count and percent, pharmacokinetic samples, and urine pregnancy tests (females of child bearing potential only). Post-treatment assessments include AEs, concomitant medications, vital signs, safety laboratory tests, HCV RNA, HIV-1 RNA, CD4 T-cell count and percent, and urine pregnancy tests (females of child bearing potential only). Quality of life surveys will be performed at Baseline/Day 1, Week 4, Week 12, Week 24 (as appropriate for the treatment regimen), Early Termination, post-treatment Week 4, and post-treatment Week 12 and post-treatment Week 24 to assess quality of life. Samples will be collected at Baseline and every visit thereafter for viral sequencing. For subjects who provide their additional and specific consent, an appropriate blood sample will be collected at the Baseline visit for human pharmacogenomic testing (this sample may be drawn after Baseline, if necessary).

Test Product, Dose, and Mode of Administration:	GS-7977 will be administered orally using a tablet strength of 400 mg. RBV will be administered orally using a tablet strength of 200 mg. Subjects will take 1000-1200 mg RBV every day in a divided daily dose (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg). The morning dose of RBV will be taken with one tablet of GS-7977 (400 mg) and with food. The evening dose of RBV will be taken with food.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	AEs, safety labs (including HIV-1 RNA and CD4 T-cell count and percent), 12-lead ECG, and vital signs will be collected throughout the study and through the Week 4 post-treatment visit. If greater than 20% of subjects enrolled on any specific ARV regimen experience virologic breakthrough, an evaluation of the safety of continuing enrollment of subjects on this specific ARV therapy will occur.
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.
PK:	A single PK blood sample will be collected at all subject visits while on treatment. The PK of GS-7977 and metabolite(s) (as appropriate) and/or ribavirin will be assessed.

Statistical Methods:	The primary efficacy endpoint is SVR12 in all enrolled and treated subjects. Secondary efficacy endpoints include SVR4 and SVR24. Subgroup analyses will be performed for SVR12. All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum). All categorical endpoints will be summarized by number and percentage of subjects who meet the endpoint definition. Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data by treatment group. With approximately 55 GT2/3 treatment-naïve subjects enrolled into the study, a two-sided 95.0% confidence interval of the SVR12 rate will extend at most 12.8% in both directions from the observed SVR12 rate, assuming the expected SVR12 rate is 62%. With approximately 55 GT2/3 treatment-experienced and 115 GT1 treatment-naïve subjects enrolled into the study, the SVR12 rate will extend at most 12.9% and 8.7% respectively, assuming the expected SVR12 rate is 40% and 65% respectively.

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
ARV	antiretroviral
AST	aspartate aminotransferase (also SGOT)
ATV	atazanavir
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
BVR	bocepravir
BW	body weight
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CMH	Cochran-Mantel-Haenszel
COPD	Chronic obstructive pulmonary disease
CRF	case report form(s)
CRO	Contract (or clinical) research organization
DAA	Direct acting antiviral
dL	Deciliter
DNA	deoxyribonucleic acid
DRV	darunavir
DSMB	Data Safety Monitoring Board
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
EFV	efavirenz
eCRF	Electronic case report form(s)
ESA	Erythropoiesis stimulating agent
Emax	maximal effect
EU	European Union
EVR	Early virologic response

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

FAS	full analysis set
FDA	(United States) Food and Drug Administration
FEV_1	forced expiratory volume in one second
FTC	emtricitabine
GCP	Good Clinical Practice (Guidelines)
GGT	gamma glutamyl transferase
GCSF	Granulocyte colony stimulating factor
GSI	Gilead Sciences, Inc.
GT	Genotype (viral)
Hb	Hemoglobin
HbA_{1c}	Hemoglobin A_{1c}
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	high-density polyethylene
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL28B	IL28B gene
IND	Investigational New Drug (Application)
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
IWRS	interactive web response system
Kg	Kilogram
L	Liter
LDH	Lactase dehydrogenase
LLN	lower limit of the normal range
LOD	Lower limit of detection
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MH	Mantel-Haenszel
mL	Milliliter
Min	Minute
mmHg	millimeters mercury

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

NS (3/4A/5A/5B)	Non-structural Protein
PBMC	peripheral blood mononuclear cell(s)
PEG	pegylated interferon
P-gp	P-glycoprotein
PI	Protease inhibitor
QD	once daily (use only in tables)
PK	Pharmacokinetic
QTcF	QT interval corrected using Fridericia' formula
r	Low dose Ritonavir (booster)
RAL	raltegravir
RBC	Red blood cell count
RBV	Ribavirin
RDRP	RNA-dependent RNA polymerase
RNA	ribonucleic acid
RPV	rilpivrine
RTV	ritonavir
RVR	rapid virologic response
SADR	Serious adverse drug reaction
SAE	serious adverse event
SD	Standard deviation
SOC	Standard of Care
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
TDF	tenofovir
Tmax	The time (observed time point) of Cmax
TND	Target not detected
TSH	Thyroid stimulating hormone
TVR	telaprevir
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)
ULN	upper limit of the normal range
US	United States
WBC	white blood cell count

1. INTRODUCTION

1.1. Background

Hepatitis C virus (HCV) infection affects an estimated 180 million people globally {10894}. It is a leading cause of chronic hepatitis, cirrhosis and liver cancer and a primary indication for liver transplantation in the Western world. There are 6 major HCV genotypes whose prevalence varies geographically. The most common genotype in the USA and in Europe is genotype 1 followed by genotype 2 and genotype 3 {19705}. Genotype 4, 5 and 6 HCV infection is most prevalent in the Middle East, South Africa and Southeast Asia, respectively. Following recent approvals of telaprevir (Incivek ™) (TVR) and boceprevir (Victrelis™) (BVR) {17653}, {17733}, the current standard of care for chronic genotype 1 HCV infection involves the combination of either one of these protease inhibitors three times daily (TID) with once-weekly subcutaneous injections of pegylated interferon (PEG) and twice-daily oral ribavirin (RBV). Although these regimens have demonstrated SVR rates which are superior to PEG+RBV alone in subjects with genotype 1 HCV infection, they are not approved for treatment of subjects infected with other HCV genotypes or with HIV and HCV coinfection and have limited efficacy in prior non-responders {17653}, {17733}.The development of an interferon-free regimen for the treatment of chronic HCV infection has the potential to make a major impact on the global incidence, prevalence and burden of HCV infections. New treatment options are especially crucial in patient populations for whom treatment with PEG is not possible or without sufficient efficacy, including those who have failed prior therapy.

Large numbers of human immunodeficiency virus (HIV)-positive patients are co-infected with the hepatitis C virus (HCV) because of the shared intravenous routes of infection. Co-infection is estimated to occur in one quarter of HIV-infected persons in Europe, Australia, and the United States, and in a study from the Veterans Affairs Medical Center in Atlanta, Georgia, HCV infection occurred in as many as 33% of the patients with HIV infection {11614}. Co-infection occurs more often in those who acquired HIV through illicit IV drug abuse, which can be as high as 60%, than via men having sex with men (about 4%) {11614}. The use of antiretroviral therapy (ARV) has markedly reduced opportunistic infections and HIV-positive persons are living longer {19452}. However, liver disease has emerged as the main cause of morbidity and mortality in the HIV positive patient, and the development of end stage liver disease seems to be unrelated to the CD4 count and the immune virological status of the patient {16008}. Co-infected patients were 5 to 6 times more likely to develop decompensated liver failure and 1.5 to 2 times more likely to develop histological cirrhosis {20740}. Additionally, the risk of death in the co-infected patients was nearly 4 times greater compared with that in mono-infected individuals {20737}. Furthermore, the previous standard of care for the treatment of HCV infection, pegylated interferon alfa plus ribavirin, appears to be less effective in patients with co-infection than in patients with HCV monoinfection {10214}, {9652}, {19911}. Because end stage liver disease is the leading cause of non-AIDS-related death in the co-infected patient, there is a significant need for increased treatment options for HCV infection in this population.

At present, the recommended first-line treatment for HCV mono-infected patients with Genotype 1 (GT1) chronic hepatitis C is an NS3/4A protease inhibitor in combination with pegylated interferon-alfa (PEG) and ribavirin (RBV) for 24 to 48 weeks {19759}. Recent updates have suggested guidelines for use of TVR and BVR in HIV/HCV coinfected population but neither is currently approved for use in this population {20739}. However, there is limited clinical efficacy and safety data with TVR and BVR in the HIV/HCV coinfected population. Recent Phase 2 data have demonstrated a significant improvement with the addition of TVR or BVR to PEG/RBV versus PEG/RBV alone in HIV/HCV coinfected subjects {20748}, {20743}. Sustained virologic response (SVR) rates of 60-74% were observed in the triple therapy combinations versus 26-45% for the PEG/RBV control groups and approach the response observed in mono-infected subjects. Safety appears comparable between the HIV/HCV coinfected and HCV monoinfected subjects. HIV viral breakthrough was observed in 8 subjects during the BVR trial, highlighting the importance of close monitoring of both HIV and HCV during treatment.

Human immunodeficiency virus (HIV) infection treatment has improved with the widespread availability of ARV and the appearance of numerous ARV drugs in the market over the past 15 years. Currently, several ritonavir (RTV) (r)-boosted protease inhibitors (PIs) in combination with other ARVs are recommended as options for first-line ARV therapy, and several are approved for and commonly used in treatment-experienced patients {20239}, {20746}. While extremely effective for treatment of HIV, r-boosted PIs are substrates for and potent inhibitors of cytochrome P450 3A4 (CYP 3A4) enzymes; as a result, drug-drug interactions with these agents are frequent {20239}, {20746}. Numerous pharmacokinetic (PK) studies and case reports provide evidence that r-boosted PIs are associated with a number of clinically relevant drug interactions as a result of PK changes related to either the protease inhibitor or the concomitant medications {20239}, {20746}. Other first-line ARV therapies include non-nucleoside reverse transcriptase inhibitors (NNRTI) and integrase inhibitors in combination with nucleoside or nucleotide reverse transcriptase inhibitors (NRTI) {20239}, {20746}. These non-nucleoside inhibitors, in particular efavirenz (EFV), are substrates and inducers of CYP-450 2B6 and 3A4, whereas the integrase inhibitor is a strong inducer of UGT1A1 {20239}, {20746}.

Both TVR and BVR are substrates and inhibitors of CYP3A4, and BVR has significant drug interactions with the ARV therapies {20736}. Drug interactions both TVR and BVR with some RTV (r) boosted PIs, have been reported and and in some cases have been contraindicated for combined use. {20743}, {20741}, {20744}. Further drug interaction studies have been reported between both drugs with EFV {20748}, {20743}. Recent data has demonstrated a significant interaction between EFV and the HCV DAAs TMC-435 and daclastavir while no interactions with TDF/FTC, raltegravir (RAL) or rilpivrine (RPV). {20738}, {20747}.The importance of evaluating DDIs between ARV and HCV DAAs is highlighted in recent FDA guidance requiring these interaction studies to be completed prior to studying these agents together in HIV/HCV coinfected subjects. {20581}.

It is clear from this early information that the use of the first generation of HCV PIs will be difficult in the coinfected population. While there is an urgency to facilitate safe and

effective therapies to the co-infected patient, the number of DDI studies required with TVR and BVR is extensive and would require marked expertise to calculate all the drug modifications required for the ARVs and/or the anti-HCV therapy. Additionally, these therapies are still used in combination with PEG/RBV and the relative and absolute contraindications to these agents will still eliminate a vast majority of patients as treatment candidates. The adverse events associated with TVR and BVR, including significant anemia, rash and GI symptoms, are additive to the already significant adverse events observed with PEG/RBV treatment. Therefore, the development of IFN-free, all-oral therapies with low-potential for drug interactions is highly desirable in this population.

Novel anti-hepatitis C treatments under study are directed against a variety of molecular targets, which include the virally encoded RNA-dependent RNA polymerase (RdRp, NS5B) and the NS5a protein. Some of the most consistently effective inhibitors for these enzymes have been nucleos(t)ide analogs, such as GS-7977. These compounds share characteristics with natural nucleoside substrates found in the cell, and once phosphorylated to the nucleoside-triphosphate, cause termination of the newly encoded viral genome.

GS-7977 is a novel nucleotide analogue that inhibits HCV RNA replication in vitro and has demonstrated high rates of sustained viral response (SVR) when given with PEG and RBV to subjects with chronic genotype 1, 2 and 3 HCV infection. Antiviral activity in genotypes 1-6 has been demonstrated in vitro and, for genotypes 1-4 and 6, clinically. More recent data indicate that PEG is not required for successful treatment of subjects with chronic genotype 2 and 3 HCV infection; 100% SVR was observed in 10/10 treatment-naïve genotype 2 or 3 HCV infected subjects treated for 12 weeks with GS-7977 and RBV (See Section 1.3.4). Emerging data indicate that treatment of treatment-experienced genotype 2 or 3 HCV-infected subjects with GS-7977 + RBV for 12 weeks results in rapid viral clearance and a high rate of sustained virologic response in HCV monoinfection for whom there is currently no recommended treatment option. Additionally, recent data with GS-7977 combined with RBV for 12-24 weeks in treatment-naïve genotype 1 HCV-infected subjects demonstrated a range of response rates comparable to the current standard of care. Initial data suggests that subjects with HIV/HCV coinfection have similar on-treatment viral kinetics as moninfected subjects when treated with GS-7977. Thus, GS-7977 + RBV for 12 or 24 weeks based upon treatment history and HCV genotype may represent a promising treatment option to HCV-infected subjects coinfected with HIV who currently are limited to treatment with PEG/RBV.

1.2. GS-7977

GS-7977 is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed HCV replication.

Please refer to the Investigator's Brochure (IB) for additional information on GS-7977 including:

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

1.3. Summary of Additional Clinical Experience

GS-7977 is being studied in combination with PEG, RBV, and other direct acting antivirals (DAAs) for the treatment of chronic HCV infection. There is an ongoing clinical pharmacology program and there are later stage studies in all genotypes. Additional drug interactions studies with key HIV antiretrovirals (ARVs) are also discussed as they are relevant to the study population of this protocol.GS-US-334-0131 evaluated GS-7977-ARV DDIs in healthy volunteers and P7977-1910 evaluated GS-7977-ARV DDIs and viral kinetics in HIV/HCV coinfected subjects.

1.3.1. GS-US-334-0131

This open-label, multiple-dose, fixed-sequence, five-cohort, single-center study was conducted in healthy volunteers and evaluated the potential for drug-drug interaction between GS-7977 and HIV medications Atripla®, Darunavir (DRV) /r, Raltegravir (RAL) and Rilpivirine (RPV). Seventy-four evaluable subjects comprised of male and non-pregnant, non-lactating female subjects between 18 and 45 years old were enrolled into one of four cohorts and received study treatments as follows:

Cohort 1 (under fasted conditions)

Days			
1	**2-4**	**5-18**	**19**
GS-7977 (400 mg tablet) single dose in the AM	Washout	Atripla® EFV/FTC/TDF (600/200/300 mg tablet, QD) in the AM	GS-7977 (400 mg tablet) single dose in the AM **PLUS** Atripla® EFV/FTC/TDF (600/200/300 mg tablet, QD) in the AM

Cohort 2 (under fed conditions)

Days			
1	**2-4**	**5-14**	**15**
GS-7977 (400 mg tablet) single dose in the AM	Washout	Darunavir/ritonavir; DRV/r; (800/100 mg tablet QD) in the AM	GS-7977 (400 mg tablet) single dose in the AM **PLUS** DRV/r; (800/100 mg tablet QD) in the AM

Cohort 3 (under fasted conditions)

Days			
1	**2-4**	**5-14**	**15**
GS-7977 (400 mg tablet) single dose in the AM	Washout	**AM/PM dose:** Raltegravir; RAL (400 mg tablet, AM/PM dose)	GS-7977 (400 mg tablet) single dose in the AM **PLUS** RAL (400 mg tablet, AM dose only)

Cohort 4 (under fed conditions)

Days			
1	**2-4**	**5-14**	**15**
GS-7977 (400 mg tablet) single dose in the AM	Washout	Rilpivirine; RPV (25 mg tablet, QD) in the AM	GS-7977 (400 mg tablet) single dose in the AM **PLUS** RPV (25 mg tablet, QD) in the AM

1.3.1.1. GS-US-334-0131 Preliminary Pharmacokinetic Analysis

Serial blood samples for PK analyses were collected on Day 1 (post GS-7977 dose) and Days 14-19 (HIV medication alone or in combination with GS-7977) at selected timepoints. The study conduct is completed and preliminary pharmacokinetic analyses have been completed. Results from Cohorts 1 to 4 are presented below.

Table 1-1. GS-US-334-0131: Cohort 1 Preliminary Pharmacokinetic Analysis

Cohort 1: Sixteen subjects completed the study procedures and the data are as follows:

Effect of ATR (EFV/FTC /TDF) on GS-7977 (n=16)			
GS-7977			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + ATR**	**%GMR (90%CI)**
AUCinf (ng.hr/ml)	827 (41.7)	777 (41.1)	93.9 (75.9-116)
Cmax (ng/ml)	1020 (47.7)	877 (64.0)	80.9 (59.6-110)
GS-566500			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + ATR**	**%GMR (90%CI)**
AUCinf (ng.hr/ml)	1140 (27.8)	895 (28.2)	79.2 (69.4-90.4)
Cmax (ng/ml)	308 (37.5)	218 (37.2)	72.1 (62.2-83.7)
GS-331007			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + ATR**	**%GMR (90%CI)**
AUCinf (ng.hr/ml)	11,300 (19.0)	9,620 (25.7)	84.0 (76.2-92.5)
Cmax (ng/ml)	1,250 (24.2)	965 (26.8)	76.7 (69.8-84.3)

Effect of GS-7977 on ATR (EFV/FTC/TDF) (n=16)			
TDF			
Mean (%CV)	**ATR alone**	**ATR + GS-7977**	**%GMR (90%CI)**
AUC_{tau} (ng.hr/ml)	2,270 (22.6)	2,210 (20.3)	97.7 (91.1-105)
C_{max} (ng/ml)	274 (32.0)	343 (29.6)	125 (108-145)
C_{trough} (ng/ml)	43.7 (23.1)	42.9 (20.6)	98.6 (91.3-106)
FTC			
Mean (%CV)	**ATR alone**	**ATR + GS-7977**	**%GMR (90%CI)**
AUC_{tau} (ng.hr/ml)	9,910 (17.6)	9,810 (17.2)	99.1 (93.7-105)
C_{max} (ng/ml)	1,840 (28.6)	1,780 (27.2	96.9 (87.6-107)
C_{trough} (ng/ml)	69.2 (22.0)	73.0 (25.6)	104 (97.6-111)
EFV			
Mean (%CV)	**ATR alone**	**ATR + GS-7977**	**%GMR (90%CI)**
AUC_{tau} (ng.hr/ml)	70,900 (56.2)	69,600 (62.7)	96.7 (90.8-103)
C_{max} (ng/ml)	4,410 (45.2)	4,250 (50.7)	94.7 (84.6-106)
C_{trough} (ng/ml)	2,310 (68.0)	2,280 (75.4)	96.9 (94.0-99.8)

Modest decreases in systemic exposure of GS-7977 and GS-566500 (GS-56500 Cmax decreased by 28%) with no effect on GS-331007 were noted on co-administration of GS-7977 with ATR.TDF, FTC and EFV PK were unaltered by GS-7977, with the exception

of a slight increase in TDF Cmax (25%) that is not considered to be clinically significant. Based on these results, GS-7977 can be co-administered with ATR or its components (TDF, FTC, FTC/TDF and EFV).

Table 1-2. GS-US-334-0131: Cohort 2 Preliminary Pharmacokinetic Analysis

Cohort 2: Eighteen subjects completed the study procedures and the data are as follows:

Effect of DRV/r on GS-7977 (n=18)			
GS-7977			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + DRV/r**	**%GMR (90%CI)**
AUCinf (ng.hr/ml)	1,130 (47.7)	1,330 (30.6)	133 (112-157)
Cmax (ng/ml)	544 (48.3)	773 (55.8)	145 (110-192)
GS-566500			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + DRV/r**	**%GMR (90%CI)**
AUCinf (ng.hr/ml)	1,410 (36.8)	2,430 (29.4)	180 (163-198)
Cmax (ng/ml)	266 (38.4)	468 (34.9)	180 (156-208)
GS-331007			
Mean (%CV)	**GS-7977 alone**	**GS-7977 +DRV/r**	**%GMR (90%CI)**
AUCinf (ng.hr/ml)	11,900 (16.0)	14,700 (16.7)	124 (117-130)
Cmax (ng/ml)	1,020 (20.7)	988 (19.8)	97.3 (90.1-105)

Effect of GS-7977 on DRV/r: Cohort 2, fed (n=18)			
DRV			
Mean (%CV)	**DRV/r alone**	**DRV/r + GS-7977**	**%GMR (90%CI)**
AUCtau (ng.hr/ml)	116,000 (25.8)	113,000 (26.2)	97.0 (94.2-99.8)
Cmax (ng/ml)	9,740 (20.3)	9,480 (19.8)	97.3 (94.1-101)
Ctrough (ng/ml)	3,330 (40.4)	2,860 (38.6)	98.6 (91.3-106)
RTV			
Mean (%CV)	**DRV/r alone**	**DRV/r + GS-7977**	**%GMR (90%CI)**
AUCtau (ng.hr/ml)	4,400 (45.2)	4,220 (46.4)	94.9 (88.1-102)
Cmax (ng/ml)	630 (50.2)	608 (46.4)	94.8 (84.3-107)
Ctrough (ng/ml)	45.8 (51.5)	42.1 (54.9)	91.4 (86.1-97.0)

DRV/r increased GS-7977and GS-566500 systemic exposure (33 to 80% respectively) but did not substantially alter the PK of GS-331007 (AUC: 24 % increase). The PK of DRV and RTV was unchanged on administration of GS-7977. The increase in GS-7977 exposure on

administration with DRV/r does not necessitate dose adjustment (based on results from P7977-1918). GS-7977 can be co-administered with DRV/r.

Table 1-3. GS-US-334-0131: Cohort 3 Preliminary Pharmacokinetic Analysis

Cohort 3: Eighteen subjects completed the study procedures and the data are as follows:

Effect of RAL on GS-7977 (n=18)			
GS-7977			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + RAL**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/ml)	876 (50.9)	1,380 (75.8)	143 (104-197)
C_{max} (ng/ml)	943 (58.5)	807 (45.1)	87.3 (70.7-108)
GS-566500			
Mean (%CV)	GS-7977 alone	GS-7977 + RAL	%GMR (90%CI)
AUC_{inf} (ng.hr/ml)	1,160 (27.5)	1,180 (33.0)	99.6 (87.7-113)
C_{max} (ng/ml)	316 (29.2)	285 (30.2)	88.9 (78.7-100)
GS-331007			
Mean (%CV)	**GS-7977 alone**	**GS-7977 +RAL**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/ml)	11,200 (21.6)	11,500 (20.7)	103 (97.3-109)
C_{max} (ng/ml)	1,100 (22.6)	1,190 (22.3)	109 (98.9-120)

Effect of GS-7977 on RAL (n=18)			
Mean (%CV)	**RAL alone**	**RAL + GS-7977**	**%GMR (90%CI)**
AUC_{tau} (ng.hr/ml)	6,480 (74.6)	5,790 (100)	73.1 (58.6-91.1)
C_{max} (ng/ml)	2,350 (83.9)	1,840 (113)	57.4 (43.7-75.4)
C_{trough} (ng/ml)	66.6 (51.0)	61.7 (45.6)	95.0 (81.0-112)

GS-7977 AUC_{inf} was 43% higher in the presence of RAL. The PK of both GS-7977 metabolites (GS-566500 and GS-331007) was unchanged by RAL. As described earlier (results from P7977-1918), the increase in GS-7977 AUC is not considered to be clinically relevant.

GS-7977 decreased RAL AUC_{tau} and C_{max} (~27 and 43% respectively) but did not alter RAL trough concentrations. The RAL prescribing information states that no dose adjustment for RAL is required on dosing with tipranavir/r which decreases RAL exposure comparable to

values seen in this study. Based on the prescribing label and considering that dosing with GS-7977 did not alter RAL trough concentrations, GS-7977 may be co-administered with RAL, 400 mg BID.

Table 1-4. GS-US-334-0131: Cohort 4 Preliminary Pharmacokinetic Analysis

Cohort 4: Seventeen subjects completed the study procedures and the data are as follows:

Effect of RPVon GS-7977 (n=17)			
GS-7977			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + RPV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/ml)	847 (30.2)	944 (37.8)	109 (93.6-127)
C_{max} (ng/ml)	463 (56.4)	587 (66.6)	120.6 (89.6-162)
GS-566500			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + RPV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/ml)	1,290 (25.9)	1,260 (26.4)	97.6 (88.1-108)
C_{max} (ng/ml)	256 (38.1)	263 (35.0)	103 (87.8-121)
GS-331007			
Mean (%CV)	**GS-7977 alone**	**GS-7977 +RPV**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/ml)	11,400 (18.6)	11,500 (19.2)	100 (96.6-104)
C_{max} (ng/ml)	1,000 (22.1)	1,060 (22.2)	106 (98.6-114)

RPV (n=17)			
Mean (%CV)	**RPV alone**	**RPV + GS-7977**	**%GMR (90%CI)**
AUC_{tau} (ng.hr/ml)	2,770 (36.7)	2,930 (37.1)	105 (102-109)
C_{max} (ng/ml)	195 (28.8)	210 (35.5)	105 (96.6-115)
C_{trough} (ng/ml)	109 (43.1)	109 (45.8)	98.9 (94.4-103)

GS-7977 and RPV are not involved in a clinically relevant drug interaction (20% increase in GS-7977 C_{max}). GS-7977 can be co-administered with RPV.

Conclusions: There were no clinically significant drug-drug interactions observed between GS-7977 and the HIV ARVs EFV, FTC/TDF, DRV/r, RAL or RPV. These data support potential use of GS-7977 with a variety of ARV regimens in the HIV/HCV co-infected population.

1.3.1.2. GS-US-334-0131 Preliminary Safety

Preliminary safety was evaluated in this population where both ARV medications and GS-7977 are considered study drugs. There were a total 65 adverse events in 33 patients, the majority of which were related to study procedure or study medication. The most frequent adverse events were dizziness, headache, diarrhea, nausea and constipation with the majority occurring in the Cohort 1 (Atripla) subjects. All events were mild with the exception of a single case of facial pain graded, unrelated to study drug, graded as moderate. The majority of these events occurred during ARV medication dosing, predominantly in Cohort 1 (Atripla), and were consistent with known early toxicities of EFV. Few events were treatment-emergent during the administration of GS-7977. No Grade 3 or 4 laboratory abnormalities observed during the study period.

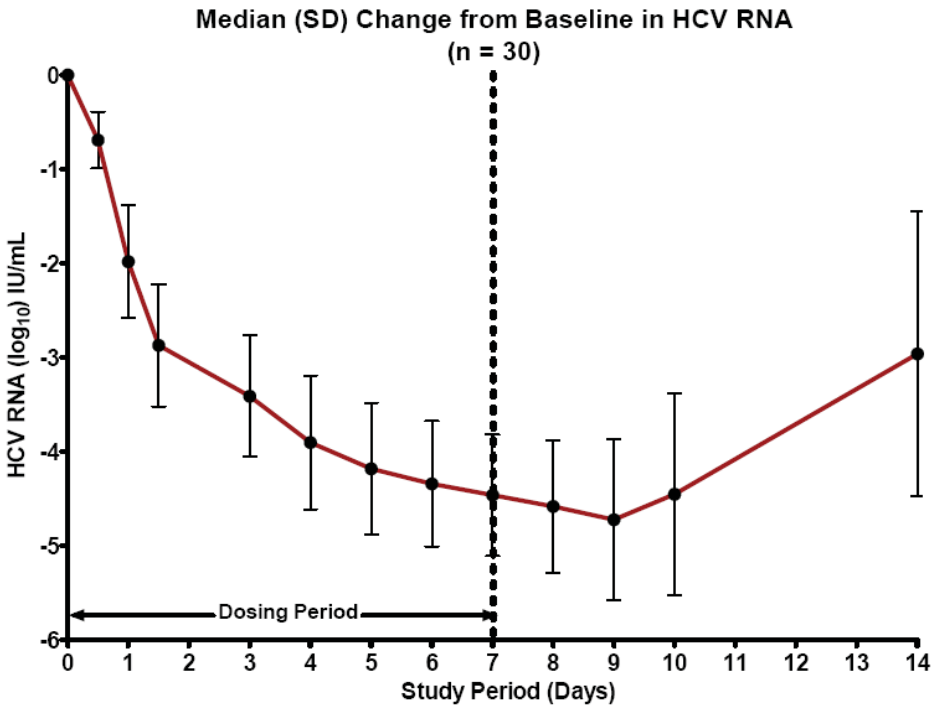
1.3.2. P7977-1910

This study is an open–label, single sequence design conducted in approximately 40 evaluable healthy HIV/HCV co-infected subjects to evaluate the pharmacokinetic interactions between GS-7977 and EFV + TDF + FTC, EFV + ZDV + 3TC, ATV/r + TDF + FTC, DRV/r + TDF + FTC, and RAL. The study consisted of 5 cohorts of 8 co-infected subjects that are using one of the above ARV combinations for a minimum of 4 weeks prior to GS-7977 dosing. Subjects were maintained on a similar timing and dosing conditions for taking their ARV regimens during the study period as taken prior to the study. During the treatment period subjects received GS-7977 in combination with one of the above regimens for 7 days. Blood samples for pharmacokinetic analysis of each ARV component were collected serially throughout the dosing interval on the day prior to initiation of GS-7977 treatment and final day of co-administration with GS-7977. GS-7977 and its metabolites, GS-352707 and GS-6206, plasma concentrations were obtained on the final day of co-administration with ARV. HIV and HCV RNA samples were collected at baseline, throughout co-administration of GS-7977 and ARV and during follow-up. The study conduct is ongoing but preliminary safety and antiviral activity is available for the first 30 subjects.

1.3.2.1. Preliminary Viral Kinetics

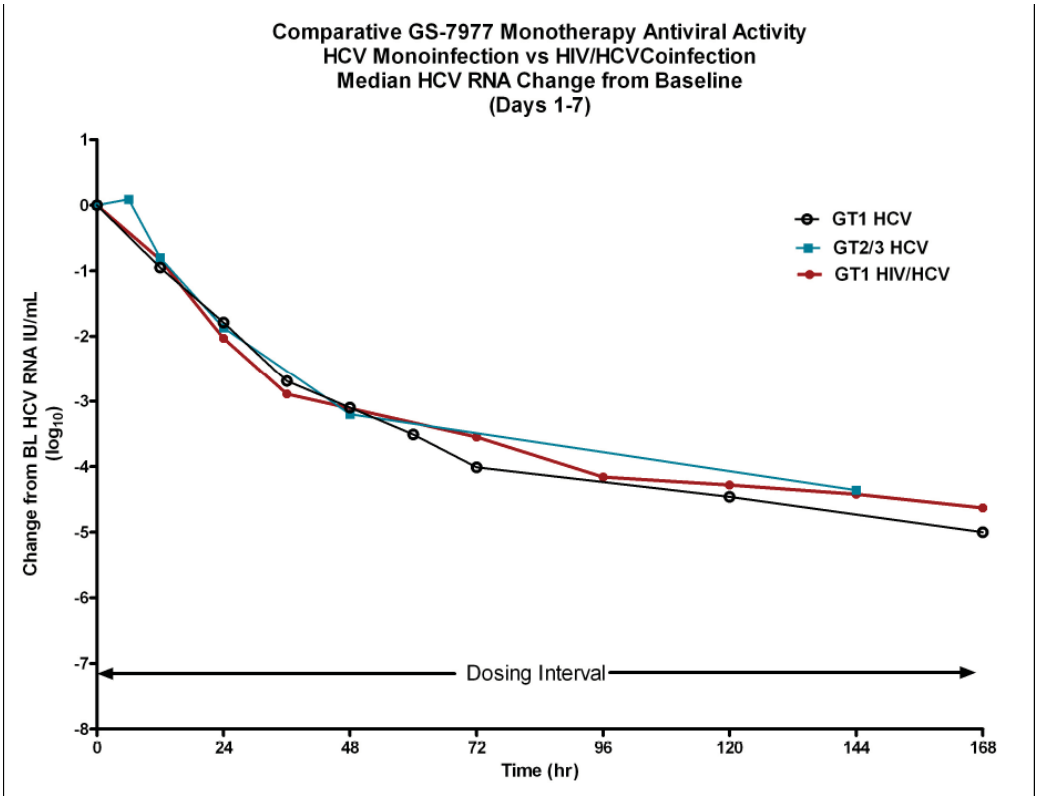
A total of 30 subjects have been enrolled to date across the 5 cohorts. All subjects were on stable ARV regimen with undetectable HIV RNA, and CD4 >350 cells/mm^3 were enrolled. There were 6 adverse events observed in 5 subjects, none of which were identified as related to study drug. Median change in HCV RNA was similar for all 5 groups during the 7-day dosing period, with >1.5 log_{10} reductions at 24 hours and a maximal HCV RNA decline from baseline >4 log_{10}. Virologic response was similar across all 5 cohorts independent of HCV genotype, and baseline HCV viral load.

Figure 1-1. GS-7977 Activity in HIV/HCV Coinfection



Additionally, patient characteristics and median HCV RNA $\log_{10}$ change from baseline were compared with results from two prior HCV monoinfected cohorts in HCV genotype (GT) 1 and GT 2/3 patients (Figure 1-2). Virologic response was similar across all 5 cohorts independent of HIV status, HCV genotype, and baseline HCV viral load. Comparable HCV early viral kinetics was observed in HIV/HCV coinfected and HCV monoinfected patients, supporting further study of GS-7977 in HIV/HCV coinfected patients.

Figure 1-2. Comparative GS-7977 Antiviral Activity in HCV Monoinfection vs HIV/HCV Coinfection



1.3.2.2. Preliminary Safety

GS-7977 has been safe and well tolerated in the study population. No new safety signals were observed during the study period or safety follow-up. Three subjects experienced CNS side-effects who were erroneously dosed with Atripla 12 hours apart on Day-1, all of which resolved with standard daily dosing of Atripla. Other adverse events reported included headache, nausea, dry mouth, and chills, all of which were mild and not related to study drug. No SAEs or deaths have occurred in the study population. No effect was observed on HIV viral load, CD4 count, or CD4%.

1.3.2.3. Preliminary Pharmacokinetics

Preliminary pharmacokinetic results are available for 8 and 2 subjects, respectively, receiving ATV/r and GS-7977 in cohort 3 (ATV/r+TDF+FTC).

Cohort 3 (ATV/r+TDF+FTC)				
Mean (%CV)		**Day 0**	**Day 7**	**%GMR (90%CI)**
ATV (n=8)	AUC_{tau} (ng*hr/ml)	49,600 (32.9)	52,500 (43.8)	100.5 (80.51, 125.4)
	C_{max} (ng/ml)	4930 (40.5)	4620 (43.9)	91.63 (76.39, 109.9)
	C_{tau} (ng/ml)	817 (35.9)	1103 (56.5)	122.5 (90.57, 165.7)
RTV (n=8)	AUC_{tau} (ng*hr/ml)	11,400 (41.2)	8,750 (30.6)	79.05 (64.63, 96.70)
	C_{max} (ng/ml)	1600 (42.7)	1050 (31.5)	67.93 (52.81, 87.37)
	C_{tau} (ng/ml)	82.7 (39.8)	84.3 (59.9)	98.13 (75.36, 127.8)

Cohort 3 (ATV/r+TDF+FTC)				
		Day 7 (Range of n=2)	**P2938-0212 Mean (%CV), (n=8)**	**Day 7 / P2938-0212 (Range of n=2)**
GS-7977	AUC_{tau} (ng*hr/ml)	2510 - 2750	538 (39.0)	4.7 – 5.1
	C_{max} (ng/ml)	1210 - 1930	603 (47.2)	2.0 – 3.2
GS-566500	AUC_{tau} (ng*hr/ml)	3,650 - 20,600	853 (45.7)	4.3 – 24.2
	C_{max} (ng/ml)	673 - 4,150	235 (38.4)	2.9 – 17.7
GS-331007	AUC_{tau} (ng*hr/ml)	16,200 - 16,500	9640 (18.7)	1.7 – 1.7
	C_{max} (ng/ml)	984 - 1470	1380 (19.2)	0.71 – 1.1

As reflected in the GMR (90% CI), co-administration of GS-7977 did not alter ATV AUC_{tau} or $C_{max,}$ and modestly increased ATV C_{tau} (23%). ATV exposures achieved in this study were comparable to historical data in HIV-infected patients (Reyataz® prescribing information for ATV/r 300/100). Reyataz® prescribing information for ATV/r 300/100*)*. The effect of GS-7977 on ritonavir pharmacokinetics was also fairly modest; ritonavir AUC_{tau} and C_{max} were decreased 21% and 32% respectively, but C_{tau} was not affected by GS-7977.

Exposures (AUC) were higher for GS-7977 (4.7-5.1-fold), GS-566500 (4.3-24-fold) and GS-331007 (1.7-fold) upon co-administration of GS-7977 and ATV/r, as compared to exposures achieved following administration of GS-7977 400 mg alone for 7 days in a previous study (study P2938-0212). Of note, the exposure (AUC) of GS-7977 and GS-331007 within this dataset is similar to values seen in other clinical trials including drug-drug interaction, thorough QT, safety, efficacy, and special population studies. The PK of the intermediate metabolite GS-566500 was highly variable and should be interpreted with caution.

The higher GS-7977 exposure 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 GS-7977 with ATV/r is ~ 4.4% to 6.2% of DRM AUC. In a previous drug-drug interaction study (P7977-1819), the AUC of GS-7977 increased from ~3 % (GS-7977 alone) to ~11% (GS-7977 with cyclosporine) of DRM AUC upon co-administration of GS-7977 with cyclosporine, a potent multi-drug transporter inhibitor. Safety margins for GS-7977 and GS-331007 on administration with cyclosporine are adequate (AUC safety margin ranges from 1.3 to 13.6) compared to exposures obtained in toxicology studies and dose modification of GS-7977 is not warranted.

1.3.3. Study P7977-0523 (ELECTRON): additional efficacy data

This ongoing Phase 2a, 4-part, 13-group study evaluated GS-7977 400 mg for 8 or 12 weeks in combination with or without RBV and/or PEG in subjects with genotypes 1, 2, or 3 HCV infection and with or without GS-5885 or GS-9669 in subjects with genotype 1 HCV infection. Preliminary HCV RNA data, including the 12 week posttreatment time point for all subjects in the first 9 groups, are tabulated in Table 1-5.

Table 1-5. P7977-0523: Percentage of Subjects with HCV RNA Below the Lower Limit of Detection at Select Timepoints in Study

	Genotype-2/3 Treatment Naive				Genotype 1 Null Responders	Genotype 1 Treatment Naive	Genotype 2/3 Treatment Experienced
Time (Week)	GS-7977+RBV 12 weeks (Group 1) (N = 10) n (%)	GS-7977+ PEG+RBV 12 weeks (Groups 2,3,4) (N = 30) n (%)	GS-7977 12 weeks (Group 5) (N = 10) n (%)	GS-7977+ PEG+RBV 8 weeks (Group 6) (N = 10) n (%)	GS-7977+RBV 12 weeks (Group 7) (N = 10) n (%)	GS-7977+RBV 12 weeks (Group 8) (N = 25) n (%)	GS-7977+RBV 12 weeks (Group 9) (N = 25) n (%)
0	0	0	0	0	0	0	0
1	2 (20.0)	8 (26.7)	5 (50.0)	6 (60.0)	1 (10.0)	8 (32.0)	8 (32.0)
2	8 (80.0)	23 (80.0)	8 (80.0)	10 (100.0)	7 (70.0)	17 (68.0)	21 (84.0)
3	9 (90.0)	25 (83.3)	10 (100.0)	10 (100.0)	10 (100.0)	22 (88.0)	25 (100.0)
4	10 (100.0)	30 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	25 (100.0)	25 (100.0)
EOT [a]	10 (100.0)	30 (100.0)	10 (100.0)	10 (100.0)	10 (100.0)	25 (100.0)	25 (100.0)
SVR4	10 (100.0)	30 (100.0)	6 (60.0)	10 (100.0)	1 (10.0)	22 (88.0)	19 (76.0)
SVR12	10 (100.0)	30 (100.0)	6 (60.0)	10 (100.0)	1 (10.0)	21 (84.0)	17 (68.0)

a EOT, End of Treatment

1.3.4. 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 GS-7977

and a NS5A inhibitor, daclatasvir (DCV), with or without RBV, in treatment naïve patients chronically infected with genotypes 1, 2, or 3 HCV. In the initial phase of this study, patients were randomized into six groups, evaluating three different dosing schedules in patients with either genotype 1 HCV (n=44) or genotype 2/3 HCV (n=44). The groups were:

- GS-7977 400 mg QD for 7 days then DCV 60 mg QD + GS-7977 400 mg QD for 23 weeks
- GS-7977 400 mg QD + DCV 60 mg QD for 24 weeks
- GS-7977 400 mg QD + DCV 60 mg QD + ribavirin 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. An additional interim analysis for antiviral efficacy was conducted four weeks post-treatment.

The study was subsequently expanded to evaluate GS-7977 + DCV ± RBV for 24 Weeks in genotype 1 HCV infected patients who have previously failed TVR or BVR treatment and for 12 Weeks in treatment-naïve genotype 1 HCV patients. These treatment groups are currently under study.

1.3.4.1. Study AI444-040 Preliminary Safety

Safety data from this ongoing study are available through 12 weeks on-treatment. 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, elevated glucose, elevated fasting glucose, lymphopenia and low serum phosphorus-all of which occurred in patients who received RBV. Grade 3-4 laboratory abnormalities reported in the RBV-sparing treatment groups were low phosphorus and elevated cholesterol. Two patients discontinued treatment for non-drug related AEs and both achieved SVR4. No patients discontinued therapy due to treatment-related AEs.

1.3.4.2. Study AI444-040 Preliminary Efficacy

In the genotype 1 HCV treatment groups, 100% of patients achieved SVR through post-treatment week 4 (SVR4) irrespective of whether RBV was or was not administered. In the genotype 2 and 3 treatment groups, 91% (40/44) of patients achieved SVR4. Two patients with HCV GT-2 infection who received DCV+GS-7977+RBV discontinued the study for non-AE-related reasons and were lost to follow-up. Two patients with HCV GT-3 infection who received GS-7977+DCV experienced virologic failure: one had viral relapse and the other met the protocol definition of viral breakthrough (confirmed HCV RNA >LOQ on or after Week 8).

On-treatment HCV RNA data are tabulated in Table 1-6.

Table 1-6. The Proportions of Patients Achieving Viral Load Below the Lower Limit of Quantification (HCV RNA < 25 IU/mL) in Study AI444-040

Dose	HCV Genotype	Week 4 On-Treatment	Week 12 On-Treatment	Week 24 On-Treatment	Week 4 Post-Treatment (SVR4)[a]
7-day lead-in dose of GS-7977, then GS-7977 + DCV for 23 weeks	GT 1	100% (15/15)	100% (15/15)	100% (15/15)	100% (15/15)
	GT 2/3	100% (16/16)	88% (14/16)	94% (15/16)	88% (14/16)[b]
GS-7977 + DCV for 24 weeks	GT 1	100% (14/14)	93% (13/14)[c]	86% (12/14)[c]	100% (14/14)
	GT 2/3	100% (14/14)	93% (13/14)	100% (14/14)	100% (14/14)
GS-7977 + DCV + RBV for 24 weeks	GT 1	100% (15/15)	100% (15/15)	93% (14/15)[c]	100% (15/15)
	GT 2/3	100% (14/14)	100% (14/14)	86% (12/14)	86% (12/14)[d]

a In this study, SVR4 was defined as viral load below the lower limit of quantification. All but one patient who achieved SVR4 also had detectable viral load (HCV RNA <10 IU/mL); this patient had undetectable viral load when retested eight days later.

b One patient experienced viral relapse and one patient experienced viral breakthrough.

c Percentages less than 100% reflect missing values.

d Two patients were lost to follow-up.

1.3.5. Study P2938-0721 QUANTUM

Two hundred thirty-nine (N=239) treatment-naïve patients with chronic HCV with or without cirrhosis were randomized to receive 12 (Groups A, B, C, D) or 24 weeks (E, F, G, H) of GS-0938 (Arms A, E), GS-0938+GS-7977 (Groups B, F), GS-7977+ RBV (Groups C, G), and GS-0938+GS-7977+RBV (Group D and H). Group I is a deferred start group (placebo) for 24 weeks. Approximately 25 patients per group were enrolled. GS-7977 was administered at a dose of 400 mg QD. GS-0938 was administered at a dose of 300 mg once-daily (QD). The RBV dose was 1200 mg or 1000 mg per day in divided (BID) doses, as determined by subject's weight (e.g., ≥ or < 75 kg).

Due to a safety signal (ALT elevations) sites were instructed, to immediately discontinue all study medications in all subjects who had been exposed to GS-0938 (Groups A, B, D, E, F, and H) patients receiving placebo were also discontinued at that time. Subjects had received fewer than 12 weeks of study medication when they were discontinued. Subjects who were randomized to receive only GS-7977+RBV (Groups C & G), continued those regimens for

12 or 24 weeks as planned. Preliminary safety and efficacy data for these arms are presented below.

1.3.5.1. P2938-0721 QUANTUM Preliminary Safety

Overall, 12 subjects reported at least one Grade 2 AE and the only AE reported in > 5% of subjects included headache (n=3, 6%). No Grade 3 or 4 AEs and no SAEs were reported. The overall safety profile was consistent with that previously observed.

1.3.5.2. P2938-0721 QUANTUM Preliminary Efficacy Data

Preliminary efficacy data, available for Groups C and G, are tabulated in Table 1-7.

Table 1-7. The Proportions of Patients Achieving Viral Load Below the Lower Limit of Quantification (HCV RNA < 25 IU/mL) in Study P2938-0721

Treatment Group	HCV Genotype	Week 4 On-Treatment	Week 4 Post-Treatment	Week 12 Post-Treatment
GS-7977+RBV for 12 weeks	GT 1	19/19 (100%)	10/19 (53%)	10/19 (53%)
	GT 2/3	6/6 (100%)	4/6 (67%)	4/6 (67%)
GS-7977+RBV for 24 weeks	GT 1	19/19 (100%)	10/19 (53%)	NAV [a]
	GT 2/3	6/6 (100%)	4/5 (80%) [b]	NAV [a]

a NAV: Not available, data acquisition is ongoing.

b One subject has no post-treatment data

In this study, there was no evidence of increased efficacy with prolonged treatment duration.

1.3.6. 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 GS-7977 400 mg QD alone or in combination with RBV to a total of 60 treatment-naïve HCV genotype 1 mono-infected individuals with less than or equal to stage 2 fibrosis. The NIAID is the sponsor of the study under IND 112,681. Subjects were enrolled into two phases to evaluate both the treatment duration as well as ribavirin dose. Phase 1 enrolled 10 subjects who were dosed with GS-7977 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. Upon completion of an interim safety review of these subjects at Week 12 of treatment, Phase 2 was initiated in fifty subjects. Subjects were randomized in a 1:1 ratio to receive 12 weeks of GS-7977 QD in combination with weight based RBV (1000 mg for participants weighing < 75 kg and 1200 mg for participants weighing ≥ 75kg) or 12 weeks of GS-7977 400 mg QD with low dose RBV (600mg). All subjects have been enrolled into both phases of the study. The population in Phase I was

comprised of 90% African American, 60% genotype 1a, median baseline HCV RNA log10 of 6.85 and all ≤ Stage 2 fibrosis.

1.3.6.1. NIAID Study 11-I-0258 Preliminary Efficacy Data (Phase 1)

Nine out of ten subjects completed treatment through SVR 4 with one subject discontinued at Week 3 due to non-adherence. All nine subjects (100%) who completed the 24 weeks of treatment achieved SVR4 independent of race, genotype 1 subtype and IL28B genotype. Phase 2 enrollment is completed with subject treatment ongoing and will include up to 20% compensated cirrhotics.

1.3.6.2. NIAID Study 11-I-0258 Preliminary Safety (Phase 1)

The interim safety analysis of these subjects at Week 12 is completed and GS-7977 was safe and well tolerated. There were no SAEs and the safety profile was consistent with that expected for RBV.

1.4. Overall GS-7977 SAE Summary

As of 02-Aug-2012, no serious adverse event signal has been associated with the use of GS-7977.

1.5. Ribavirin (RBV)

Ribavirin is a guanosine analogue that inhibits the in vitro replication of a wide range of RNA and DNA viruses{15572}, {15668}. Ribavirin monotherapy has little or no effect on the replication of HCV but can result in normalization of serum ALT activity and improvement in liver histology. When combined with interferon or PEG therapy, RBV decreases substantially the relapse rate seen after cessation of interferon therapy {12557}, {12558}.

Ribavirin is a known teratogen (FDA category X). Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment. A comprehensive review of RBV is contained in the package insert/SmPC.

1.6. Rationale for the Current Study

This is a Phase 3 open label study designed to examine the efficacy and safety of treatment with GS-7977+RBV in treatment naive or treatment experienced subjects with chronic genotype 1, 2 or 3 HCV infection who are co-infected with HIV-1.

Currently, PEG + RBV for 48 weeks is the approved standard of care for Genotype 1 patients with HIV/HCV coinfection. Response rates from large clinical trials range from 15-35% depending on various baseline predictors of response. Recent data with PEG + RBV and either TVR or BVR demonstrated improved response rates to 60-70% with 48 weeks of

treatment. Treatment naïve genotype 1 subjects receiving GS7977 + RBV in the ELECTRON, QUANTUM and NIAID (IND 112,681) studies achieved SVR4 rates ranging from 53-100% following treatment with GS-7977+RBV for 12 to 24 weeks. This range of response rates is a significant improvement over the current standard of care and is comparable to those achieved with PEG+RBV+TVR/BVR regimens while eliminating PEG and shortening duration of therapy. As patients with HIV/HCV coinfection have historically demonstrated lower response rates with treatment for HCV, GS-7977 + RBV will be administered for the longer treatment duration of 24 weeks to maximize the probability of achieving SVR with this regimen.

The response rates for the currently approved PEG+RBV for 48 weeks in treatment naïve genotype 2 and 3 patients with HIV/HCV coinfection is 60%. There are currently no approved treatments or investigational therapies for genotype 2 and 3 treatment experienced subjects with coinfection. An ongoing clinical study (P7977-0523 ELECTRON) has demonstrated that 12 weeks of treatment with GS-7977 + RBV is well tolerated and results in very high SVR rates in treatment naïve genotype 2 or 3 HCV infected subjects. Emerging data indicate that treatment of treatment-experienced genotype 2 or 3 HCV-infected subjects with GS-7977 + RBV for 12 weeks results in rapid viral clearance and a high rate of SVR, but lower than that observed in treatment naïve patients. Thus, we have again opted to utilize the longer treatment duration in these treatment-experienced patients.

The development of treatment regimen without PEG for genotype 1, 2 or 3 patients co-infected with chronic HCV infection and HIV-1 infection would allow for increased access to successful treatment to a significant proportion of the HCV-infected population. Improvements in tolerability may be expected to result in higher SVR rates if this leads to better compliance with the treatment regimen and if subjects do not require early treatment discontinuation due to safety or tolerability issues. The early viral kinetics demonstrated a similar response between HIV/HCV coinfected and HCV monoinfected subjects, supporting the evaluation of similar regimens to those under evaluation in HCV monoinfection in other difficult to treat populations.

1.7. Rationale for Dose Selection of GS-7977

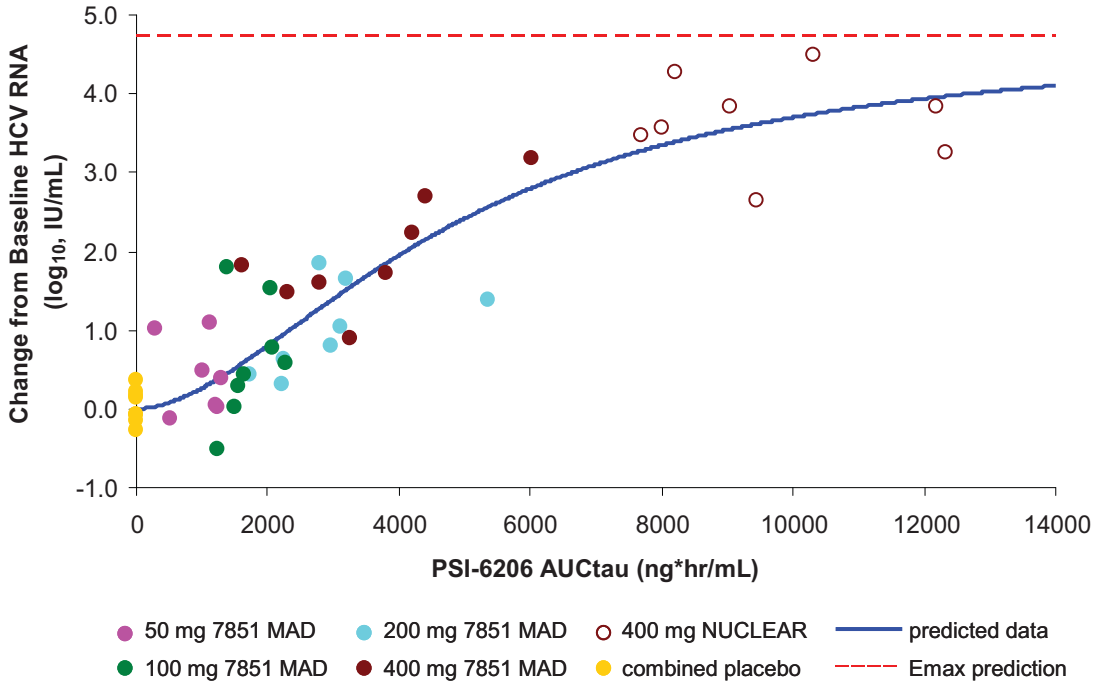
The GS-7977 dose selected for further development in Phase 3 studies is 400 mg QD. This dose was associated with higher SVR rates in genotype 1 HCV infected subjects as compared to the 200 mg QD dose when given in conjunction with PEG+RBV for 24 weeks in P7977-0422. Safety and tolerability appeared similar across both dose levels and was similar to the PEG+RBV control arm. In addition, when GS-7977 400 mg QD+RBV was given to genotype 2 or 3 HCV treatment naïve infected subjects, 100% SVR24 was observed. There appears to be an advantage for the 400 mg dose based on the occurrence of viral breakthroughs in HCV genotype 1 subjects who received GS-7977 200 mg, but not in subjects who received GS-7977 400 mg in P7977-0422 (PROTON). GS-7977 400 mg with PEG+RBV is being studied in P7977-0724 (ATOMIC) which is assessing treatment durations of 12 and 24 weeks in HCV genotypes 1, 4, 5, and 6. GS-7977 400 mg is now being studied in the Phase 3 P7977-1231 (FISSION) study which is evaluating 12 week

GS-7977+RBV versus standard of care (PEG+RBV x 24 weeks) in HCV genotype 2 and 3. Additionally, GS-7977 is also being studied in the Phase 3 GS-US 334-0107 (POSITRON) study which is evaluating 12 week GS-7977+RBV versus placebo in HCV genotype 2 and 3.

Further support for the 400 mg dose can be derived from E_{max} modeling with early virologic and human exposure data which also supports the selection of a 400 mg GS-7977 dose utilizing the current 200 mg tablet formulation over others tested. Standard pharmacodynamic models were fit to individual HCV change from Baseline after three days of GS-9851 monotherapy from Study P7851-1102 and of GS-7977 monotherapy in Study P2938-0212 and various GS-9851/GS-7977 and GS-331007 steady-state pharmacokinetic parameters.

The mean GS-331007 AUC_{tau} for the 400 mg dose in Study P2938-0212 is associated with approximately 77% of the maximal HCV RNA change from Baseline achievable as determined by this model, a value which is on the cusp of the plateau of the exposure-response sigmoidal curve. In a sigmoidal E_{max} model, there is a relatively linear exposure-response relationship in the 20 to 80% maximal effect range. Therefore, given that GS-7977 exposure with 200 mg tablets appears dose-proportional with single doses up to 1200 mg based upon results from QT Study P7977-0613, doses below 400 mg are expected to yield considerable reductions in the magnitude of HCV RNA change from Baseline. Similarly, in order to improve upon an efficacy prediction of 77% in the plateau of the exposure-response curve, substantial increases in exposure (and hence dose) are needed for an appreciable increase in antiviral effect (see model prediction in (Figure 1-3).

Figure 1-3. Day 3 Change from Baseline HCV RNA vs GS-331007 (PSI-6206) AUC_{tau} during GS-7977 or GS-9851 Monotherapy



1.8. Rationale for Selection of Allowed Concomitant ARV Regimens

The dose(s) of the ARV (EFV/FTC/TDF 600/200/300 mg QD, FTC/TDF 200/300 mg QD, TDF 300 mg QD, DRV/r 800/100 mg QD, RAL 400 mg BID, RPV 25 mg QD) is the recommended dose of the marketed product to be used alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment naïve and/or treatment experienced subjects. GS-7977 and ARVs (EFV/FTC/TDF, ATV /r, DRV/r, RAL or RPV) are not involved in any clinically significant drug interactions (GS-US-334-0131; Section 1.3.2.1).

1.9. Overall Risk/Benefit Assessment

No clinical safety issues specifically related to GS-7977 have been identified to date in HCV monoinfected or HIV/HCV coinfected subjects. During the conduct of the study the sponsor will perform an ongoing review of safety data. An external Data Safety Monitoring Board (DSMB) will meet regularly to review safety data and to ensure subject welfare.

The expected benefits to patients being treated with GS-7977 is a rapid and durable eradication of HCV virus without the side effects associated with the use of PEG and a shortened treatment period. Potential risks include unforeseen safety issues and unknown implications of virologic failure due to the emergence of resistant virus.

For the population of HIV/HCV coinfected subjects, the potential benefit of achieving SVR with 12 to 24 weeks of an interferon-free regimen outweighs the risks associated with the possible development of previously unidentified safety issues or the emergence of quasispecies resistant to GS-7977.

If high rates of SVR can be obtained with a shortened, interferon-free regimen, without frequent emergence of resistant HCV, the anticipated improvements in safety and tolerability would offer a favorable risk-benefit determination for individuals with chronic HCV infection who otherwise have no available treatment options.

2. OBJECTIVES

The primary objectives of this study are:

- To determine the efficacy of treatment with GS-7977 + RBV as measured by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)

- To evaluate the safety and tolerability of GS-7977 + RBV as assessed by review of the accumulated safety data, including HIV-RNA and CD4 T-cell percent

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 GS-7977 during treatment and after treatment discontinuation

The exploratory objectives of this study are:

- To identify or validate genetic markers that may predict the natural history of disease, response to therapy and/or the tolerability of medical therapies through genetic discovery research (e.g., pharmacogenomics), in subjects who provide their separate and specific consent

- To assess the effect of treatment on health related quality of life

3. STUDY DESIGN

3.1. Treatment Plan and Regimen

This is an open-label study that will examine the safety, tolerability and antiviral efficacy of GS-7977 and RBV in treatment naïve and experienced subjects with chronic genotype 1, 2 or 3 HCV infection who are coinfected with HIV-1.

A total of 230 subjects will be enrolled and treated with GS-7977 400 mg QD + RBV BID for 12 or 24 weeks based on genotype and prior treatment history. Treatment duration will be 12 weeks for Genotype 2 and 3 HCV treatment naïve subjects and 24 weeks for Genotype 1 HCV treatment naïve and Genotype 2/3 HCV treatment experienced subjects.

115 subjects with genotype 2 and 3 will be enrolled. Equal enrollment of genotype 2 versus 3 as well as treatment naïve versus treatment experienced will be targeted. An additional 115 subjects with genotype 1 will be enrolled. Approximately 20% of the entire study population may have evidence of cirrhosis at Screening.

The total time to complete all study visits is approximately 40 weeks for subjects treated with 12 weeks of therapy and 52 weeks for subjects treated with 24 weeks of therapy:

- 28 day (4 week) screening period
- 12 or 24 week treatment period
- Up to 24 week post-treatment period

3.2. Visit Schedule

All subjects will complete screening, on-treatment and post-treatment assessments. Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. All subjects will complete a 4-Week Post-Treatment visit regardless of treatment duration. Subjects with HCV RNA < LLOQ at the 4-Week Post-Treatment Visit will complete 12-Week and 24-Week Post-Treatment visits unless confirmed viral relapse occurs.

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

3.3. HCV Virologic Response-Based Stopping Criteria

Since HCV RNA will be blinded to Investigator and Sponsor except at Screening, independent monitoring will occur to assess for HCV virologic failure and the need for confirmatory HCV RNA samples. Sponsor employees involved in the virologic analysis of samples from subjects that fail to respond to treatment (virologic failures) will have access to HCV RNA data in order to identify the appropriate subject samples for virologic analyses.

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

- Confirmed HCV RNA ≥LLOQ after 2 consecutive HCV RNA <LLOQ
- Confirmed >1 log10 increase from nadir
- HCV RNA ≥LLOQ through 8 weeks of treatment

Confirmation should be performed as soon as possible but within 2 weeks after determination of initial observation.

3.4. HIV Virologic Rebound Criteria

Subjects who meet the criteria listed below will be considered to have HIV virologic rebound:

- At any visit, have at least two consecutive plasma HIV-1 RNA levels ≥ 50 copies/mL (at least two weeks apart)

Following the unconfirmed HIV virologic rebound, subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw for confirmation of HIV virologic rebound. If HIV virologic rebound is confirmed at the scheduled or unscheduled visit, the blood samples from this visit will be used for HIV-1 genotype/phenotype testing if the HIV-1 RNA is ≥ 400 copies/mL. Plasma samples with < 400 copies/mL of HIV-1 RNA will not be analyzed as the protease/reverse transcriptase genotype/phenotype assays used in this study are not validated when plasma HIV-1 RNA levels are < 400 copies/mL.

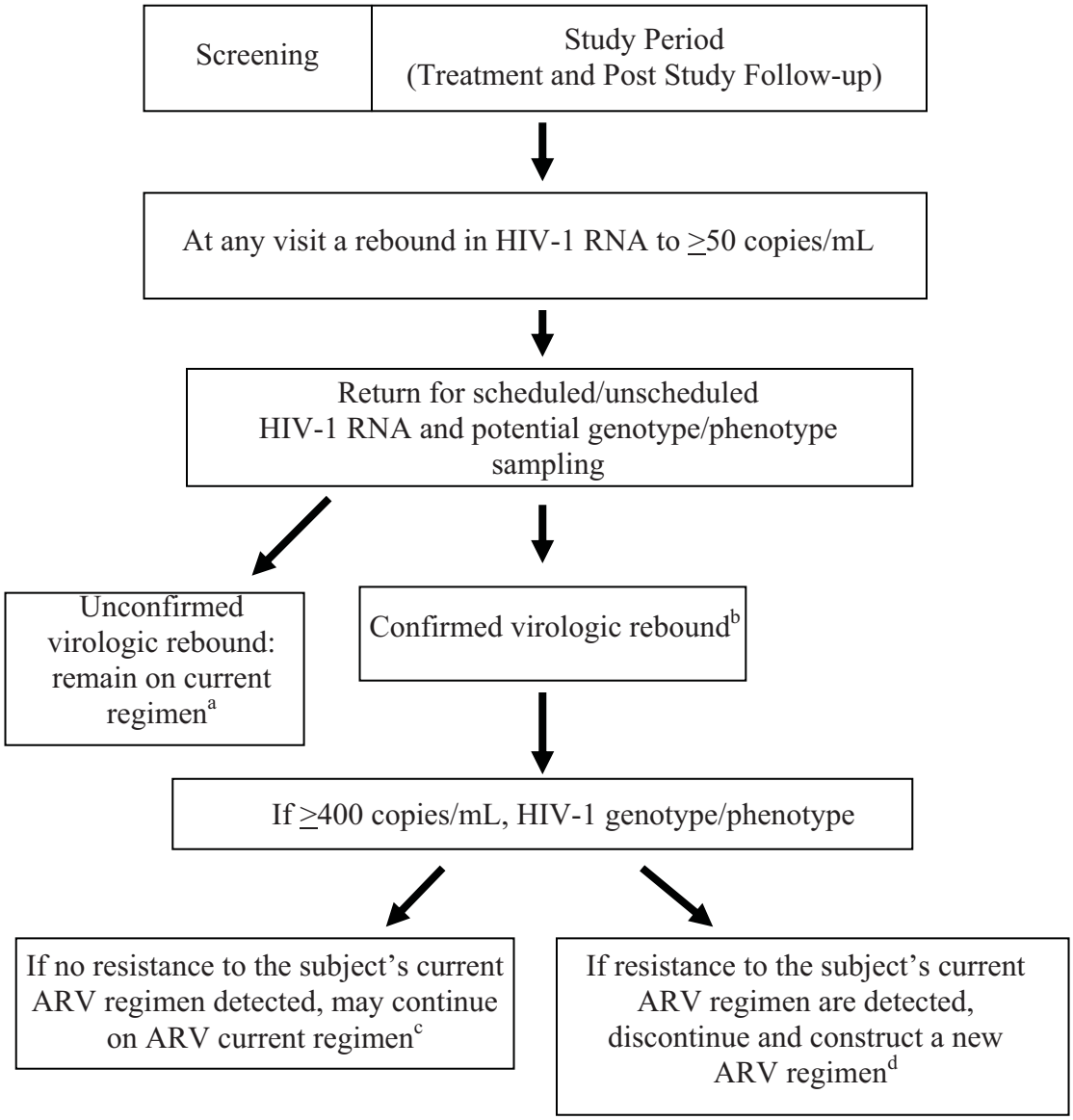
If greater than 20% of subjects enrolled on any specific ARV regimen experience virologic breakthrough, an ad-hoc DSMB meeting will be convened to evaluate the safety of continuing enrollment of subjects on this specific ARV therapy.

HCV medications should be continued unless safety events warrant the discontinuation of these medications, as outlined is Section 3.7 of the protocol.

These criteria only apply to subjects currently on ARV treatment and have HIV-1 RNA levels < 50 copies/ml. These do not apply to subjects meeting the ARV untreated parameters outlined in the Inclusion criteria of the protocol.

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

Figure 3-1. HIV Virologic Rebound Schema



a If virologic rebound is not confirmed, the subject will remain on their current ARV regimen.

b If virologic rebound is confirmed, the HIV-1 genotype and phenotype (reverse transcriptase and protease) will be analyzed, only if the HIV-1 RNA is ≥400 copies/mL.

c Based on the results of the genotype/phenotype assays, the subject may remain on their ARV at the discretion of the Investigator (e.g. virologic rebound due to non-adherence). If the genotyping/phenotyping assay fails to provide results, a new ARV regimen will be configured at the discretion of the Investigator.

d A new ARV regimen will be configured, at the Investigator's discretion

3.5. HCV Resistance Monitoring

Plasma samples for viral sequencing and possible phenotypic monitoring will be collected at baseline (pre-treatment) and every visit there after. Sequencing of the HCV NS5B-encoding region of the viral polymerase will be performed on all baseline (pre-treatment) viral samples and at any rebound time points while receiving therapy or relapse time points during off-therapy follow up where the HCV RNA ≥1,000 IU/mL.

3.6. HIV Resistance Monitoring

Plasma samples for HIV resistance testing will be collected from subjects who experienced HIV virologic rebound. Following the unconfirmed HIV virologic rebound, confirmation should be performed as soon as possible but within 2 weeks after determination of initial observation. If HIV rebound is confirmed, the samples will be used for HIV-1 genotype/phenotype testing.

3.7. Treatment Discontinuations Criteria

The Medical Monitor should be consulted prior to subject discontinuation when medically feasible. Study medication may 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, or of female partner of male subject
- HCV efficacy failure as defined in Section 3.3.
- Significant protocol violation including non-compliance with study assessments.
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy or other reason.
- Discontinuation of the study at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

If a subject meets discontinuation criteria during treatment, an early termination visit will be required (Section 6.2.5). All subjects should complete the 4-week Post-treatment visit.

3.8. Discontinuations

Subjects discontinuing treatment prior to completion of the assigned dosing period should complete an Early Termination visit (see Section 6.2.4). All subjects should also complete a

4-Week Post Treatment visit. Subsequent visits will be determined by the virologic response to treatment as outlined in Section 3.3.

If GS-7977 is discontinued, subjects should discontinue ribavirin. Under no condition should the subject remain on ribavirin monotherapy.

3.9. Pharmacogenomic Substudy

All subjects will be eligible to participate in the Pharmacogenomic Substudy. A blood sample should be drawn at the Baseline/Day 1 visit. Subject s must sign a separate informed consent to participate in this Substudy. If not obtained at Baseline/Day 1, the sample may be drawn at any time during the study.

3.10. Registry Studies

3.10.1. Sequence Registry Study

Subjects who do not achieve SVR as well as those who achieve SVR and later become detectable will be eligible for enrollment in the Sequence Registry Study. The purpose of the Sequence Registry Study will be to monitor the persistence of resistant mutations for up to 3 years after the last dose of study medication. The Sequence Registry Study is described in a separate protocol (GS-US-248-0123).

3.10.2. SVR Registry Study

Subjects who achieve SVR at 24-weeks post treatment will be eligible for enrollment in the SVR Registry Study. The purpose of the SVR Registry Study will be to evaluate durability of SVR for up to 3 years post-treatment. The SVR Registry Study is described in a separate protocol (GS-US-248-0122).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 230 subjects will be enrolled in this study consisting of 115 treatment naïve genotype 1 subjects and 115 treatment naïve and treatment experienced genotype 2/3 subjects. In order to manage the total study enrollment, Gilead Sciences, Inc., at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

4.2. Inclusion Criteria

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

1. Willing and able to provide written informed consent

2. Male or female, age ≥ 18 years with chronic HCV and HIV-1 infection

3. HCV RNA $\geq$ 1 x 10^4 IU/mL at Screening

4. Infection with HCV genotype 1, 2 or 3 as determined at Screening

5. HIV-1 infection confirmed with positive ELISA and Western blot at Screening (if necessary)

6. The subject's medical records must be sufficient to be categorized on IFN eligibility or prior treatment with PEG/RBV into one of the following categories as defined in Section 6.4.2:

    a) **Treatment Naïve - IFN-eligible**

    b) **Treatment Naïve - IFN-ineligible**:

Subjects treated in the Drug Interaction portion (Part A) of the P7977-1910 protocol will be considered treatment-naïve.

    c) **Treatment Experienced - IFN Intolerant (genotype 2/3 only)**

    d) **Treatment Experienced - Non-Response (genotype 2/3 only)**

    e) **Treatment Experienced - Relapse/Breakthrough (genotype 2/3 only)**

7. Confirmation of chronic HCV infection documented by either:

    - 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

- a liver biopsy performed prior to the Baseline/Day 1 visit with evidence of chronic HCV infection

8. Ability to determine the presence/absence of cirrhosis

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

      - Liver biopsy within 2 years of screening showing cirrhosis
      - A FibroTest® score of >0.75 AND an AST:platelet ratio index (APRI) of >2 performed during screening

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

      - Liver biopsy within 2 years of Screening showing absence of cirrhosis
      - A FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 performed during Screening

In the absence of a definitive diagnosis of presence of cirrhosis by the above criteria, a liver biopsy is required.

If both a biopsy and FibroTest® plus APRI results are obtained, the liver biopsy results will supersede for the determination of cirrhosis.

9. HIV antiretroviral therapy (ARV) criteria of one of the following:

   a) ARV untreated, for ≥ 8 weeks preceding the Screening visit, with a CD4 T-cell count >500 cells/mm^3 [up to 10% of study subjects may be ARV untreated], or

   b) On a stable, protocol-approved, ARV for >8 weeks prior to Screening with a CD4 T-cell count >200 cells/mm^3 and a documented undetectable plasma HIV-1 RNA level for ≥ 8 weeks by local assay preceding the Screening visit. HIV-1 RNA levels should be measured within 1 year of the Screening visit. Screening HIV RNA must be < 50 cp/mL as measured by the COBAS AMPLIPREP/COBAS TaqMan 2.0 HCV RNA assay.

      Subjects who switched from atazanavir/ritonavir (boosted) to darunavir/ritonavir (boosted) prior to Amendment 2 will be exempt from the 8 week stable ARV regimen requirement as defined in Section 6.4.2.

   c) HIV antiretroviral medications allowed in this study include the following and should be administered per the prescribing information in the package insert:
      - emtricitabine/tenofovir plus:
        - atazanavir/ritonavir (boosted); or
        - darunavir/ritonavir (boosted); or

- efavirenz; or
- raltegravir; or
- rilpivirine

Alternative combinations of the above listed medications may be allowed on a case by case basis. ARV regimens not on the above list are excluded from this study.

10. Body mass index (BMI) ≥ 18 kg/m^2

11. Screening ECG without clinically significant abnormalities as determined by the investigator

12. Subjects must have the following laboratory parameters at screening:

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

    b) AST ≤ 10 × ULN

    c) Hemoglobin ≥ 12 g/dL for male, ≥11 g/dL for female subjects

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

    e) Albumin ≥ 3 g/dL

    f) Direct bilirubin ≤ 1.5 × ULN

    - For subjects receiving an atazanavir/ritonavir (boosted) regimen, a direct bilirubin > 1.5 x ULN will be allowed if <25% of the total bilirubin.

    g) HbA1c ≤ 10%

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

13. Subject has not been treated with any investigational drug or device within 30 days of the Screening visit

14. A female subject is eligible to enter the study if it is confirmed that she is:

    a. Not pregnant or nursing

    b. Of non-childbearing potential (i.e., women who have had a hysterectomy, have both ovaries removed or medically documented ovarian failure, or are postmenopausal – women > 50 years of age with cessation (for ≥ 12 months) of previously occurring menses), or

c. Of childbearing potential (i.e., women who have not had a hysterectomy, have not had both ovaries removed, or no medically documented ovarian failure). Women ≤ 50 years of age with amenorrhea will be considered to be of childbearing potential. These women 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 6 months after last dose of RBV:

- Complete abstinence from intercourse. Periodic abstinence from intercourse (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 6 months after the last dose of RBV. Women of childbearing potential must not rely on hormone-containing contraceptives as a form of birth control during the study. Female subjects using a hormone-containing contraceptive prior to Screening may continue their contraceptive regimen in addition to the study specified methods of birth control.
  - 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

15. All male study participants must agree to consistently and correctly use a condom, while their female partner agrees to use either 1 of the non-hormonal methods of birth control listed above or a hormone-containing contraceptive listed below, from the date of Screening until 7 months after their last dose of RBV:

- implants of levonorgestrel
- injectable progesterone
- oral contraceptives (either combined or progesterone only)
- contraceptive vaginal ring
- transdermal contraceptive patch

16. Male subjects must agree to refrain from sperm donation for at least 7 months after the last dose of RBV.

17. Subject must be of generally good health as determined by the Investigator.

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

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

4.3. Exclusion Criteria

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

1. Non-genotype 1/2/3 or mixed genotype at Screening

2. Genotype 1 with prior treatment for HCV

3. Poor control with ARV regimen requiring a possible dose modification of therapy within 4 weeks of GS-7977 dosing

4. Prior exposure to a direct-acting antiviral targeting the HCV NS5B polymerase. Subjects participating in the Drug Interaction portion (Part A) of P7977-1910 protocol are an exception to this criteria

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

6. Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, α1 antitrypsin deficiency, cholangitis)

7. A new AIDS-defining condition diagnosed within 30 days prior to screening

8. Active, serious infection (other than HIV or HCV) requiring parenteral antibiotics, antivirals or antifungals within 30 days prior to Baseline

9. Infection with hepatitis B virus (HBV)

10. Contraindication to RBV therapy

11. History of malignancy diagnosed or treated within 5 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to screen); subjects under evaluation for malignancy are not eligible.

12. History of clinically significant hemoglobinopathy (e.g., sickle cell disease, thalassemia)

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

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

15. History of solid organ transplantation

16. Current or prior history of clinical hepatic decompensation (e.g., ascites, jaundice, encephalopathy or variceal hemorrhage)

17. History of a gastrointestinal disorder (or post operative condition) that could interfere with the absorption of the study drug

18. History of significant pulmonary disease, significant cardiac disease or porphyria

19. History of difficulty with blood collection and/or poor venous access for the purposes of phlebotomy

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

21. History of clinically-significant illness or any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol

22. Use of any prohibited concomitant medications as described in Section 5.6 within 28 days of the Baseline/Day 1 visit

23. Known hypersensitivity to RBV, the study investigational medicinal product, the metabolites, or formulation excipients

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization and Blinding

This is an open label study. An Interactive Web Response System (IWRS) will be employed to manage enrollment and study drug assignment.

5.2. Description and Handling of GS-7977

5.2.1. Formulation

GS-7977 tablets, 400 mg, are yellow, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "7977" on the other side. In addition to the active ingredient, GS-7977 tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinylalcohol, titanium dioxide, macrogol, talc, and yellow iron oxide,

5.2.2. Packaging and Labeling

GS-7977 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.

GS-7977 bottles to be distributed to centers in the US will be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA) and/or other local regulations as applicable.

5.2.3. Storage and Handling

GS-7977 bottles should be stored at a controlled room temperature until required for administration. Controlled room temperature is defined as 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F to 86 °F).

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

Sufficient quantities of GS-7977 tablets to complete the entire study will be shipped to the investigator or qualified designee from Gilead Sciences Materials & Logistics (or its designee).

5.3. Ribavirin

5.3.1. Description and Handling of RBV

5.3.1.1. Formulation

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

5.3.1.2. Packaging and Labeling

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

Ribavirin bottles to be distributed to centers in the US, EU and the rest of the countries will be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA) and/or other local regulations as applicable.

5.3.1.3. Storage and Handling

RBV tablets should be stored at 25 °C (77 °F); excursions are permitted between 15 and 30 °C (59 and 86 °F).

5.3.2. Dosage and Administration of RBV

RBV will be administered as 1000–1200 mg po daily (1000 mg for subjects weighing < 75 kg and 1200 mg for subjects weighing ≥ 75 kg) given in a divided daily dose. Subjects, who are to receive total daily doses of 1000 mg, should be instructed to take 3 tablets in the morning and 2 tablets in the evening (or 2 tablets in the morning and 3 in the evening). For those who are to receive 1200 mg of RBV, subjects should take 3 tablets twice daily. RBV should be dosed with food.

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

5.4. Co-administration of GS-7977 and RBV

Each subject will be given instructions to maintain approximately the same daily dosing interval between study drug doses.

For **morning doses**, subjects will be instructed to take study drugs with food as follows:

- GS-7977: one tablet;
- Weight-based RBV (as per Section 5.3.2).

For **evening doses**, subjects will be instructed to take study drug with food as follows:

- Weight-based RBV (as per Section 5.3.2).

If a subject forgets to take the medication at the correct time, it may be taken later in the day; however, no more than 400 mg dose of GS-7977 should be taken on any calendar day. The subject should resume the standing dosing schedule on the next day. Study medications should not be cut or split. No food restrictions apply to GS-7977, however, GS-7977 should be taken with RBV and with food for optimal adherence.

5.5. Study Drug Compliance

Subjects will be instructed to return any unused GS-7977 and RBV in the original container at post-baseline study visits.

Returned medication will be reconciled by the investigator in order to monitor the subject's compliance with the medication regimen.

5.6. Concomitant Medications

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

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

- Chronic systemic immunosuppressants including corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab)
- Investigational agents or devices for any indication
- Drugs disallowed per prescribing information for ribavirin, emtricitabine/tenofovir, atazanavir/ritonavir, darunavir/ritonavir, efavirenz, raltegravir, and rilpivirine
- Concomitant use of certain medications or herbal/natural supplements (inducers of drug transporters i.e. P-gp) with study drug(s) may result in pharmacokinetic interactions resulting in decreases in exposure of study drug(s). Examples of representative medications which are prohibited from 28 days prior to Baseline/Day 1 through the end of treatment are listed below:

Drug	Agents Disallowed	Concomitant use with GS-7977 may potentially result in changes of study drug concentration as listed below
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	Decrease in concentration of study drug
Antimycobacterials	Rifamycins, Isoniazid	Decrease in concentration of study drug
Herbal/Natural Supplements	St. John's Wort, Echinaccea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	Decrease in concentration of study drug
Other	Modafinil	Decrease in concentration of study drug

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

5.6.1. Colony Stimulating Agents

Under no circumstances are potential subjects to be treated with colony stimulating agents (CSA) during Screening to elevate hematology laboratory parameters to facilitate entry into the study. CSAs, such as erythropoiesis stimulating agents (ESA) or granulocyte colony-stimulating factor, should not be used while the subject is receiving study treatment.

5.6.2. Acceptable HIV Antiretroviral Regimens

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

- emtricitabine/tenofovir plus:
  - — atazanavir/ritonavir (boosted); or
  - — darunavir/ritonavir (boosted); or
  - — efavirenz; or
  - — raltegravir; or
  - — rilpivirine

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

5.6.3 Administration of Antacids with Raltegravir

Previous studies with dolutegravir and elvitegravir found decreases in the overall exposure, maximal concentration and trough concentration when antacids were simultaneously administered, presumably due to the binding of the integrase inhibitors to divalent cations in the antacid. Although RAL binds very poorly to magnesium, studies evaluating the impact of antacids on RAL pharmacokinetics are limited. Therefore, although this is not currently in the RAL prescribing information, the protocol recommends that antacids not be administered 2 hours before or after RAL dosing.

6. STUDY PROCEDURES

All subjects will complete screening, on-treatment and post-treatment assessments. All subjects will complete a 4-week Post-Treatment visit regardless of the treatment duration. Subjects with HCV RNA < LLOQ at the end of treatment and 4-Week Post-Treatment visit will complete 12-week and 24-week Post-Treatment visits unless confirmed viral relapse occurs. Completion of the study will occur at the 24-Week Post-Treatment visit.

The schedule of assessments is provided below. Details of the study procedures to be conducted for each subject enrolled in the study are presented in Study Procedures Table located in Appendix 2. Information on the specific laboratory parameters to be measured and clinical assessments to be performed are provided in Section 6.4.

6.1. Screening Assessments

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

Subjects will complete all screening assessments within 28 days of the Baseline/Day 1 visit. The screening window can be extended to 42 days for subjects requiring biopsy or in extenuating circumstances.

The following procedures will be performed and documented:

- Obtain signed informed consent
  - — A separate informed consent will be required from subjects participating in the pharmacogenomic substudy.
- Obtain medical history
- Obtain information on prior HIV treatments
- Obtain information on IFN eligibility and prior treatment history with PEG-IFN as per Section 6.4.2. The following are the required source documents and medical information required for each of the defined criteria by genotype and treatment arm (redacted data to be provided to the sponsor prior to enrollment):
  - IFN Eligibility
    - — Treatment naïve Genotype 1, 2 and 3
    - — A redacted source document confirming IFN eligibility or ineligibility must be received and approved by the Sponsor/CRO prior to the subject being enrolled.

- IFN Intolerance
  - — Treatment experienced Genotype 2 and 3 only
  - — Start dates and stop dates for treatment with PEG-IFN (and RBV if applicable)
  - — A redacted source document confirming IFN intolerance must be received and approved by the Sponsor/CRO prior to the subject being enrolled.
- Viral Response Data
  - — Treatment experienced Genotype 2 and 3 only
  - — In order to categorize the subject's prior response as either Non-Response or Relapse/Breakthrough, the following information must be provided to the Sponsor/CRO prior to enrollment:
    - Prior Treatment Dates (start and stop)
    - Prior Viral Response Data
    - HCV RNA assay
      - RT-PCR, TMA or bDNA
      - Undetectable as <LLOQ, BLOQ or <LLOD

- Cirrhosis determination as per Section 4.2
  - — If the presence of cirrhosis is determined, then appropriate diagnostic imaging (CT or Ultrasound) should be performed to exclude the presence of hepatocellular carcinoma (HCC)
- Obtain details of concomitant medications and adverse events
- Perform complete physical examination including vital signs, body weight, and height.
- Perform 12-lead ECG
- Obtain blood samples for safety testing as well as:
  - — HCV RNA
  - — HIV RNA
  - — CD4 T-lymphocyte Absolute Count and %
  - — Determination of HCV viral genotype
  - — HCV antibody, HIV 1/2 antibody, and HBs antigen

- — HbA_{1c}
- — TSH
- — IL28B
- — Serum β-hCG pregnancy test for females of childbearing potential only
- — Fibrotest® plus APRI

- Obtain urine samples

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

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the Baseline/Day 1 visit assessments and dosing/dispensing.

6.2. Treatment Assessments

The schedule of assessments is provided below. Details of the study procedures to be conducted for each subject enrolled in the study are presented in Study Procedures Table located in Appendix 2. Information on the specific laboratory parameters to be measured and clinical assessments to be performed are provided in Section 6.4.

6.2.1. Baseline/Day 1 Visit

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

- Confirmation of stable ARV treatment
- Perform complete physical examination, vital signs, and body weight.
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Subject completes quality of life surveys
- Obtain blood samples
- Pharmacogenomic testing (for subjects who have consented to participate in the Pharmacogenomic Substudy)
- Urine β-hCG pregnancy test for females of childbearing potential only

6.2.1.1. Drug Administration

- Dispense study drugs as directed by the IWRS
- Instruct the subject on the appropriate RBV dose after weight-based dosage is calculated using Baseline/Day 1 weight
- Instruct the subject on the packaging, storage and administration of all study drugs
- Observe the subject taking the first dose of study drugs (with food) and record the time of first dose

6.2.2. Weeks 1, 2, 6 and 10 (± 3 days)

The following procedures/assessments are to be completed at Weeks 1, 2, 6 and 10:

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples
- Review medication compliance with subject including the date and time of the subject's last dose of study medication prior to the PK draw
  - — Subjects should take the AM dose at home prior to the visit.

6.2.3. Weeks 4, 8, (16 and 20 for the 24-week treatment group only) (± 3 days)

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Subject completes quality of life surveys (Week 4 only)
- Obtain blood samples
- Urine β-hCG pregnancy test for females of childbearing potential only
- Review medication compliance with subject including the date and time of the subject's last dose of study medication prior to the PK draw
  - — Subjects should take the AM dose at home prior to the visit.
- Dispense study drugs as directed by the IWRS

6.2.4. Week 12 (and 24 for the 24-week treatment group only) or Early Termination Visit (± 3 days)

- Perform complete physical examination following the last dose of study medication (Week 12 for the 12-week treatment arm, Week 24 for the 24-week treatment arm)
- Obtain vital signs and body weight (weight is obtained at Week 12 for the 12-week treatment group and Week 24 for the 24-week treatment group)
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling (Week 12 for the 12-week treatment group and Week 24 for the 24-week treatment group)
- Subject completes quality of life surveys
- Obtain blood samples
- Urine β-hCG pregnancy test for females of childbearing potential only
- Review medication compliance with subject including the date and time of the subject's last dose of study medication prior to the PK draw (subject should return all study drugs at their last scheduled treatment visit).
  - — Subjects should take the AM dose at home prior to the visit.

All subjects will attend the 4-Week Post-Treatment Visit 4 weeks after last dose.

The Sponsor/CRO should be informed when a subject comes off treatment due to an adverse event. If a subject discontinues treatment then the assessments outlined above should be performed.

6.2.5. Unscheduled Visit

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments are at the investigator's discretion.

6.3. Post-Treatment Assessments

6.3.1. 4-Week Post-Treatment Visit (± 3 days)

- Obtain vital signs
- Assessment of AEs and concomitant medications

- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
  - HIV RNA
  - CD4 T-lymphocyte Absolute Count and %
  - Viral sequencing (archive)
- Urine β-hCG pregnancy test for females of childbearing potential only
- Pregnancy prevention counseling
- Subject completes quality of life surveys

Female subjects of childbearing potential should be provided with Urine Pregnancy Test-Kits, instructed on their use and requested to continue to self-monitor for pregnancy for 6-months after their last dose of RBV. If required by regulations, additional pregnancy tests beyond 6 months may be added. The subject should be contacted every 4 weeks and asked to report results of the urine pregnancy tests. If a positive urine pregnancy test is reported, the subject should return to the clinic for a serum pregnancy test.

Subjects with HCV RNA < LLOQ at the 4-Week Post-Treatment Visit will attend the 12-Week Post-Treatment Visit.

Subjects with a confirmed HCV RNA ≥ LLOQ at the Post-Treatment Week 4 Visit will be offered participation in the Sequence Registry Study.

6.3.2. 12-Week and 24-Week Post-Treatment Visit (± 3 days)

- Obtain vital signs and body weight
- Subject completes quality of life surveys
- Obtain blood samples for:
  - HCV RNA
  - HIV RNA
  - CD4 T-lymphocyte Absolute Count and %
  - Viral sequencing (archive)

- Urine β-hCG pregnancy test for females of childbearing potential only
- Pregnancy prevention counseling

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

Subjects with confirmed HCV RNA ≥ LLOQ at the 12 or 24-Week Post-Treatment Visit will be offered participation in the Sequence Registry.

Subjects with HCV RNA < LLOQ at the Post-Treatment Week 24 Visit will be offered participation in the SVR Registry Study.

6.4. Procedures and Specifications

6.4.1. 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), Glucose, Lipase, Potassium, Sodium, Fibrotest® , APRI, and Gamma-glutamyl transferase (GGT).

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. HIV RNA will be measured using the AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0. If HIV-1 virologic rebound is confirmed, HIV-1 genotype/phenotype will be determined using the PhenoSense™ Integrase HIV, GeneSeq™ Integrase HIV, PhenoSense™ HIV, GenoSure MG, GeneSeq™ HIV, and PhenoSense GT™. Gilead reserves the right to use alternate assays for HCV RNA, HIV RNA, HCV genotype, and HIV-1 genotype/phenotype should the above assays become unavailable.

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 right to use alternate assays for IL28B determination should the above assay become unavailable.

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

Pharmacokinetic Tests: The exact time of the dose taken prior to collection of the PK sample and the exact time the PK sample is drawn will be recorded on the appropriate eCRF. Information on food intake prior to dosing on days of PK assessments will be collected.

Additional Tests: Urine Drug screen (for Amphetamines, Cocaine, Methadone, Opiates), Hemoglobin A1c (HbA1c). TSH (reflex T3 and T4). CD4 T-lymphocyte Absolute Count and %

6.4.2. 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.

Categorization of IFN eligibility or prior treatment with PEG/RBV based on the following:

1. **IFN Eligibility:**

Subject is deemed IFN-eligible if there has been no prior treatment for HCV with an IFN-based regimen and/or direct acting antivirals and has no medical contraindication to treatment with an IFN-based regimen. Subjects treated in the Drug Interaction portion (Part A) of the P7977-1910 protocol will be considered treatment-naïve.

Subject is deemed ineligible by the investigator for treatment with IFN due to at least one of the following co-morbidities that is deemed at risk for worsening with IFN treatment:

- Autoimmune disorders including but not limited to: dermatomyositis, immune (idiopathic) thrombocytopenic purpura, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, polymyositis, psoriasis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus

- Significant psychiatric disease necessitating hospitalization or period of disability or a history of psychosis, schizophrenia, bipolar disorder, moderate depression, schizoaffective disorder, suicidal ideation, or suicide attempt

- Seizure disorder

- Poorly controlled thyroid dysfunction; hypothyroidism (TSH ≥ 2 x the upper limit of normal (ULN) and ≤ 10 x ULN) or hyperthyroidism (TSH < the lower limit of normal (LLN) and > 0.1 μIU/mL)

- Retinal disease

- Poorly controlled diabetes
- Other relative IFN contraindications, including age, not specifically listed above, but which may be approved after discussion with the Gilead Medical Monitor

2. **IFN Intolerance**:

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 Gilead Medical Monitor

3. **Prior Treatment History:**

- Start dates and stop dates for treatment with PEG-IFN (and RBV if applicable)
- HCV Viral Response Data

- HCV RNA assay may be either branched-chain DNA [bDNA], real time-polymerase chain reaction [RT-PCR] or transcription mediated amplification [TMA]-based assay (undetectable can be interpreted as < LLOQ, BLOQ, or < LOD). Both the result of the assay and the date of the assay/date of collection should be available

- Requirements for Non-Response (subject never had undetectable HCV RNA during treatment)

  — Pre-treatment HCV RNA (the date must be within 1 year prior to or within the first 24 hours of starting treatment)

  — Nadir HCV RNA

- Requirements for Relapse/Breakthrough (subject had undetectable HCV RNA during treatment)

  — Pre-treatment HCV RNA (the date must be within 1 year prior to or within the first 24 hours of starting treatment)

  — Undetectable HCV RNA during treatment or within 4 weeks of the end of treatment

  — Detectable HCV RNA after the undetectable HCV RNA and ≤ 1 year after stopping treatment

4. Criteria for Switching from ATV/r to DRV/r

Subjects who switched from ATV/r to DRV/r prior to Amendment 2 will be allowed to enroll if there is documented history of the following criteria:

  — > 8 weeks of an undetectable HIV-1 RNA level on ATV/r prior to the switch to DRV/r

  — > 4 weeks of an undetectable HIV RNA level on DRV/r by local assay preceding the Screening visit. Screening HIV RNA must be < 50 cp/mL as measured by the COBAS AMPLIPREP/COBAS TaqMan 2.0 HCV RNA assay.

6.4.3. 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.

6.4.4. 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.

6.4.5. 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)

6.4.6. Body Mass Index (BMI)

BMI is calculated by the following equation.

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

6.4.7. 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 gross abnormalities.

6.4.8. Pharmacogenomic Testing

An additional and distinct informed consent document will be provided to allow the Sponsor to obtain and test a subject's blood sample taken on Baseline/Day 1 for pharmacogenomic discovery research. If not obtained at Baseline/Day 1, the sample may be drawn at any time during the study. Providing this blood sample is optional and not required for participation in the primary study.

6.4.9. Viral Sequencing (Archive)

Plasma samples will be collected at Baseline/Day 1 and each visit for viral sequence analysis. Unused samples may be archived.

6.4.10. Quality of Life Surveys

Quality of life surveys included in this study are SF-36, Chronic Liver Disease Questionnaire (CLDQ-HCV), Fatigue Index (FACIT-F), Work Productivity and Activity Impairment Questionnaire: Hepatitis C, v2.0 (WPAI: Hepatitis C) which will be completed by patients at Baseline/Day 1, Week 4, Week 12, Week 24 (depending on treatment regimen), Early Termination, 4-Week Post-Treatment, 12-Week Post-Treatment, and 24-Week Post-Treatment visits. The subject should read and complete the surveys by himself/herself and write/mark answers directly onto the questionnaire.

6.4.11. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period and for a minimum of 6 months following the last dose of RBV. If required by local regulations, additional pregnancy tests beyond 6 months may be added. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drugs immediately and return to the clinic as soon as possible for a serum pregnancy test.

Pregnancy test kits will be dispensed to female subjects of child bearing potential at the 4-Week Post-Treatment visit. The subject will be contacted by telephone monthly to confirm that urine pregnancy testing has been performed post-treatment and to record the outcome.

Alternatively, if required by local regulations or preferred by the investigator or subject, the subject may return to the clinic for urine pregnancy tests.

7. TOXICITY MANAGEMENT

7.1. Modification of Dose/Schedule Due to Toxicity

7.1.1. RBV Dose Adjustments

Dose reduction of RBV due to toxicity should be performed according to the product label. Information is provided in Table 7-1.

RBV may be permanently discontinued due to toxicity without stopping GS-7977.

Table 7-1. RBV Dose Reduction Guidelines

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

a 1 tablet in AM, 2 tablets in PM.

Once RBV has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart RBV at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that RBV be increased to the original assigned dose.

7.2. Subject Stopping Rules for GS-7977

The Gilead Medical Monitor should be consulted prior to dose discontinuation of GS-7977 unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject.

Administration of GS-7977 may be discontinued due to a clinical or laboratory event. There is no option for GS-7977 dose reduction. If GS-7977 is stopped for toxicity, it should not be restarted; RBV should be stopped and the subject should complete an Early Termination Visit, followed by a Week 4 post treatment visit. Subjects with HCV RNA <LLOQ at the time of discontinuation of study medication(s) should remain in the study and complete Post-treatment follow-up visits as planned.

Subjects who meet any of the following laboratory criteria should stop treatment with GS-7977 and RBV:

- Confirmed elevation of ALT and/or AST >5x Baseline/Day 1 or nadir, confirmed by immediate repeat testing
- Confirmed elevation of ALT >3x Baseline/Day 1 and total bilirubin >2 x ULN
- Confirmed elevation of ALT or AST >15 x ULN
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 event assessed as related to treatment with GS-7977

8. ADVERSE EVENTS MANAGEMENT

8.1. Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs also include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure (e.g. such as venipuncture, biopsy) during or after screening (before the administration of study investigational medicinal product).

- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study investigational medicinal product phase of a human clinical trial, will also be considered an AE.

- Complications and termination of pregnancy (see Section 8.6.2.1 for additional information)

- All AEs that occur from the Baseline/Day 1 Visit onwards and throughout the duration of the study, including the follow-up off study medication period should be recorded as an AE.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an adverse event

- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

- Overdose without clinical sequelae (see Section 8.6.1)

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

- Uncomplicated pregnancy.

- An induced elective abortion to terminate a pregnancy without medical reason.

8.2. Assessment of Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded on the AE CRF page. The AE entry should indicate whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to investigational medicinal product or to a study procedure, the action taken with investigational medicinal product due to the AE, and the severity of the AE. The investigator is responsible for final review and confirmation of accuracy of events, relationship and severity confirmed by the signature on the CRF book. The relationship to investigational medicinal product therapy should be assessed using clinical judgment and the following considerations:

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

- **Yes**: A temporal relationship exists between the AE onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational medicinal product. In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon rechallenge.

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

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

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol-mandated procedures such as venipuncture or biopsy.

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 3).

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

Quality of life surveys will be collected from all subjects if a site is approved to use the survey

8.3. Serious Adverse Events

A **serious adverse event** (SAE) is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at **immediate** risk of death)
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product
- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Examples of such events are as follows:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself. In reports of death due to "Disease Progression," where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the investigational medicinal product(s).
- The subject may not have been on investigational medicinal product at the occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.

- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 4. An event is defined as "serious" when it meets one of the predefined outcomes described above in Section 8.3.

8.4. Serious Adverse Event Reporting Requirements

8.4.1. All Serious Adverse Events

Gilead Sciences is required to expedite to worldwide regulatory authorities reports of SAEs, Serious Adverse Drug Reactions (SADRs) or Suspected Unexpected Serious Adverse Reactions (SUSARs) in line with relevant legislation, including the applicable US FDA Code of Federal Regulation, the European Commission Clinical Trials Directive (2001/20/EC); therefore, Gilead Sciences (or the CRO on the behalf of Gilead Sciences) must be notified immediately regarding the occurrence of any SAE or SADR that occurs after the subject consents to participate in the study, including SAEs/SADRs resulting from protocol-associated procedures as defined in relevant legislation including 2001/20/EC. The procedure for reporting all SAEs, regardless of causal relationship, is as follows:

- Record the SAE on the AE CRF and complete the "Serious Adverse Event Report" form.

- Include details of alternate SAE reporting method (i.e., SAE eCRF).

- Email or fax the SAE form to the attention of the CRO Pharmacovigilance Representative within 24 hours of the investigator's knowledge of the event. Contact information is as follows:

CRO Pharmacovigilance Representative US:	Name:	PPD PVG
	Phone:	+1 888 483-7729
	Fax:	+1 888 529-3580
Gilead Sciences Medical Monitor:	Name:	Stephen J. Rossi
	Phone:	+1 650 522-4212
	Mobile	+1 650 223-9075
	Fax:	+1 650 522-1975
	E-mail:	stephen.rossi@gilead.com

- For fatal or life-threatening events, also e-mail or fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable. Transmission of such documents should occur with Personal Subject Details de-identified, without losing the traceability of a document to the Subject Identifiers.

- Gilead Sciences may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF and the event description section of the SAE form.

Follow-up of AEs will continue through the last day on study (including the follow-up off-study medication period of the study) and/or until a conclusive outcome (e.g., resolved, resolved with sequelae, lost to follow-up, fatal) is achieved.

8.4.2. Investigator and Sponsor Reporting Requirements for SAEs

An SAE may qualify for reporting to regulatory authorities. Expectedness of SAEs will be determined by Gilead Sciences using reference safety information specified in the Investigator's Brochure.

All Investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the IRB as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead will notify worldwide regulatory authorities and the relevant Ethics Committees (EC) in concerned Member States of applicable SUSARs.

8.4.3. Reporting Requirements

All AEs, regardless of causal relationship, must be reported for subjects on treatment and through the 4-Week Post-Treatment Visit.

All SAEs, including deaths, regardless of causal relationship, must be reported from signing of the informed consent through the end of the study. Investigators are not obligated to actively seek SAEs beyond this point. However, if the investigator learns of any SAEs that occur after study participation and the event is deemed relevant to the use of investigational medicinal product(s), he/she should promptly document and report the event to the CRO Pharmacovigilance Representative or to Gilead Sciences, DSPH if the study has been completed. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

8.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or Serious AEs

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 8.1 and 8.3. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

Severity should be recorded and graded according to the GSI Grading Scale for Severity of AEs and Laboratory Abnormalities (Appendix 3). Quality of life surveys will be collected from all subjects if a site is approved to use the surveys.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

8.6. Special Situations Reports

8.6.1. Definitions of Special Situations

Special situation reports include pregnancy reports, reports of medication error, abuse, misuse, or overdose, reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints.

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

Medication error is any preventable event that can cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare professional, patient or consumer.

Abuse is defined as persistent, sporadic or intentional excessive use of a medicinal product by a patient accompanied by harmful, physical, and/or psychological effects.

Misuse refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol or the maximal recommended daily dose as stated in the Product Labelling (as it applies to the daily dose for the subject/patient in question).

In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s) or the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

8.6.2. Instructions for Reporting Special Situations

8.6.2.1. Instructions for Reporting Pregnancies

The Investigator should report all pregnancies to the CRO Pharmacovigilance Representative using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the Investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the Investigator.

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 adverse event term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in the Adverse and Serious Adverse Events section. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the CRO.

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

Clinical staff should also report any pregnancies to the Ribavirin Pregnancy Registry at 1-800-593-2214 (see also http://www.ribavirinpregnancyregistry.com).

8.6.2.2. Reporting Other Special Situations

All other Special Situation reports must be reported on the Special Situations Report Form and forwarded to the CRO Pharmacovigilance Representative within 24 hours.

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

9. STATISTICAL CONSIDERATIONS

9.1. Analysis Objectives and Endpoints

9.1.1. Analysis Objectives

The primary analysis objectives of this study are:

- To determine the efficacy of treatment with GS-7977 + RBV as measured by the proportion of subjects with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of GS-7977 + RBV as assessed by review of the accumulated safety data

The secondary analysis objectives of this study include the following:

- 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 GS-7977 during treatment and after treatment discontinuation

The exploratory objectives of this study are:

- To identify or validate genetic markers that may predict the natural history of disease, response to therapy, and/or tolerability of medical therapy through genetic discovery research (e.g., pharmacogenomics) in subjects who provide separate and specific consent
- To assess the effect of treatment on health related quality of life

9.1.2. Primary Endpoint

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

9.1.3. Secondary Endpoints

Secondary efficacy endpoints include the proportion of subjects with: HCV RNA < LLOQ at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24); HCV RNA < LLOQ on-treatment virologic failure, and change in HCV RNA from baseline through Week 8.

Safety Endpoints

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

9.1.4. Other Endpoints of Interest

Additional efficacy evaluations may include ALT normalization; quality of life endpoints; and viral kinetic parameters.

9.2. Analysis Conventions

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

9.2.1. Analysis Sets

9.2.1.1. Efficacy

The analysis set for antiviral activity analyses will be the Full Analysis Set (FAS) which includes subjects with genotype 1, 2 or 3 HCV infection who were enrolled into the study and received at least one dose of study drug.

9.2.1.2. Safety

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

9.2.1.3. Pharmacokinetics

The PK analysis set will include all subjects who are enrolled and have received at least one dose of study medication and for whom concentration data of study drug [GS-7977 and metabolite(s), as appropriate] could be adequately estimated. The PK analysis set will be used for analyses of general PK.

9.2.2. Data Handling Conventions

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

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

Any subject with missing data due to premature discontinuation of the study medication will be considered a failure at the date of premature discontinuation and all time points subsequent to the date of 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.

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

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

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

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

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.

9.2.3. Interim Analysis

No formal interim analyses are planned for this study.

9.3. Demographic Data and Baseline Characteristics

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

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

Baseline characteristic data will include body mass index, presence or absence of cirrhosis, HCV RNA level (log_{10} IU/mL), HCV genotype, prior treatment experience, response to previous treatment (if applicable), and additional endpoints as necessary.

9.4. Efficacy Analysis

9.4.1. Primary Analysis

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

The primary analysis will be performed after subjects have been followed through 12 weeks post-treatment or discontinued from study.

9.4.2. Secondary Analysis

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

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

Exploratory analyses may be performed to assess the relationship between demographic, baseline characteristics, (including baseline viral load, genotype, age, sex, race, ethnicity, presence/absence of cirrhosis, baseline ALT level, prior treatment experience, response to previous treatment [if applicable], and BMI) and antiviral activity (HCV RNA reduction, proportion of subjects with HCV RNA < LLOQ at various time points during and following discontinuation of all therapy). Predictive factors of antiviral activities may be examined using regression type of analysis.

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

9.5. Safety Analysis

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

All safety data collected while "on treatment" (i.e., on or after the first dose of study drug administration up to 30 days after the last dose of study drug) will be summarized by treatment arm according to the study drug received..

9.5.1. Extent of Exposure

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

9.5.2. Adverse Events

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

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

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

- 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.

9.5.3. Laboratory Evaluations

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

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

9.6. Pharmacokinetic Analysis

Plasma concentrations of the study drug over time will be summarized using descriptive statistics. PK parameters (e.g., C_{max}, AUC_{tau}) will be listed and summarized for study drug [GS-7977 and metabolite(s)] using descriptive statistics. Details of the analysis plan will be provided in the pharmacokinetic reporting and analysis plan.

9.7. Data Safety Monitoring Board

An external multidisciplinary DSMB will review the progress of the study and perform interim reviews of safety data in order to protect subject welfare and preserve study integrity. The DSMB is to recommend to the sponsor whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

Reviews will be conducted after all GT2/3 treatment-naïve subjects have completed through Week 4 on study therapy. Additional meetings will be scheduled at regular intervals based on enrollment rate. The DSMB will provide recommendations as needed regarding study design, conduct and the need for additional meetings or an alternative meeting schedule.

While the DSMB will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9.8. Sample Size

With approximately 55 GT2/3 treatment-naïve subjects enrolled into the study, a two-sided 95.0% confidence interval of the SVR12 rate will extend at most 12.8% in both directions from the observed SVR12 rate, assuming the expected SVR12 rate is 62%. With approximately 55 GT2/3 treatment-experienced and 115 GT1 treatment-naïve subjects enrolled into the study, the SVR12 rate will extend at most 12.9% and 8.7% respectively, assuming the expected SVR12 rate is 40% and 65% respectively.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

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

Since this is a "covered" clinical trial, the Investigator will ensure that 21 CFR, Part 54, "Financial Disclosure by Clinical Investigators", is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Investigators and all subinvestigators must provide documentation of their financial interest or arrangements with Gilead Sciences, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any subinvestigator. The Investigator and subinvestigator agree to notify Gilead Sciences of any change to reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

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

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

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB (for studies conducted in the United States) or IEC (for studies conducted outside of the United States). Approval from the IRB or IEC must be obtained **before** starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

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

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

10.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

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

10.1.5. Study Files and Retention of Records

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

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

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

- Subject identification (name, date of birth, gender);

- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in trial (including trial number);
- Trial discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- Record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity);
- Concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- Date of trial completion and reason for early discontinuation, if applicable.

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

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

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

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

10.1.6. Case Report Forms

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

10.1.7. Drug Accountability

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

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

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

10.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Gilead Sciences or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.9. Protocol Compliance

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

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead Sciences. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

10.2.2. Study Report and Publications

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

After conclusion of the study and without prior written approval from Gilead Sciences, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met:***

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

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

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead Sciences' request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information for Monitoring

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

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

10.3.2. Access to Information for Auditing or Inspections

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

10.3.3. Study Discontinuation

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

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12. APPENDICES

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

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects

GS-US-334-0123, Amendment 2, 20 September 2012

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

Stephen Rossi PharmD (Printed) Study Director	Signature
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 2 Table 1. Screening and On-Treatment Study Visits– Genotype 2 and 3 Treatment Naïve

			Visit identified by on-treatment study week							
	Screening	Baseline/Day 1[c]	1	2	4	6	8	10	12	Early Termination
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X							X	X
Height	X									
Weight	X	X							X	X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X									
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X	X
Quality of Life Surveys[f]		X			X				X	X
Review of Study Medication Compliance			X	X	X	X	X	X	X	X
Study Drug Dispensing[b]		X			X		X			

	Screening	Baseline/Day 1[c]	Visit identified by on-treatment study week							
			1	2	4	6	8	10	12	Early Termination
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X							X	X
FibroTest® / APRI	X									
HCV RNA	X	X	X	X	X	X	X	X	X	X
HIV RNA	X	X	X	X	X	X	X	X	X	X
CD4 T-lymphocyte Count and %	X	X	X	X	X	X	X	X	X	X
HCV Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X
HIV Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X
Urinalysis	X									
Urine Drug Screen	X									
HCV Genotyping, IL28B	X									

	Screening	Baseline/Day 1[c]	Visit identified by on-treatment study week							
			1	2	4	6	8	10	12	Early Termination
HCV, HIV, HBV Serology	X									
HbA1c	X									
TSH	X									
Pharmacogenomic[e]		X								

a Vital signs include blood pressure, pulse, respiratory rate and temperature

b The IWRS will provide direction on the specifics of each subject's study drug dispensing. Subjects to dose in-clinic at baseline/day1 after all assessments are completed. On subsequent visit days (after baseline/day 1) subjects can dose in the AM prior to the visit, this will not affect PK.

c Baseline/ Day 1 assessments must be performed prior to dosing

d Plasma samples will be collected and stored for potential HCV and HIV sequencing and other virology studies

e Only for subjects who have consented to this testing. If not obtained at Baseline/Day, the sample may be drawn at any time during the study.

f Quality of life surveys will be collected from all subjects if a site is approved to use the survey.

Appendix 2 Table 2. Screening and On-Treatment Study Visits – Genotype 1 and Genotype 2/3 Treatment Experienced

			Visits identified by on-treatment study week										
	Screening	**Baseline/Day 1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**Early Termination**
Clinical Assessments													
Informed Consent	X												
Determine Eligibility	X	X											
Medical History	X												
Physical Examination	X	X										X	X
Height	X												
Weight	X	X										X	X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X												
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X										X	X
Quality of Life Surveys[f]		X			X				X			X	X
Review of Study Medication Compliance			X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing[b]		X			X		X		X	X	X		

			Visits identified by on-treatment study week										
	Screening	**Baseline/Day 1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**Early Termination**
Laboratory Assessments													
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X							X			X	X
FibroTest® / APRI	X												
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4 T-lymphocyte Count and %	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X	X	X	X
HIV Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X	X	X	X
Urinalysis	X												
Urine Drug Screen	X												

			Visits identified by on-treatment study week										
	Screening	**Baseline/Day 1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**Early Termination**
HCV Genotyping, IL28B	X												
HCV, HIV, HBV Serology	X												
HbA1c	X												
TSH	X												
Pharmacogenomic[e]		X											

a Vital signs include blood pressure, pulse, respiratory rate and temperature

b The IWRS will provide direction on the specifics of each subject's study drug dispensing. Subjects to dose in-clinic at baseline/day1 after all assessments are completed. On subsequent visit days (after baseline/day 1) subjects can dose in the AM prior to the visit, this will not affect PK.

c Baseline/ Day 1 assessments must be performed prior to dosing

d Plasma samples will be collected and stored for potential HCV and HIV sequencing and other virology studies

e Only for subjects who have consented to this testing. If not obtained at Baseline/Day, the sample may be drawn at any time during the study.

f Quality of life surveys will be collected from all subjects if a site is approved to use the survey.

Appendix 2 Table 3. Post Treatment Visits Following Primary Study – All Treatment Regimens

	4 Weeks Post Treatment	12 Weeks Post Treatment	24 Weeks Post Treatment
Clinical Assessments			
Vital Signs	X	X	X
Weight		X	X
AEs	X		
Concomitant Medications	X		
Quality of Life Surveys[a]	X	X	X
Laboratory Assessments			
Hematology, Chemistry	X		
HCV RNA	X	X	X
HIV RNA	X	X	X
CD4 T-lymphocyte Count and %	X	X	X
Viral Sequencing	X	X	X
Urine Pregnancy Test[b]	X	X	X
Pregnancy Prevention Counseling	X	X	X

a Quality of life surveys will be collected from all subjects if a site is approved to use the survey.

b Refer to Section 6.3.1 and Section 6.4.11 for details on Post-Treatment pregnancy tests.

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)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infant, 2 – ≤ 7 Days	1250 to 1500/mm^3 1.25 to 1.50 GI/L	1000 to < 1250/mm^3 1.00 to < 1.25 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	< 750/mm^3 < 0.75 GI/L
Infant, 1 Day	4000 to 5000/mm^3 4.00 to 5.00 GI/L	3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 1500/mm^3 < 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL	> 40 to 50 µg/mL	> 50 to 60 µg/mL	> 60 µg/mL

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	20 to 40 mg/L	> 40 to 50 mg/L	> 50 to 60 mg/L	> 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
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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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 1.12 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**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting)	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

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

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:

a 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.

b 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.

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

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

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

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

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

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

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

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle 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	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

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

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

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

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

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

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

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

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects
Study Number:	GS-US-334-0123
Name of Test Drug:	Sofosbuvir
Indication:	HCV/HIV Co-infection
Sponsor:	Gilead Sciences, Inc.
Protocol Version/Date:	Original: 06 June 2012 Amendment 1: 07 August 2012 Amendment 2: 20 September 2012
Analysis Type:	EMEA 120 Day Response and AASLD Analysis
Analysis Plan Version:	Draft
Analysis Plan Date:	23 Sept 2013
Analysis Plan Author:	Liyun Ni

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate transaminase
BMI	body mass index
CI	confidence interval
CSR	clinical study report
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMEA	European Medicines Agency
FAS	full analysis set
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLT	high level term
HLGT	high level group term
IFN	interferon
LLT	lower level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PEG	pegylated interferon
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
RBV	ribavirin
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOF	Sofosbuvir (GS-7977)
SVR	sustained virologic response
SVRx	sustained virologic response x weeks after stopping study drug
TE	treatment- emergent
TFLs	tables, figures, and listings
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in European Medicines Agency (EMEA) 120-day response and American Association for the Study of Liver Diseases (AASLD) analysis for Study GS-US-334-0123 to support the New Drug Application (NDA) of sofosbuvir (GS-7977; SOF) for use in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults.

1.1. Study Objectives

1.1.1. Primary Study Objectives

- To determine the efficacy of treatment with Sofosbuvir (GS-7977; SOF) + ribavirin (RBV) by proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)

- To evaluate the safety and tolerability of SOF + RBV as assessed by review of the accumulated safety data

1.1.2. Secondary Study Objectives

- 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 during treatment and after treatment discontinuation

1.1.3. Exploratory Study Objectives

- To identify or validate genetic markers that may predict the natural history of disease, response to therapy and/or the tolerability of medical therapies through genetic discovery research (eg, pharmacogenomics), in subjects who provide their separate and specific consent

- To assess the effect of treatment on health related quality of life

1.2. Study Design

1.2.1. Design Configuration, Subject Population and Treatment Groups

This is an open-label study in subjects with chronic genotype 1, 2, and 3 HCV infection who are coinfected with HIV-1. A total of 230 subjects with HCV infection (115 genotype 2 or 3 and 115 genotype 1) will be enrolled and treated with oral SOF 400 mg once daily plus weight based RBV (1000 or 1200 mg/day) in a divided daily dose for 12 or 24 weeks, depending on genotype and prior treatment experience as following:

- Group 1: Treatment-naive subjects with genotype 2 or 3 HCV infection received 12 weeks of treatment followed by 24 weeks of follow-up
- Group 2: Treatment-experienced subjects with genotype 2 or 3 infection received 24 weeks of treatment followed by 24 weeks of follow-up
- Group 3: Treatment-naive subjects with genotype 1 HCV infection received 24 weeks of treatment followed by 24 weeks of follow-up

Subjects will be categorized based on interferon (IFN) eligibility or prior treatment with PEG+RBV into 1 of the following categories:

- Treatment naive and IFN-eligible
- Treatment naive and IFN-ineligible
- IFN intolerant
- Nonresponse
- Relapse/Breakthrough

Equal enrollment of subjects with genotype 2 or 3 HCV infection and treatment-naive and treatment-experienced subjects will be targeted. Approximately 20% of the subjects enrolled will have evidence of compensated cirrhosis at Screening. Approximately 10% of the subjects enrolled will not be on antiretroviral (ARV) treatment.

Subjects will be maintained on similar timing of administration and dosing conditions for their ARV regimens during the study period as those prior to the study. Posttreatment follow-up visits will be performed for all subjects at 4 weeks following the last dose of study drug. Subjects with HCV RNA < lower limit of quantification (LLOQ) at posttreatment Week 4 will return at posttreatment Week 12 and 24 unless confirmed HCV relapse occurs. Safety assessments, including monitoring of HIV RNA and CD4 T-cell counts, will be performed at all study visits.

Depending on subject outcome of HCV RNA, subjects may subsequently be enrolled into 1 of 2 registry studies: Sequence Registry Study and SVR Registry Study.

Sequence Registry Study

Subjects who do not achieve SVR, as well as those who achieve SVR and later become detectable, will be eligible for enrollment in the Sequence Registry Study. The purpose of the Sequence Registry Study will be to monitor the persistence of resistant mutations for up to 3 years after the last dose of study drug. The Sequence Registry Study is described in a separate protocol (GS-US-248-0123).

SVR Registry Study

Subjects who achieve SVR at 24-weeks posttreatment will be eligible for enrollment in the SVR Registry Study. The purpose of the SVR Registry Study will be to evaluate durability of SVR for up to 3 years posttreatment. The SVR Registry Study is described in a separate protocol (GS-US-248-0122).

1.2.2. Study Duration

The total time to complete all study visits is up to approximately 40 weeks for subjects treated with 12 weeks of therapy and 52 weeks for subjects treated for 24 weeks of therapy including the following periods:

- 28-day (4-week) screening period
- 12 or 24 week treatment period
- Up to 24-week post-treatment period

1.3. Sample Size and Power

With approximately 55 treatment-naive subjects with genotype 2 or 3 HCV infection enrolled into the study, a 2-sided 95.0% confidence interval of the SVR12 rate will extend at most 12.8% in both directions from the observed SVR12 rate, assuming the expected SVR12 rate is 62%. With approximately 55 treatment-experienced subjects with genotype 2 or 3 HCV infection and 115 treatment-naive subjects with genotype 1 HCV infection enrolled into the study, the SVR12 rate will extend at most 12.9% and 8.7% respectively, assuming the expected SVR12 rate is 40% and 65% respectively.

2. TYPE OF PLANNED ANALYSIS

2.1. EMEA 120-Day Response and AASLD Analysis

After all group 1 and group 3 subjects (group 1: genotype 2/3 treatment-naive subjects, SOF+RBV 12 weeks; group 3: genotype 1 treatment-naive subjects, SOF+RBV 24 weeks) have completed the posttreatment Week 12 visit or prematurely discontinued from study, an analysis will be conducted on key safety and efficacy data for all treatment groups to be included in the 120-day EMEA response and AASLD analysis to support the NDA of SOF for use in combination with other agents for the treatment of CHC in adults.

The last visit date for the posttreatment week 12 visit for group 1 and group 3 subjects (defined as LPLV date) is approximately September 9, 2013. The database finalization date for this analysis is approximately September 30, 2013.

All safety and efficacy eCRF data collected up to the LPLV date specified above will be cleaned and included in the analysis. Data between LPLV date and database finalization date will be included in the database, but may or may not be cleaned and/or reconciled.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

Analysis sets define which subjects are included in an analysis. A summary of the number and percentage of subjects in each analysis set will be provided by treatment group and in total as part of the subject disposition summary.

3.1.1. Full Analysis Set

The full analysis set (FAS) includes the following subjects who were enrolled into the study and received at least one dose of study drug:

- Treatment-naive subjects with genotype 1, 2 or 3 HCV infection
- Treatment-experienced subjects with genotype 2 or 3 infection who have completed the posttreatment Week 12 visit or prematurely discontinued from study

The study drugs in this study include SOF and RBV. Efficacy analysis of antiviral activity will be based on FAS.

3.1.2. Safety Analysis Set

The safety analysis set includes subjects who were enrolled and received at least one dose of study drug.

The safety analysis set will be used for all the analyses in the safety update except any efficacy analysis which will be based on the FAS and the summary of subject disposition which will be based on all screened subjects.

3.2. Subject Groups

All subjects will receive oral SOF 400 mg QD plus weight based RBV (1000 or 1200 mg/day) BID for 12 or 24 weeks, depending on genotype and prior treatment experience. Since this is an open-label study, it is unlikely that subjects could be enrolled into the wrong treatment group. Therefore, subjects will be grouped for analyses according to the treatment group they are enrolled into for all the analyses.

Specifically, subjects will be grouped into the following treatment groups for analyses:

Table 1.1: Treatment groups for efficacy analyses:

SOF+RBV 12 weeks			SOF+RBV 24 weeks					
Genotype 2/3 treatment-naive			Genotype 2/3 treatment-experienced			Genotype 1 treatment-naive		
Total	Genotype 2	Genotype 3	Total	Genotype 2	Genotype 3	Total	Genotype 1a	Genotype 1b

Table 1.2: Treatment groups for summary of demographics, disposition and exposure:

SOF+RBV 12 weeks			SOF+RBV 24 weeks					
Total Genotype 2/3 treatment-naive	Genotype 2 treatment-naive	Genotype 3 treatment-naive	Total Genotype 2/3 treatment-experienced	Genotype 2 treatment-experienced	Genotype 3 treatment-experienced	Genotype 1 treatment-naive	Total of SOF+RBV 24 Weeks	Grand Total

Table 1.3: Treatment groups for safety analyses:

SOF+RBV 12 weeks	SOF+RBV 24 weeks			
Genotype 2/3 treatment-naive	Genotype 2/3 treatment-experienced	Genotype 1 treatment-naive	Total of SOF+RBV 24 weeks	Grand Total

3.3. Strata and Covariates

There is no stratification in this study.

3.4. Examination of Subject Subsets

The efficacy endpoints SVR4 and SVR12 will be analyzed for the following subsets:

- age group on date of first dose of study regimen (< 50 years, ≥ 50 years)
- sex (male, female)
- race (black, non-black)

- ethnicity (hispanic or latino, non-hispanic or latino)
- cirrhosis(presence, absence)
- HCV genotype (1, 2, 3)
- baseline HCV RNA (< 6 $\log_{10}$ IU/mL, ≥ 6 $\log_{10}$ IU/mL)
- baseline BMI (< 30 kg/m^2, ≥ 30 kg/m^2)
- baseline ALT (≤1.5 x ULN, > 1.5 x ULN)
- IL28B (CC, non-CC)
- prior HCV treatment experience and response to prior HCV treatment (IFN-eligible treatment naive, IFN-ineligible treatment-naive, IFN intolerant, non-response, relapse/breakthrough)
- study drug completers and subjects who prematurely discontinued from drug
- ARV treatment experience at enrollment (untreated, treated)
- ARV regimen at enrollment

3.5. Data Handling Conventions and Transformations

The COBAS® Taqman® HCV Test v2.0 for use with the High Pure System assay was used to determine HCV RNA results in this study. The lower limit of quantitation (LLOQ) of the assay is 25 IU/mL.

When the calculated IU/mL is within the linear range of the assay, then the result will be report as the "<< numeric value>> IU/mL". This result will be referred to in this document as the numeric result or as "≥ LLOQ detected" for categorical result.

When HCV RNA is not detected, the result is reported as "HCV RNA not detected" or "target not detected". This result will be referred to in this document as "< LLOQ target not detected" or "< LLOQ TND".

When the calculated HCV RNA IU/mL is below LLOQ of the assay, the result is reported as "< 25 IU/mL, HCV RNA detected". This result will be referred to in this document as "< LLOQ detected".

For numerical HCV RNA data, values below LLOQ will be set to the LLOQ minus 1 (ie, 24 HCV RNA IU/mL). HCV RNA values returned as "target not detected" will also be set to 24 IU/mL.

For selected analyses, HCV RNA data (IU/mL) will be transformed to the logarithmic (base 10) scale (log_{10} IU/mL).

Total bilirubin values entered as < 0.2 mg/dL will be analyzed as 0.1 mg/dL; direct bilirubin values entered as < 0.1 mg/dL will be analyzed as 0.05 mg/dL {20502}. In general, other than the above 2 exceptions, laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing data point for a given study visit may be due to any one of the following reasons:

- A visit occurred but data were not collected or were unusable
- A visit did not occur
- A subject permanently discontinued from the study before reaching the window

For subjects in the FAS, missing HCV RNA data will only be imputed up to the posttreatment Week 12 visit, unless the subject has completed the study, his posttreatment Week 24 visit missing HCV RNA data will be imputed. HCV RNA data at posttreatment Week 24 visit will not be included in tables and figures, but will be listed.

For subjects in safety analysis set but not in FAS, missing HCV RNA data will not be imputed unless (1) it is preceded and followed in time by values which are not missing (i.e., bracketed). (2) the subject has completed the study. (3), SVR4 is a failure then SVR12 will be imputed as failure. No tables and figures will be generated for these subjects. Their HCV RNA data will be listed.

For analyses of categorical HCV RNA data, if a data point is missing and is preceded and followed in time by values that are "< LLOQ TND", then the missing data point will be set to "< LLOQ TND". If a data point is missing and preceded and followed by values that are "< LLOQ detected", or preceded by "< LLOQ detected" and followed by "< LLOQ TND", or preceded by "< LLOQ TND" and followed by "< LLOQ detected", then the missing value will be set to "< LLOQ detected"; otherwise the data point will be termed a failure (ie, ≥ LLOQ detected).

Subjects with missing data due to premature discontinuation of the study will have missing data imputed up to the time of their last dose (for on-treatment displays). If study days associated with the last dosing date is greater than the lower bound of a visit window, and the value at the visit is missing, then the value will be imputed. If the study days associated with the last dosing date is less than the lower bound of a visit window then the on-treatment value at that visit will remain missing.

If no HCV RNA values are obtained after the last dose of any study drug, the subject will be considered a treatment failure for SVR endpoints.

For the analyses of continuous HCV RNA efficacy data, any subject with a missing value in a visit window that is bracketed by prior and subsequent values of "< LLOQ TND" will be set to "< LLOQ TND" (ie, 24 IU/mL). Subjects with a missing data point preceded and followed by values that are "< LLOQ detected", preceded by "< LLOQ detected" and followed by "< LLOQ TND", or preceded by "< LLOQ TND" and followed by "< LLOQ detected" will be set to "< LLOQ detected" (ie, 24 IU/mL). No other imputation will be performed for continuous data.

Missing cirrhosis will be imputed as no cirrhosis.

Except for the imputation rules described above, values for other missing data (including all safety data) will not be imputed.

3.6.2. Outliers

Outliers will be identified during data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes. All data will be included in the data analysis.

3.7. Visit Windows

3.7.1. Definition of Study Day 1, Last Dosing Date, and Baseline

The **first dose date of individual study drug** will be calculated separately for each study drug (ie, SOF or RBV). **Study Day 1** is defined as the **first dose date of any study drug**, which is the minimum of the first dose dates of individual study drugs.

The **date of last dose of individual study drug** will be calculated separately for each study drug. The date of last dose for an individual study drug will be the end date on study drug administration CRF for the record where the "subject permanently discontinued" flag is 'Yes'. The **last dose date of any study drug** will be defined as the maximum of the last dosing dates of individual study drugs.

If there are subjects for whom the date of last study drug is unknown due to the reason that the subject was lost to follow-up, the date of last dose will be estimated using the maximum of nonmissing study drug start or stop dates and on-treatment visit dates and laboratory collection dates (Post-treatment visits and unscheduled visits are not included).

In general, the **baseline value** will be the last nonmissing value on or prior to the first dose date of study drug. If multiple measurements occur on the same day, the last non-missing value prior to the time of first dose of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or time is not available, the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be considered as baseline value.

3.7.2. Analysis Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purposes of analysis, visit windows will be utilized when a single value at a visit is required for analysis.

Visit windows are defined for HCV RNA data, safety laboratory data (which includes HIV RNA and CD4 counts). No analysis windows will be defined for health related quality of life data and pregnancy test.

All available HCV RNA data will be included in efficacy analysis, unless a subject starts alternative HCV medication. HCV RNA data collected after starting alternative HCV medication will be excluded. Imputation for missing HCV RNA values are described in Section 3.6.1. For safety data, subjects who are permanently discontinued from study drug will be included in safety analyses to the ***last dose date of any study drug*** + 30 days, unless otherwise specified. For interim DMC analyses, subjects still on study drug will have all available data included in the interim snapshot database included in analysis.

HCV RNA, vital signs, and safety laboratory test data collected up to the ***last dose date of any study drug*** + 2 days are considered to be on-treatment data and HCV RNA, vital signs and safety laboratory data collected after the ***last dose date of any study drug*** + 2 days are considered posttreatment data. On-treatment and posttreatment data will follow 2 different sets of visit windows.

Visit windows will be calculated from **Study Day 1** (ie, Study Day = collection date minus date **Study Day 1**; +1 if result is ≥ 0) for HCV RNA, vital signs and other safety laboratory data as shown in Table 2.

Table 2. On-Treatment Visit Windows[a]

Visit ID	On-Treatment Visit Windows for Group 1 (GT2/3 TN Subjects, SOF+RBV 12 weeks)	On-Treatment Visit Windows for Group 2 and 3 (GT2/3 TE and GT1 TN Subjects, SOF+RBV 24 weeks)
Baseline	Study Day ≤ 1	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11	2 ≤ Study Day ≤ 11
Week 2	12 ≤ Study Day ≤ 21	12 ≤ Study Day ≤ 21
Week 4	22 ≤ Study Day ≤ 35	22 ≤ Study Day ≤ 35
Week 6	36 ≤ Study Day ≤ 49	36 ≤ Study Day ≤ 49
Week 8	50 ≤ Study Day ≤ 63	50 ≤ Study Day ≤ 63
Week 10	64 ≤ Study Day ≤ 77	64 ≤ Study Day ≤ 77
Week 12	78 ≤ Study Day ≤ 98	78 ≤ Study Day ≤ 98
Week 16	NA	99 ≤ Study Day ≤ 126
Week 20	NA	127 ≤ Study Day ≤ 154
Week 24	NA	155 ≤ Study Day ≤ 182

a. This table will apply to all HCV RNA, vital signs and safety labs including HIV RNA and CD4 counts.

HCV RNA, vital sign, and safety laboratory data collected after the ***last dose date of any study drug*** + 2 days will be assigned to the posttreatment FU visit windows. Windows will be calculated from the ***last dose date of any study drug*** (ie, FU Day = collection date minus the ***last dose date of any study drug***) as shown in Table 3.

Table 3. **Post-treatment Visit Windows for Selected Tests**

Off-Treatment FU Visit ID	Post-treatment Visit Windows for HCV RNA [a] (Days from Last Dose Date)	Post-treatment Visit Windows for HIV RNA and CD4 Count [b] (Days from Last Dose Date)	Other Safety Labs[b] (Days from Last Dose Date)
FU-4	21 ≤ FU Day ≤ 69	3 ≤ FU Day ≤ 56	3 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	57 ≤ FU Day ≤ 126	N/A
FU-24	147 ≤ FU Day ≤ 190	127 ≤ FU Day ≤ 190	N/A

a SVR follow-up visit window (lower bound) must occur within 7, 14, and 21 days of target for SVR4, SVR12, and SVR24, respectively.

b Vital signs and safety labs (except HIV RNA and CD4 counts) will only be summarized for the 4-week follow up visit (up to 30 days post last dose)

c HIV RNA and CD4 counts will be summarized through 24-week follow up visit.

3.7.3. Selection of Data in the Event of Multiple Records in a Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window. When a single value is needed, the following rules will be used:

- Select the record closest to the nominal day (ie, visit weeks x 7 days) for that visit except for HCV RNA posttreatment follow-up visits, for which the latest record in the analysis window should be selected.

- If there are 2 visits equidistant from the nominal day within the analysis window, take the latest.

- If there is more than 1 record on the selected day, take the average (for continuous data) or the worst (for categorical data). If there are 2 values on the same day, the second may be a retest because there was a problem with the first test (eg, specimen hemolyzed). In cases where the first test is cancelled, the retest value should be used.

4. SUBJECT DISPOSITION

4.1. Disposition of Subjects

A summary of subject disposition will be provided by treatment group and overall. This summary will present the number of subjects who were screened, enrolled, enrolled and treated (ie, safety analysis set), and FAS and the number and percentage of subjects meeting the following criteria:

- Completed study treatment
- Did not complete study treatment (with summary of reasons for not completing the study treatment period)
- On study treatment (if applicable)
- Completed the study
- Did not complete the study (with summary of reasons for not completing the study)
- On study

The denominator for the percentages of subjects in each category will be the number of subjects in the safety analysis set.

No inferential statistics will be generated.

A data listing of date of informed consent, first dose date, last dose date of any study drug (study day), completed study treatment (yes/no), completed study (yes/no) and reasons for premature study treatment/study discontinuation will be provided. The last available observed nonmissing HCV RNA value prior to discontinuation and for up to 2 days after last dose will be included in this listing.

4.2. Extent of Exposure

4.2.1. Duration of Exposure to Study Regimen

Duration of exposure to study regimen will be defined as (last dose date of any study drug – first dose date of any study drug + 1), regardless of temporary interruptions in study drug administration and will be expressed in weeks (recorded to 1 decimal place, eg, 12.1 weeks). For subjects ongoing at the time of an analysis, the last dosing date will be estimated based on the last available eCRF or laboratory date available in the snapshot database.

Duration of exposure to study regimen will be summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3],

minimum and maximum) and as the number of subjects exposed ***through*** (ie, cumulative counts): Baseline (Day 1); Week 1 (Day 7); Week 2 (Day 14); Week 4 (Day 28); Week 6 (Day 42); Week 8 (Day 56); Week 10 (Day 70); Week 12 (Day 84); Week 16 (Day 112); Week 120(Day 140); Week 24 (Day 168).

Summaries will be provided by treatment group for the safety analysis set.

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

The following subject demographic and baseline characteristics will be summarized by treatment group and overall using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percent of subjects for categorical data. Variables to be summarized include the following:

- age (on date of first dose of study regimen) as a continuous variable
- sex (male, female)
- race
- ethnicity (hispanic or latino, non-hispanic or latino)
- body mass index as a continuous variable and for categories (< 30 kg/m^2, ≥ 30 kg/m^2)
- HCV genotype (1, 2, 3)
- cirrhosis (yes/no)
- IL28B (CC, CT, TT)
- baseline HCV RNA as a continuous variable and for categories (<6 $\log_{10}$ IU/mL, ≥ 6 $\log_{10}$ IU/mL)
- baseline ALT as a continuous variable and for categories ($\leq$1.5 x ULN, $>$ 1.5 x ULN)
- estimated glomerular filtration rate (eGFR) using Cockcroft-Gault formula
- CD4 counts at baseline as a continuous variable and for categories ($<$ 200 cells/mm^3, 200 cells/mm^3 $\leq$ CD4 count $<$ 350 cells/mm^3, 350 cells/mm^3 $\leq$ CD4 count $\leq$ 500 cells/mm^3, or $>$ 500 cells/mm^3)
- on ARV treatment at enrollment (yes, no)
- ARV regimen at enrollment
- interferon classification (IFN-eligible, IFN-ineligible, IFN-intolerant, non-response, relapse/breakthrough)

Age is calculated as the integer of age in years at first dose of study regimen for subjects dosed and calculated as the integer of age in years at enrollment for subjects enrolled but not dosed. eGFR will be calculated by the Cockcroft-Gault method: $eGFR_{CG}$ (mL/min) = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] / (serum creatinine (mg/dL) × 72), where weight is total body mass in kilograms..

The summary of demographic data and baseline characteristics will be provided for the safety analysis set.

In addition, number and percentage of subjects for each interferon ineligibility reason and number and percentage of subjects for each interferon intolerant reason will be provided. The denominator for the percentages will be the number of subjects in safety analysis set who are interferon ineligible and number of subjects in safety analysis set who are interferon intolerant, respectively.

5.2. Medical History

General medical history (ie, conditions not specific to the disease being studied) data will be listed only. General medical history data will not be coded.

6. EFFICACY ANALYSES

6.1. Definition of the Efficacy Endpoints

The efficacy endpoints for this safety update include the following:

- SVR12 defined as HCV RNA < LLOQ (ie, < 25 IU/mL) at 12 weeks after study drug cessation for the full analysis set. The Roche COBAS® Taqman® HCV Test v2.0 for use with the High Pure System will be used to measure HCV RNA.

- Sustained virologic response 4 weeks after stopping all study drugs (SVR4) defined as HCV RNA < LLOQ (ie, < 25 IU/mL) at 4 weeks after study drug cessation for the full analysis set

- The proportion of subjects with HCV RNA below LLOQ (ie, < 25 IU/mL) while on treatment by study visit

- The proportion of subjects with on-treatment and posttreatment virologic failure, defined as the following:

  — On-treatment virologic failures

    o HCV RNA ≥ 25 IU/mL after having previously had HCV RNA < 25 IU/mL while on treatment, confirmed with 2 consecutive values (Note: second confirmation value can be posttreatment) or last available on-treatment measurement with no subsequent follow-up values (ie, breakthrough)

    o >1 log10IU/mLincrease in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values (Note: second confirmation value can be posttreatment)or last available on-treatment measurement with no subsequent follow up values (ie, rebound)

    o HCV RNA persistently ≥ 25 IU/mL through 8 weeks of treatment (ie, nonresponse)

  — Relapse

    o HCV RNA ≥ 25 IU/mL during the posttreatment period having achieved HCV RNA < 25 IU/mL at end of treatment, confirmed with 2 consecutive values or last available posttreatment measurement

6.2. Analysis of the Efficacy Endpoint

The efficacy endpoints will be derived for all subjects in safety analysis set using observed HCV RNA data and imputation rule specified in section 3.6.

For analyses of HCV RNA < LLOQ (ie, < 25 IU/mL) by visit while on treatment, subjects will be assigned a value at each visit based on the categorical imputation rules described in Section **Error! Reference source not found.**. The 2-sided 95% exact confidence interval (CI) based on Clopper-Pearson method will be provided for the proportion {20839}. The overall category for "HCV RNA < LLOQ" will be split into the following 2 subcategories: "< LLOQ TND" for subjects with target not detected and "< LLOQ detected" for subjects with < LLOQ in tabular displays.

The point estimate of SVR4 and SVR12 rate and 2-sided 95% exact confidence interval (CI) will be provided for each treatment group and for each treatment group within each subgroup specified in section 3.4. A Forest plot will graphically present estimates and 95% confidence intervals of SVR4 and SVR12 rates for each treatment group within each subgroup.

For the SVR12 endpoint analysis, a summary table of the number and percentage of subjects with SVR12, virologic failure, and other will be created. All subjects who achieve SVR12 will be categorized as SVR12. Virologic failure will be descriptively summarized as "on-treatment virologic failure" and relapse (which will be summarized by study drug completed yes or no). Subjects who do not achieve SVR12 and do not meet criteria for virologic failure will be categorized as other. The denominator for relapse will be the number of subjects who had HCV RNA < LLOQ on their last observed on-treatment HCV RNA measurement; otherwise, the denominator will be the number of subjects in the FAS.

Details regarding SAS programming are provided in the programming specifications in **Error! Reference source not found.** of this SAP.

A data listing of HCV genotype, cirrhosis, IL28B, scheduled visit, analysis visit window, date of HCV RNA sample collection, HCV RNA load (categorical and numeric), and change from baseline for on-treatment visits will be provided for the following:

- 1), subjects with HCV virologic failure in the FAS;
- 2), all subjects in the FAS
- 3), all subjects in the safety analysis set but not in FAS

7. SAFETY ANALYSES

Safety data will be summarized for subjects included in the safety analysis set. Summaries of safety data (treatment-emergent [TE] adverse events [AEs], TE maximum toxicity grades and marked abnormalities, changes from baseline in laboratory and vital signs parameters) will include all data collected on or after the first dose date of study regimen through the last dose date of any study drug plus 30 days (except HIV RNA and CD4 data, which is through the end of study) for subjects who have stopped all study drugs, and all available data at the time of the database snapshot for subjects still on treatment at the time of this analysis.

All safety data (except for laboratory tests with results that were cancelled by the lab) will be included in data listings based on the safety analysis set.

7.1. Adverse Events

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be attached to the clinical database.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator according to the Gilead Sciences, Inc. (Gilead) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities as specified in the clinical study protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

The relationship of AE to study drug will be assessed by investigators as “Yes” or “No”. Events for which the investigator did not record the relationship to study drug will be considered to be related to study drug for summary purposes. However, data listings will present the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those identified as serious in the clinical database. The clinical database will be reconciled with the SAE database from the Drug Safety and Public Health Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Treatment-emergent AEs are events that meet one of the following criteria:

- Events with onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of all the study medications,
- The continuing adverse events diagnosed prior to the start of treatment and worsening in severity grade, or non-serious adverse events at baseline which become serious, or adverse events resulting in treatment discontinuation after the start of treatment

7.1.5.2. Incomplete Dates

If the date of onset is incomplete, then the month and year (or year alone if month is not recorded) of onset determine whether the AE is treatment emergent. The event is treatment emergent if the month and year of onset (or year of onset) of the event meets both of the following criteria:

- The same as or after the month and year (or year) of the first dose of any study drug
- The same as or before the month and year (or year) of the 30th day after the date of the last dose of any study drug

7.1.6. Summaries of Adverse Events and Deaths

A brief summary of AEs will show, by treatment group, the number and percentage of subjects who (1) had any TE AE, (2) had any Grade 3 or higher TE AE, , (3) had any Grade2 or higher TE AE, (4) had any TE treatment-related AE, (5) had any Grade 3 or higher TE treatment-related AE, (6) had any Grade 2 or higher TE treatment-related AE, (7) had any TE SAE, (8) had any TE treatment-related SAE, (9) had any AE leading to permanent discontinuation from any study drug, (10) had any AE leading to permanent discontinuation from SOF, (11) had any AE leading to modification or interruption of any of the drugs, and (12) TE death during the study.

Summaries (number and percentage of subjects) of adverse events (by SOC and PT) will be provided using the safety analysis set as follows:

- All TE AEs
- Combined Grade 3 or 4 TE AEs
- TE non-serious AEs occurring in at least 5% of subjects in any treatment group (this will be produced for ClinicalTrials.gov website)

- TE AEs treatment-related drug
- Combined Grade 3 or 4 TE treatment-related AEs
- TE SAEs
- TE treatment-related SAEs
- AEs leading to permanent discontinuation from any of the study drugs
- AEs leading to permanent discontinuation from SOF

Multiple events will be counted once only per subject in each summary. For data presentation, SOC will be ordered alphabetically, with PT sorted by decreasing total frequency within an SOC. For summaries by severity grade, the most severe event will be selected.

Data listings, with a variable indicating whether the event is treatment-emergent, will be provided for the following:

- All AEs
- SAEs
- Deaths
- AEs leading to permanent discontinuation of any of the study drugs
- AEs leading to permanent discontinuation from SOF
- Grade 3 or 4 Adverse Events

7.1.7. Analysis Related to HIV RNA

Proportion of subjects with HIV virologic rebound during the study will be summarized by treatment group for subjects who are on ARV treatment at enrollment.

Subjects with HIV virologic rebound is defined as meeting all three following criteria:

- at least two HIV RNA >= 50 copies/mL at 2 consecutive post-baseline visits which are at least 2 weeks apart based on actual dates;
- on ARV at baseline;
- HIV RNA < 50 copies/mL at baseline.

Listing of subjects with HIV virologic rebound will be presented together with their information on HIV RNA, CD4 counts (absolute and %), HCV RNA, current ARV regimen, HIV and HCV history and HCV treatment during the study.

HIV RNA, change and percentage change from baseline in HIV RNA for subjects not on ARV at baseline will be listed by visit for each treatment group.

7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the safety analysis set and will include data collected up to last dose of any study drug plus 30 days (except HIV RNA and CD4 data, which is through the end of the study) for subjects who have stopped all study drugs and all available data at the time of the database snapshot for subjects who are ongoing at the time of this analysis. Analysis will be based on values reported in conventional units. Laboratory results cancelled by the central laboratory will not be included in analysis.

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be provided by treatment group for ALT, AST, total bilirubin, alkaline phosphatase, white blood cell (WBC) counts, neutrophils, lymphocytes, hemoglobin, platelets, reticulocytes, PT, and INR, and CD4 counts (absolute and %) as follows:

- Baseline values
- Values at each post-baseline analysis window
- Change from baseline at each post-baseline analysis window

The mean, median, Q1, Q3, minimum and maximum will be displayed to reported number of digits, standard deviation to reported number of digits +1 for visits up to end of treatment.

Median (Q1, Q3) of the absolute values for these laboratory parameters will be plotted by treatment group and visit. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.3.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assignment of toxicity grades to laboratory results for purposes of analysis as Grade 0, Grade 1 (mild) , Grade 2 (moderate), Grade 3 (severe) or Grade 4 (potentially life threatening). Grade 0 includes all values that do not meet criteria for an abnormality of at least Grade 1.

Some laboratory tests have laboratory toxicity criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any time post-baseline up to the last dose of any study drug plus 30 days (except CD4 which is through the end of the study) for subjects who have stopped all study drugs or all available data in the database snapshot for subjects still on treatment at the time of this analysis.

If the relevant baseline laboratory data are missing, then any abnormality of at least Grade 1 will be considered treatment emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase at least 3 grades from baseline at any time postbaseline up to last dose of any study drug plus 30 days (except CD4 which is through the end of the study) for subjects who have stopped all study drugs or all available data in the database snapshot for subjects still on treatment at the time of this analysis.

If the relevant baseline laboratory data are missing, then any Grade 3 or 4 on-treatment values will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) of laboratory abnormalities using the Gilead Grading Scale will be provided (subjects categorized according to most severe post-baseline abnormality grade):

- TE graded laboratory abnormalities
- TE Grade 3 and 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with non-missing post-baseline values (up to 30 days after last dose of any study drug (except CD4 and HIV RNA data which will use data collected through the end of the study) for the laboratory parameter of interest.

A listing of TE Grade 3 or Grade 4 laboratory abnormalities will be provided. This listing will include the complete laboratory test profile for each laboratory test with the graded result throughout the study.

All laboratory values will be listed. Values falling outside of the relevant reference range and/or meeting Gilead Grading Scale will be flagged, as appropriate, in the data listings.

7.3. Body Weight, Height, BMI and Vital Signs

A listing of height (at screening), body weight, BMI, SBP, DBP, pulse, and temperature will be provided.

7.4. Prior and Current HIV Medications

A list of subjects' prior and current HIV medication data will be provided.

7.5. Other Safety Measures

A data listing for cirrhosis determination will be provided for all subjects at screening.

A data listing will be provided for subjects who become pregnant during the study.

The shift in toxicity grade for total bilirubin from baseline to maximal grade at post-baseline will be summarized by Atazanavir (ATV) status at enrollment for each treatment group.

In addition, the following analysis will be conducted for subjects on ARV at baseline and for subjects not on ARV at baseline respectively:

- SVR12 endpoint analysis with the virologic outcome
- Summary of absolute value and change from baseline by visit for the following laboratory analytes: CD4 counts (absolute and %).

8. REFERENCES

20502 Nehls G, Akland G. Procedures for Handling Aerometric Data. Journal of the Air Pollution Control Association 1973;23 (3):180-4.

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

9. SOFTWARE

SAS® Software Version 9.1. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 7.0. Statistical Solutions, Cork, Ireland.

10. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

11. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings
Appendix 2. Programming Specifications

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

Table Number	Title	Analysis Set
1	Subject Disposition	Screened Subjects
2	Demographics and Baseline Characteristics	Safety Analysis Set
3.1	Summary of Interferon Ineligible Reason	Safety Analysis Set
3.2	Summary of Interferon Intolerant Reason	Safety Analysis Set
4	Duration of Exposure to Study Regimen	Safety Analysis Set
5	HCV Virologic Outcome	Full Analysis Set
6	SVR by Visit during Posttreatment Follow Up (SVR4 and SVR12)	Full Analysis Set
6.1	SVR by Visit during Posttreatment Follow Up (SVR4 and SVR12) by Subgroup	Full Analysis Set
7	Proportion of subjects with HCV RNA Less than LLOQ (25 IU/mL) While on Treatment by Visit	Full Analysis Set
8	Adverse Events: Brief Summary	Safety Analysis Set
9	All Treatment-Emergent Adverse Events	Safety Analysis Set
10	Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set
11	Grade 3 or 4 Treatment-Emergent Adverse Events	Safety Analysis Set
12	Grade 3 or 4 Treatment-Emergent Treatment-Related Adverse Events	Safety Analysis Set
13	Adverse Events Leading to Permanent Discontinuation from Any of the Study Drugs	Safety Analysis Set
14	Adverse Events Leading to Permanent Discontinuation from SOF	Safety Analysis Set
15	Treatment-Emergent Serious Adverse Events	Safety Analysis Set
16	Treatment-Emergent Treatment-Related Serious Adverse Events	Safety Analysis Set
17	Treatment-Emergent Non-Serious Adverse Events Occurring in At Least 5% of Subjects in Any Treatment Group	Safety Analysis Set
18.1	ALT (U/L) and Change from Baseline by Visit	Safety Analysis Set
18.2	AST (U/L) and Change from Baseline by Visit	Safety Analysis Set
18.3	Total Bilirubin (mg/dL) and Change from Baseline by Visit	Safety Analysis Set
18.4	Alkaline Phosphatase (U/L) and Change from Baseline by Visit	Safety Analysis Set
18.5	WBC (x 10^3 /μL) and Change from Baseline by Visit	Safety Analysis Set
18.6	Neutrophils (x 10^3 /μL) and Change from Baseline by Visit	Safety Analysis Set
18.7	Lymphocytes (x 10^3 /μL) and Change from Baseline by Visit	Safety Analysis Set

Table Number	Title	Analysis Set
18.8	Hemoglobin (g/dL) and Change from Baseline by Visit	Safety Analysis Set
18.9	Platelets (x 10^3 /μL) and Change from Baseline by Visit	Safety Analysis Set
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18.11	CD4 Counts (cells/mm^3) and Change from Baseline by Visit	Safety Analysis Set
18.12	CD4 Counts (%) and Change from Baseline by Visit	Safety Analysis Set
19.1	Treatment-Emergent Graded Laboratory Abnormalities	Safety Analysis Set
19.2	Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set
20	Shift in Toxicity Grade for Total Bilirubin from Baseline to Maximal Post-baseline Grade by Atazanavir Status at Enrollment	Safety Analysis Set
21	Proportion of Subjects with HIV Virologic Rebound for Subjects Who Were on ARV Treatment at Enrollment	Safety Analysis Set
22.1	HCV Virologic Outcome for Subjects on ARV at Baseline	Full Analysis Set
22.2	HCV Virologic Outcome for Subjects Not on ARV at Baseline	Full Analysis Set
23.1	CD4 Counts (cells/mm^3) and Change from Baseline by Visit for Subjects on ARV at Baseline	Safety Analysis Set
23.2	CD4 Counts (cells/mm^3) and Change from Baseline by Visit for Subjects Not on ARV at Baseline	Safety Analysis Set
23.3	CD4 Counts (%) and Change from Baseline by Visit for Subjects on ARV at Baseline	Safety Analysis Set
23.4	CD4 Counts (%) and Change from Baseline by Visit for Subjects Not on ARV at Baseline	Safety Analysis Set

Figure Number	Title	Analysis Set
1.1	Median (Q1, Q3) ALT (U/L) by Visit	Safety Analysis Set
1.2	Median (Q1, Q3) AST (U/L) by Visit	Safety Analysis Set
1.3	Median (Q1, Q3) Total Bilirubin (mg/dL) by Visit	Safety Analysis Set
1.4	Median (Q1, Q3) Alkaline Phosphatase (U/L) by Visit	Safety Analysis Set
1.5	Median (Q1, Q3) WBC (x 10^3 /µL) by Visit	Safety Analysis Set
1.6	Median (Q1, Q3) Neutrophils (x 10^3 /µL) by Visit	Safety Analysis Set
1.7	Median (Q1, Q3) Lymphocytes (x 10^3 /µL) by Visit	Safety Analysis Set
1.8	Median (Q1, Q3) Hemoglobin (g/dL) by Visit	Safety Analysis Set
1.9	Median (Q1, Q3) Platelets (x 10^3 /µL) by Visit	Safety Analysis Set
1.10	Median (Q1, Q3) Reticulocytes (x 10^3 /µL) by Visit	Safety Analysis Set
1.11	Median (Q1, Q3) CD4 Counts (cells/mm^3) by Visit	Safety Analysis Set
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2.1	Median (Q1, Q3) CD4 Counts (cells/mm^3) by Visit by ARV at Baseline	Safety Analysis Set
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3.1	Forest Plot of SVR4 by Subgroup	Full Analysis Swet
3.2	Forest Plot of SVR12 by Subgroup	Full Analysis Swet

Listing Number	Title	Analysis Set
1	Subject Disposition	Safety Analysis Set
2	Subject Demographics and Baseline Characteristics	Safety Analysis Set
3	Medical History	Safety Analysis Set
4	Study Drug Administration	Safety Analysis Set
5	Prior and Current HIV Medications	Safety Analysis Set
6	Subjects with HCV Virologic Failure	Full Analysis Set
7.1	HCV RNA (log10 IU/mL) and Change from Baseline for All Subjects in the FAS	Full Analysis Set
7.2	HCV RNA (log10 IU/mL) and Change from Baseline for All Subjects in the Safety Analysis Set but Not in FAS	Safety Analysis Set
8	All Adverse Events	Safety Analysis Set
9	Grade 3 or 4 Adverse Events	Safety Analysis Set

10	Adverse Events Leading to Permanent Discontinuation from Any of the Study Drugs	Safety Analysis Set
11	Adverse Events Leading to Permanent Discontinuation from SOF	Safety Analysis Set
12	Serious Adverse Events	Safety Analysis Set
13	Pregnancy	Safety Analysis Set
14	Deaths	Safety Analysis Set
15	Central Laboratory (Covance) Reference Ranges	Safety Analysis Set
16	Subjects with Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set
17.1	Hematology: RBC, Reticulocyte Count, WBC, Lymphocytes, and Neutrophils	Safety Analysis Set
17.2	Hematology: Monocytes, Eosinophils, and Basophils	Safety Analysis Set
17.3	Hematology: Hemoglobin, Hematocrit, Platelets, and MCV	Safety Analysis Set
18	Coagulation and Thyroid Function: INR, PT, APTT	Safety Analysis Set
19.1	Chemistry: Albumin, Alkaline Phosphatase, ALT, AST, Total Bilirubin, and Direct Bilirubin	Safety Analysis Set
19.2	Chemistry: Serum Creatinine, Estimated GFR (Cockcroft-Gault	Safety Analysis Set
19.3	Chemistry: Lipase, Potassium, Sodium, and Glucose	Safety Analysis Set
20	CD4 T-Lymphocyte Absolute Count and % and HIV RNA (copies/mL)	Safety Analysis Set
21	Height, Weight, BMI and Vital Signs	Safety Analysis Set
22.1	Subjects with HIV Virologic Rebound	Safety Analysis Set
22.2	HIV RNA, Change and Percent Change from Baseline by Visit for Subjects Not on ARV at Baseline	Safety Analysis Set

Appendix 2. Programming Specifications

The following code will be used to calculate AGE on the DATE OF FIRST DOSE:

```
if n(brthdtn,_dtday1)=2 then do;
   age = int(intck('month', brthdtn, _dtday1)/12) ;
   if month(brthdtn)=month(_dtday1) & day(brthdtn)>day(_dtday1) then
   age=age-1 ;
   ageu = "YEARS";
end;
```

HCV Genotype will be determined from the results of LiPA 2.0 assay. If LiPa 2.0 returns a value of 'Indeterminate' or missing, then the Abbott Real time HCV Genotype 2 assay will be used. If both assays return a result of 'Indeterminate', then NS5B sequencing will determine genotype.

The following code will be used to create the 95% exact CI on the proportion:

```
data SVR12;
input resp count;
cards;
0 10
1 50
;
run;

proc freq data = SVR12 ;
weight count;
tables resp / binomial alpha=0.05;
run;
```