An Open Label Trial to Assess Safety, Tolerability, and Efficacy of the Fixed Dose Combination of GS-7977 and GS-5885 in HCV Genotype 1 Subjects Coinfected with HIV

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Protocol #:	13-I-0159
Sponsored by:	National Institute of Allergy and Infectious Diseases (NIAID)
Pharmaceutical Support:	Gilead Sciences, Inc.
IND Sponsor:	Regulatory Compliance and Human Subjects Protection Branch
IND #:	117444
GS-7977 and GS-5885	Provided by: Gilead Sciences, Inc.
Version:	7
Version Date:	April 11, 2014

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ABBREVIATIONS

AA	African American
AE	Adverse Events
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
ARV	Antiretroviral
ATR	Atripla®
AUC	Area under the curve
BOC	Boceprevir
BMI	Body mass index
BMS	Bristol-Myers Squibb
COMP	Complera®
DAA	Direct acting antiviral
DC-PFAP	DC Partnership for AIDS Progress
ESA	Erythropoiesis stimulating agent
DRM	Drug related material
eGFR	Estimated glomerular filtration rate
EFV	Efavirenz
ETR	End of treatment response: <LLOQ HCV RNA at the end of treatment
EVR	Early virologic response: <LLOQ HCV RNA or 2-log decline at Week 12 (partial EVR)
FDA	Food and Drug Administration
FDC	Fixed dose combination
FTC	Emtricitabine
G-CSF	Granulocyte colony stimulating factor
GMR	Geometric mean ratios
GT-1, -2, and -3	Genotype 1, 2, and 3
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
IB	Investigators brochure
IL28B	Interleukin 28B
IFN	Interferon
IRB	Institutional Review Board
ISG	Interferon-stimulated gene
ITT	Intent-to-treat
LAI	Lead Associate Investigator

LI	Lead Investigator
LIR	Laboratory of Immunoregulation
LOD	Level of detection (3 international units/mL with assay being used)
LLOQ	Lower Level of quantification
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PBMC	Peripheral blood mononuclear cell
PegIFN	Pegylated Interferon
PBMC	Peripheral blood mononuclear cell
PI	Principal Investigator
RAL	Raltegravir
RBV	Ribavirin
RPV	Rilpiverene
RVR	Rapid virologic response; <LLOQ HCV RNA at Week 4
SAE	Serious adverse events
SOC	Standard of care
SVR_{12}	HCV RNA < LLOQ 12 weeks after completion of treatment
SVR_{24}	Sustained virologic response <LLOQ HCV RNA 24 weeks (or 6 months) after the end of treatment
TDF	TDF Disoproxil Fumarate

ABBREVIATIONS FOR HCV STUDY AGENTS & FDA APPROVED AGENTS

GS-7977, SOF	Sofosbuvir, nucleotide NS5B inhibitor (formerly PSI-7977)
GS-5885, LEV	Ledipasvir, NS5a inhibitor
FDC	Fixed Dose Combination (FDC) including GS-7977 400 mg and GS-5885 90 mg
BMS-790052	NS5A inhibitor
GS-9190, TGV	Tegobuvir, non-nucleoside NS5B polymerase inhibitor
GS-9451	NS3 protease inhibitor
GS-9669	Non-nucleoside NS5B inhibitor
IFN, PegIFN	Interferon, the FDA approved standard of care treatment for HCV when used with ribavirin (additionally can be used with Boceprevir or Telaprevir which are HCV protease inhibitors), known as pegylated IFN or pegIFN
RBV	Ribavirin, the FDA approved standard of care treatment for HCV when used with Interferon (additionally can be used with Boceprevir or Telaprevir which are HCV protease inhibitors)
TVR	Telaprevir, an FDA approved standard of care treatment for HCV when used with Interferon and ribavirin (NS3 protease inhibitor)
BOC	Boceprevir, an FDA approved standard of care treatment for HCV when used with Interferon and Ribavirin (NS3 protease inhibitor)

PROTOCOL SUMMARY

Full Title:	An Open Label Trial to Assess Safety, Tolerability and Efficacy of the Fixed Dose Combination of GS-7977 and GS-5885 in HCV Genotype 1 Subjects Coinfected with HIV
Short Title:	Fixed Dose Combination **(**GS-7977 / GS-5885**)** in HIV/HCV Coinfected Subjects / ERADICATE
Clinical Phase:	Phase 2
Conducted by:	LIR/NIAID OP-8 Clinic
Principal Investigator:	Shyam Kottilil, MD, PhD
Sample Size:	N=50
Accrual Ceiling:	100
Study Population:	HIV/HCV Genotype 1 infected individuals who are Interferon (IFN)-treatment naïve.
Accrual Period:	9 months
Study Design:	Open-label study using fixed dose combination (GS-7977/GS-5885) tablets for 12 weeks duration in HIV/HCV Genotype 1(GT-1) coinfected, IFN-treatment naïve subjects.
Study Duration:	Start Date: 05/15/2013 End Date: 04/10/2015

Objectives:

Primary Objective: To assess the safety, tolerability and efficacy of a fixed dose combination (FDC) of GS-7977/GS-5885 tablets for 12 weeks in HIV/HCV GT-1 coinfected subjects who are IFN-treatment naïve.

Secondary Objectives:

1. To compare the immunologic, virologic and host genetic/proteomic predictors of response to treatment with a fixed dose combination of GS-7977/GS-5885 in subjects treated for 12 weeks.

2. To compare HCV quasispecies evolution from baseline and throughout 12 weeks of treatment (especially during relapse or viral breakthrough) and assess the influence on virologic response to treatment in HIV/HCV GT-1 coinfected patients.

3. To assess the fitness of NS5A/B viral mutants in vivo in the presence or absence of a fixed dose combination of GS-7977/ GS-5885 in vitro by performing NS5A/B site directed mutagenesis.

4. To evaluate the effect of HCV viral clearance on host immunity to HIV as well as HIV viral kinetics.

5. To determine the pharmacokinetics of a fixed dose combination of GS-7977/GS-5885 in HIV infected patients not on antiretrovirals (ARV).

6. To determine the decline in extra hepatic HCV reservoir in peripheral blood mononuclear cells (PBMC) and its role in predicting relapse or sustained virologic response 12 weeks after completion of treatment (SVR_{12}).

7. To evaluate the kinetics of plasma HCV RNA during treatment and after treatment discontinuation.

8. To evaluate the effect of a fixed dose combination of GS-7977/GS-5885 (FDC) treatment on HIV VL and CD4 T cell counts.

9. To determine whether suppression of HIV has an influence on SVR_{12} with a fixed dose combination of GS-7977 and GS-5885.

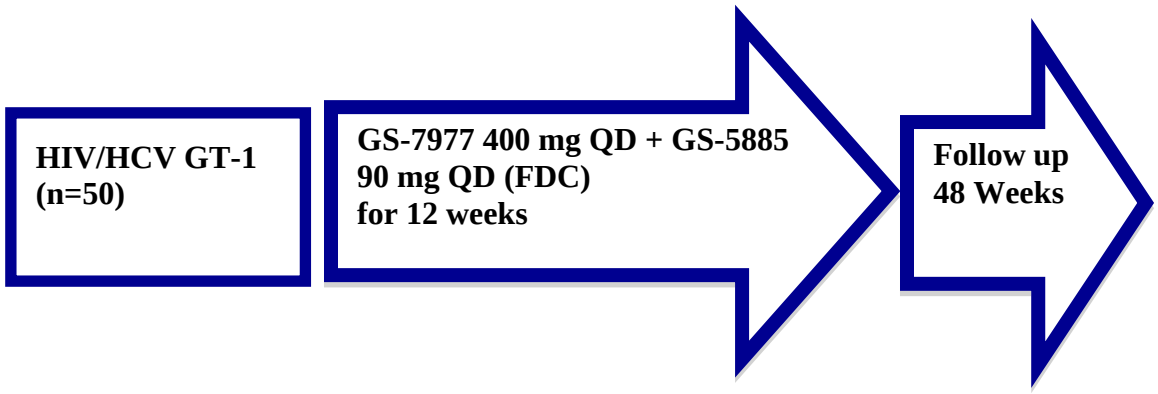
10. To assess the change from baseline of serum creatinine at the end of treatment and at post-treatment weeks 12 and 24.

PRÉCIS

Chronic hepatitis C virus (HCV) infection is a major public health problem with an estimated 180 million people infected worldwide. In the US an estimated 4.1 million people are infected with HCV which is the principal cause of death from liver disease and leading indication for liver transplantation. Significant advances have been made with the approval of directly acting antivirals (DAA) namely the protease inhibitors, telaprevir (TVR) and boceprevir (BOC) which have been shown to significantly improve rates of sustained virologic response (SVR). Response rates to these new combinations in HIV/HCV are also very promising, however treatment has been characterized with high rates of toxicities.

Recently several trials have confirmed the efficacy of potent DAA therapy without concomitant IFN in the treatment of HCV monoinfected individuals. Given the improved response rates achieved with a combination of DAAs with fast HCV suppression and improved side-effect profiles; and the need for better therapy for HIV/HCV co-infected subjects, we propose a study to determine the safety, tolerability and efficacy of 12 weeks of treatment with a fixed dose combination of GS-7977 and GS-5885 in HIV/HCV Genotype 1 (GT-1) subjects. We hypothesize that anti-HCV therapy that does not rely on the host immune system will provide an enhanced rate of SVR among HIV/HCV GT-1 coinfected subjects. The findings from this study will aid in our understanding of determinants of response to an IFN-free regimen in HIV/HCV coinfected individuals.

Figure 1: Study Schema



INTRODUCTION

Chronic hepatitis C virus infection is a major public health problem with an estimated 180 million people infected worldwide [1, 2]. In the United States, an estimated 4.1 million people are infected with hepatitis C, which is the principal cause of death from liver disease and leading indication for liver transplantation in the U.S [2-4]. In 2007 alone, it is estimated that over 15,000 people in the United States died from HCV-related complications. HCV now surpasses human immunodeficiency virus (HIV) as a cause of death in the United States [5]. It is estimated that 20 -30% of HIV-infected individuals are also infected with HCV [6]. While the use of antiretroviral therapy (ART) has dramatically reduced the mortality from AIDS and opportunistic infections, liver disease has now become a leading cause of death. The natural history of HCV among HIV infected individuals demonstrates faster rates of progression and a higher likelihood of development of end stage liver disease and decompensated liver failure [7, 8]. Treatment with the current standard of care which is pegylated interferon (pegIFN) and ribavirin (RBV) in HIV/HCV coinfected individuals is associated with decreased rates of response and further complicated by drug interactions and higher rates of toxicities including psychiatric illness, constitutional side effects, and cytopenias [9, 10].

Significant advances have been made with the approved protease inhibitors, telaprevir (TVR) and boceprevir (BOC), which have been shown to significantly improve rates of sustained virologic response (SVR) in IFN treatment naïve and treatment experienced patients [11, 12] [13]. Response rates of TVR/PegIFN/RBV in HIV/HCV co-infected patients are promising with SVR rates of 74% observed after 48 weeks of treatment, however there was a high frequency of adverse events such as fatigue, headache, pruritus, nausea and depression [13]. Similarly BOC/PegIFN/RBV therapy in HIV/HCV coinfection resulted in SVR rates of 61% but was also characterized by a high frequency of adverse events such as fever, anorexia, headache, dysgeusia and vomiting [14]. Safety appears comparable between the HIV/HCV coinfected and HCV monoinfected subjects, however these regimens are not yet approved for the treatment of subjects infected with HIV, both TVR and BOC are substrates and inhibitors of CYP3A4 with significant drug interactions with ARV therapies [15]. Therefore, the development of IFN-free, all-oral therapies with low-potential for drug interactions is highly desirable in this population.

More recently, several trials have confirmed the efficacy of potent DAA therapy without concomitant IFN in the treatment of HCV [16] [17]. In a study of dual therapy with GS-7977 and BMS-790052, an NS5A inhibitor with or without RBV in HCV monoinfected GT-1 treatment naïve individuals, 100% achieved an SVR_4 after 24 weeks of treatment [18]. A combination of GS-7977 and GS-5885 and RBV in HCV genotype 1 subjects for 12 weeks also showed SVR_{12} rate of 100% [19]. Finally a combination of GS-7977 and GS-5885 in a fixed dose combination (FDC) with and without RBV for 8 weeks in treatment-naïve subjects without cirrhosis showed SVR_8 rate of 95% in either arm.

Given the improved response rates achieved with a combination of DAAs with fast HCV suppression, improved side-effect profile, and the need for better therapy for HIV/HCV co-infected subjects, we propose a study to determine the safety, tolerability and efficacy of 12 weeks of treatment with a fixed dose combination of GS-7977 and GS-5885 in HIV/HCV GT-

1 subjects. These new treatment options are especially crucial in patient populations for whom treatment with pegIFN is not possible, undesired, complicated or without sufficient efficacy.

1.1 GS-7977

GS-7977 (formerly PSI-7977) is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed hepatitis C virus (HCV) replicon RNA replication in vitro and is intended for the treatment of chronic HCV infection.

GS-7977, a prodrug of 2′-deoxy-2′-fluoro-2′-C-methyluridine monophosphate, is ultimately converted to the active uridine triphosphate form, GS-461203, within the hepatocyte. GS-7977 is one of 2 diastereoisomers (stereoisomers) in a mixture designated GS-9851 (formerly PSI-7851). Chemical interconversion of the 2 stereoisomers is unlikely, and there is no evidence to date to suggest that the isomers interconvert in vivo. In animals, both stereoisomers are converted to the same metabolites, so that equimolar doses of either the mixture GS-9851 or the single isomer GS-7977 yield the same metabolite exposures. With either compound, systemic exposure to 2 metabolites (GS-566500 and GS-331007) accounts for the majority of the total systemic exposure in all species studied to date, including humans. Both GS-566500 and GS-331007 have no antiviral activity.

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

1.1.1 Clinical Experience with GS-7977

1.1.1.1 P7977-0523 Electron Study

An initial cohort of 40 treatment-naïve patients with HCV genotype 2 or HCV genotype 3 were randomized to receive GS-7977 400 mg QD+RBV 1,000/1,200 mg for 12 weeks in combination with various durations of PEG: no PEG (GS-7977+RBV alone, Arm 1), PEG x 4 weeks (Arm 2), PEG x 8 weeks (Arm 3), or PEG x 12 weeks (Arm 4). ClinicalTrials.gov Identifier: NCT01260350).

The study was amended to add a 12-week GS-7977 monotherapy arm (Arm 5) in HCV genotypes 2 and 3, an 8-week GS-7977+PEG +RBV arm in HCV genotypes 2 and 3 (Arm 6), and an arm evaluating GS-7977+RBV treatment in HCV genotype 1 null responders (Arm 7). A subsequent amendment incorporated 2 additional arms: GS-7977 400 mg QD+RBV for 12 weeks in genotype 1 treatment naïve patients (Arm 8) and a 12 week 400 mg QD GS-7977+RBV arm in HCV genotype 2 and 3 treatment experienced patients (Arm 9). Treatment Arms 1-6 and 8 have completed dosing; Arms 7 and 9 are ongoing.
Arms 12 and 13 are evaluating GS-7977 with GS-5885, as individual tablets, plus RBV, in 9

null responder and 25 treatment-naïve GT-1 HCV infected subjects. Enrollment is complete. Arms 14 and 15 will evaluate GS-7977 with GS-9669, as individual tablets, plus RBV, in 10 null responder and 25 treatment-naïve GT-1 HCV infected subjects. Arms 16-22 evaluate the fixed-dose combination of GS-7977 and GS-5885 in various subject populations with and without RBV. Enrollment is ongoing.

Results:

Results demonstrated antiviral potency and sustained viral response (100% SVR_{12}) in subjects with chronic HCV genotype-2/3, regardless of the presence of PEG. GS-7977 monotherapy was less efficacious with only 60% of subjects achieving SVR_{12}.

In genotype-1 treatment naïve subjects (Arm 8), treatment with GS-7977 400 mg QD +RBV elicited SVR_{12} in 22 of 25 subjects (88%). In genotype-2/3 treatment experienced subjects (Arm 9), treatment with GS-7977 and RBV elicited a rapid decline in HCV RNA with all subjects achieving HCV RVR and HCV RNA was maintained < LLOD through the end of treatment. To date, 16 of 21 subjects (73%) have achieved SVR_4.

In genotype 1 treatment naïve non-cirrhotic patients, 100% of subjects (25 of 25) treated with GS-7977 + GS-5885 +RBV attained $SVR_{12.}$ Similarly, in genotype 1 non-cirrhotic, null responder patients, 100% of subjects (9 of 9) treated with this same regimen achieved $SVR_{12.}$

Table 1: Additional data ELECTRON Arm 21 (FDC+RBV): Available SVR Data

Arm No.	Duration	N (GT1)	RVR % (n)	SVR4 % (n)	SVR8 % (n)	SVR12 % (n)	Relapse % (n)	BT % (n)	LTFU % (n)
Arm 21 GT1 TN	6 wks	25 (25/25)	100 (25/25)	88 (22/25)	80 (20/25)	TBD	20 (5/25)	0 (0)	0 (0)

1.1.1.2 NIH SPARE Study

Sixty (N=60) treatment naïve patients with chronic HCV with or without cirrhosis were treated in 2 phases with GS-7977 and RBV. (ClinicalTrials.gov Identifier: NCT01188772)

The first phase enrolled 10 patients who received GS-7977 and weight-based (1,000-1,200 mg daily) RBV. The second phase randomized 50 patients to receive GS-7977 with either weight based on low dose (600 mg daily) RBV.

Results:

Preliminary results show that 90% (ITT) of subjects in the first phase achieved SVR_{48} with one drop out at week 3. In the 2nd phase, 68% (ITT) of patients receiving weight based RBV achieved SVR_{24} compared to 48% (ITT) of patients receiving low dose RBV.

1.1.1.2.1 GS-US-337-0118 (LONESTAR)

GS-US-337-0118 is a Phase 2, single center, randomized, open-label study. The study is investigating the efficacy and safety of (a) Groups 1 and 2: the FDC (GS-7977/GS-5885) with and without RBV for 8 weeks in treatment-naïve subjects without cirrhosis; (b) Group 3: the

FDC without RBV for 12 weeks in treatment naïve subjects without cirrhosis; and (c) Groups 4 and 5: the FDC with and without RBV for 12 weeks in treatment-experienced, protease inhibitor failure subjects with and without cirrhosis. Enrollment is complete and the study is ongoing.

Preliminary efficacy data for Groups 1 (FDC) and 2 (FDC + RBV) is presented in Table 2.

Table 2: LONESTAR Groups 1 and 2: SVR Data

Grp. No.	Duration	N (GT-1)	RVR % (n)	SVR4 % (n)	SVR8 % (n)	SVR12 % (n)	Relapse % (n)	BT % (n)	LTFU % (n)
1 GT1 TN FDC	8 wks	20 (20)	100 (20/20)	100 (20/20)	95 (19/20)	TBD	5 (1/20)*	0 (0)	0 (0)
2 GT1 TN FDC+RBV	8 wks	21 (21)	100 (21/21)	95** (20/21)	95** (20/21)	TBD	0 (0/21)	0 (0)	0 (0)

BT: breakthrough; LTFU: lost to follow up

*Subject 2504 experienced relapse on post-treatment Day 39

**Subject 2522 is currently incarcerated. Data is anticipated at the 12 week post-treatment time point.

1.1.2 Activity of GS-7977 against Human Immunodeficiency Virus

The antiviral activity of PSI-7851(precursor molecule of GS-7977) was assessed in cell culture against human immunodeficiency virus (HIV). The isomeric mixture PSI-7851 has no activity against these viruses; consequently, the single diastereoisomer GS-7977 also has no antiviral activity against HIV.

1.1.3 Overall GS-7977 SAE Summary

As of 15 July 2012, 560 healthy subjects had been dosed with GS-7977 in Phase 1 clinical studies and a total of 1,765 HCV infected subjects have been dosed with GS-7977 in ongoing or completed clinical efficacy studies. In addition, 280 subjects have been randomized in an ongoing, blinded study of GS-7977 (randomized 3:1 active to placebo).

Twenty-eight subjects in total have experienced SAEs, and the majority have occurred in subjects treated with GS-7977 along with PEG and RBV. One subject with severe hepatic impairment from a study P9238-0515 (see IB), experienced 5 SAEs: abdominal distension, asthenia, discomfort, peripheral edema, and fluid retention. These events were all mild, unrelated to study drug, and resolved. In another study P7977-0221 (see IB), 4 SAEs were reported in subjects treated with GS-7977+PEG+RBV: pancreatitis acute, anemia, depression, and peripheral ischemia. These events were considered not related to study drug and all events except anemia resolved without sequelae.

The safety of GS-7977 400 mg once daily+PEG+RBV for 12 to 24 weeks has been assessed in over 500 subjects across several Phase 2 studies (Studies P7977-0422, P7977-0724, and P7977-0523). SAEs were reported in 4% (4 of 95 subjects), 5% (15 of 332 subjects), and 3% (4 of 120 subjects) of subjects receiving GS-7977+PEG+RBV for 12 weeks, GS-7977 +PEG

+RBV for 12 to 24 weeks, and GS-7977 +RBV, with or without PEG for 8 to 12 weeks, respectively. The majority of the SAEs were considered either unlikely to be related or unrelated to GS-7977. A subject in Study P7977-0724 experienced an arrhythmia considered possibly related to GS-7977 and PEG+RBV that resolved with sequelae.

Data from August 1, 2012 reports that GS-7977 administered as single doses up to 1,200 mg and multiple daily doses of 400 mg up to 24 weeks were generally well tolerated in healthy subjects and subjects with HCV infection, respectively, without evidence of clinically important drug-related AEs. The AE profile observed for GS-7977+RBV is similar to that expected for RBV. The AE profile for GS-7977+PEG+RBV treatment is similar to that previously observed for PEG+RBV treatment.

Additional details about these AEs are included in the IB.

1.2 GS-5885

GS-5885 is a novel HCV NS5A inhibitor that has demonstrated potent anti-HCV activity against genotype (1a and 1b) HCV infection.

Please refer to the Investigator's Brochure (IB) for additional information on GS-5885 including:

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

1.2.1 Summary of Additional Clinical Experience with GS-5885

The adult safety database for GS-5885 includes data for over 500 healthy volunteers and over 1,000 subjects exposed to at least one dose of GS-5885 in the 6 ongoing Phase 2 studies. Over 700 subjects have been exposed to ≥12 weeks of GS-5885 containing regimens.

1.2.2 Ongoing Clinical Pharmacology Studies

Study GS-US-248-0117

GS-US-248-0117 was an open-label, Phase 1, multiple-dose, parallel-cohort, pharmacokinetic study in subjects with Child-Pugh-Turcotte B (moderate) hepatic impairment and matched healthy subjects. The pharmacokinetics, safety and tolerability of a 12-day regimen of dual or triple combination treatments of GS-5885 30 mg once daily plus GS-9451 200 mg once daily (Cohort 1) and GS-5885 30 mg once daily plus GS-9451 200 mg once daily plus GS-9190 30 mg twice daily (Cohort 2) were being evaluated. Fifty subjects (n = 20 in Cohort 1; n = 30 Cohort 2) were enrolled and received study drugs. Pharmacokinetic analyses are ongoing.

Based on preliminary safety data review, GS-5885 was generally well tolerated when administered to healthy subjects and subjects with moderate hepatic impairment. No SAEs,

Grade 3 or 4 AEs, deaths, or withdrawal due to AEs were reported in the study. The frequency of treatment-emergent adverse events (AEs) reported in the CPT B (moderate) hepatic impaired subjects were similar to those reported in matched healthy subjects. The most frequently reported AEs (in >1 subject) overall were diarrhea, abdominal distension, fatigue, muscle tightness, and headache. A Grade 3 hyperbilirubinemia was noted in 2 subjects coadministered GS-5885 and GS-9451, a result consistent with the known inhibition of bilirubin transporters by GS-9451.

1.2.3 Ongoing Phase 2 Studies

Study GS-US-248-0120 is an ongoing, all oral, Phase 2 study that will examine the safety, tolerability and antiviral efficacy of GS-5885 administered with GS-9451, GS-9190 and RBV in treatment naïve, genotype 1 HCV infected subjects. Enrollment is complete.

Study GS-US-248-0121 is an ongoing Phase 2 study that will examine the efficacy, safety, and tolerability of response guided therapy of combinations GS-5885 + GS-9451 + PegIFN/RBV for 6 or 12 weeks, compared to PegIFN/RBV for 24 weeks in genotype 1 HCV infected, IL28B CC subjects. Enrollment is complete.

Study GS-US-248-0131 is an ongoing, all oral, Phase 2 study that will examine the safety, tolerability and antiviral efficacy of GS-5885, GS-9451, GS-9190 and RBV compared with GS-5885 and GS-9451 with or RBV in treatment-experienced subjects with chronic genotype (1a or 1b) HCV infection. Enrollment is complete.

Study GS-US-248-0132 is an ongoing, all oral, Phase 2 study that will examine the safety, tolerability and antiviral efficacy of GS-5885, GS-9451, GS-9190 and RBV; GS-5885, GS-9451 and GS-9190; GS-5885, GS-9451 and RBV in IFN ineligible or intolerant subjects with chronic genotype (1a or 1b) HCV infection. Enrollment is complete.

Study GS-US-256- is an ongoing Phase 2b study that will examine the efficacy, safety, and tolerability of response guided therapy with GS-5885, PegIFN and RBV with or without GS-9451 in genotype 1 HCV infected, treatment-naïve subjects. Enrollment is complete.

Study GS-US-256-0124 is an ongoing Phase 2b study that will examine the efficacy, safety, and tolerability of response guided therapy of combinations of oral antivirals (GS-5885, GS-9190, and/or GS-9451) with PegIFN and RBV in treatment experienced subjects with chronic genotype 1 HCV infection. Enrollment is complete.

1.2.3.1 Adverse Events in Ongoing Phase 2 Studies

The treatment-emergent adverse events (AEs) reported through September 2012 for all patients enrolled in the GS-US-248-0120, GS-US-248-0131, GS-US-248-0132, GS-US-248-0121 (Arm 1), GS-US-256-0124, GS-US-256-0148, aggregated by treatment regimen, is shown in Table 3.

Table 3: Treatment-emergent adverse events experienced by ≥10% of patients in any interferon-free regimen

Preferred Terms	GS-5885 + GS-GS-9451 + GS-9190 (N=109)	GS-5885 + GS-GS-9451 + GS-9190+ RBV (N=251)	GS-5885 + GS-GS-9190 + RBV (N=109)	GS-5885 + GS-GS-9451 + PEG + RBV (N=506)	GS-5885 + PEG + RBV (N=116)
Patients experiencing any AE with ≥10% incidence	81%	88%	83%	96%	98%
Fatigue	27%	30%	27%	45%	46%
Headache	31%	26%	28%	38%	35%
Nausea	18%	16%	18%	27%	34%
Rash	6%	13%	9%	24%	22%
Insomnia	11%	12%	13%	22%	22%
Pruritus	10%	14%	12%	18%	22%
Cough	6%	10%	11%	18%	17%
Diarrhea	6%	11%	6%	16%	15%
Anaemia	0	6%	11%	16%	16%
Dizziness	12%	7%	3%	12%	10%

1.2.3.2 Treatment-Related SAEs in All Completed and Ongoing Studies Containing GS-5885

A preliminary review of SAEs in all completed and ongoing studies that contain GS-5885 alone or as part of combination regimen identified 20 cases with one or more events that were assessed as related to study drugs. These cases contained 29 separate event terms.

One of these 29 events, abdominal pain, was assessed as related to open-label GS-5885. This event occurred in study GS-US-248-0104, which evaluated the relative bioavailability and PK of GS-5885 and GS-9451 co-administered with representative histamine type-2-receptor antagonist or proton pump inhibitor. This subject had an SAE of abdominal pain during GS-5885+omeprazole treatment that led to discontinuation. The subject had a medical history significant for recurrent abdominal pain. This event resolved after 2 days and was considered related to study drug. The specific etiology could not be clearly defined despite extensive evaluation; intermittent biliary obstruction was considered a probable cause for the reported event

Seven events were assessed as related to peginterferon alpha 2a only: abscess (1), agitation (1), insomnia (1), neutropenia (1), pericarditis (1), psychotic disorder (1), and suicidal ideation (1). One event, anemia, was assessed as related only to RBV. The 20 other events were assessed as related to study drugs (including, PegIFN + RBV, when these drugs were present) in the

corresponding study regimen (blinded and unblinded). The events included the following: accidental overdose (1), anxiety (1), chest pain (1), dyspnea (2), hemorrhagic stroke (1), hallucinations (1), hypersensitivity (1), interstitial lung disease (1), neutropenia (1), pancreatitis (1), pulmonary fibrosis (1), pyrexia (1), rash (5), sensorimotor disorder (1), and skin ulcer (1).

Additional details about these AEs are included in the IB.

1.2.4 Deaths

Across all completed and ongoing GS-5885 containing studies (as of June 2012), one death was reported from hemorrhagic stroke within 30 days following treatment with a regimen containing GS-5885. The subject, a 59-year-old male in Study GS-US-256-0148, on GS-5885, GS-9451, and PegIFN plus RBV with a past medical history notable for hypertension, presented with a sudden onset headache and paralysis of the left arm. The computed tomography (CT) scan on admission was notable for an 8.2 cm hemorrhagic focus, with a 1 cm midline shift. At the time of admission, the subject's laboratory results were notable for a normal complete blood count, including a platelet count of 193,000 per μL, a normal International Normalized Ratio (1.13) and activated partial thromboplastin time (0.94 seconds), as well as normal alanine aminotransferase and aspartate aminotransferase values. Due to the timing of the event while the subject was on study and within 30 days of dosing, it was considered related to each of the 4 study drugs: PegIFN, RBV, GS-9451 and GS-5885.

1.2.5 Safety Summary

In summary, the safety and PK data support ongoing evaluation of GS-5885 in 2 or 3 drug combination regimens. An unblinded Data Monitoring Committee (DMC), which met 3-4 times/year, monitored the Phase 2 studies listed above. The last meeting of the DMC was in August 2012, during which continued clinical development of GS-5885 was endorsed.

1.3 GS-7977/GS-5885 Fixed Dose Combination (FDC)

GS-7977/GS-5885 fixed dose combination (FDC) tablets combine these 2 HCV specific direct acting antiviral (DAA) agents into a single tablet for the treatment of chronic HCV infection.

Please refer to the Investigator's Brochure (IB) for additional information on the GS-7977/GS-5885 FDC including:

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

1.3.1 Summary of Additional Clinical Experience

1.3.1.1 GS-US-334-0101

Study GS-US-334-0101 was a Phase 1 study evaluating the potential for drug-drug interaction

between GS-7977 and GS-5885. The study was an open-label fixed-sequence study in healthy volunteers, in which Cohort 1 subjects received single doses of GS-7977 (400 mg, once daily) alone or in combination with multiple doses of GS-5885 (90 mg, spray-dried dispersion, once daily), under fasted conditions.

Preliminary PK results for the combination of GS-7977 with GS-5885 (Cohort 1) are presented in Table 4 below and demonstrate lack of a clinically significant interaction between GS-7977 and GS-5885.

Table 4 shows increases in GS-7977 levels when co-administered with GS-5885. The effect of GS-5885 on GS-7977 is likely due to inhibition of P-glycoprotein of which GS-7977 is a known substrate. P-glycoprotein is a transporter protein, and inhibition of which results in accumulation of GS-7977. This increase in GS-7977 (GS-7977, top panel) is not considered clinically significant due to its very low and transient exposure relative to total drug related material (DRM) exposure (DRM, calculated as the sum of the AUCs for each of the analytes, corrected for molecular weight). Based on this calculation, the AUC of GS-7977 with GS-5885 is only ~ 5.6% of DRM AUC. As presented previously, safety margins for all analytes continue to remain adequate (AUC safety margin ranges from 1.2 to 16.6) compared to exposures obtained in toxicology studies and dose modification of GS-7977 is not warranted.

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

Table 4: Study GS-US-334-0101: Preliminary Pharmacokinetic Data for GS-7977, Metabolites (GS-566500 and GS-331007) and GS-5885 on Administration of GS-7977 (GS-7977) and GS-5885 Alone or in Combination

GS-7977 (n=17)			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + GS-5885**	**%Geometric Mean Ratios (GMR) (90%CI)**
AUC_{inf} (ng.hr/mL)	795 (36.3)	1750 (27.8)	229 (190, 275)
AUC_{last} (ng.hr/mL)	787 (36.6)	1750 (27.9)	230 (191, 277)
C_{max} (ng/mL)	929 (52.3)	1870 (27.9)	221 (176, 278)
GS-566500 (n=17)			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + GS-5885**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	1110 (31.5)	1950 (22.7)	179 (155, 207)
AUC_{last} (ng.hr/mL)	1060 (32.6)	1890 (22.7)	182 (157, 210)
C_{max} (ng/mL)	312 (38.7)	553 (26.6)	182 (154, 216)
GS-331007 (n=17)			
Mean (%CV)	**GS-7977 alone**	**GS-7977 + GS-5885**	**%GMR (90%CI)**
AUC_{inf} (ng.hr/mL)	10900 (17.3)	13000 (16.8)	119 (113, 126)
AUC_{last} (ng.hr/mL)	10200 (17.9)	12100 (15.5)	119 (113, 125)
C_{max} (ng/mL)	1060 (17.3)	864 (20.1)	81.2 (76.9, 85.8)
GS-5885 (n=17)			
Mean (%CV)	**GS-5885 alone**	**GS-7977 + GS-5885**	**%GMR (90%CI)**
AUC_{tau} (ng.hr/mL)	11900 (26.2)	11400 (27.0)	95.7 (92.1, 99.5)
C_{max} (ng/mL)	755 (24.7)	734 (27.0)	96.5 (89.9, 104)
C_{tau} (ng/mL)	375 (28.8)	360 (31.2)	95.5 (91.9, 99.1)

Data presented as 3 significant figures.

1.3.1.2 GS-US-337-0101

Study GS-US-337-0101 is a single-center, Phase 1, single-dose study evaluating the relative bioavailability and the effect of food on the pharmacokinetics of GS-7977 400 mg/GS-5885 90 mg FDC in healthy volunteers.

In Cohort 1, the pharmacokinetics of GS-7977 400 mg/GS-5885 90 mg FDC was evaluated relative to that of GS-7977 400 mg + GS-5885 90 mg, coadministered as individual

components.

Similar plasma exposures of GS-7977, its metabolites GS-566500 and GS-331007, and GS-5885 were achieved upon administration of GS-7977/GS-5885 FDC and GS-7977+GS-5885, coadministered as individual components. The lower bounds of the 90% confidence intervals (CIs) for the primary PK parameters (AUC and C_{max}) of GS-7977, GS-566500 and GS-5885 were greater than 70%. The GMR% and 90% CIs for GS-331007 primary PK parameters were contained within the bioequivalence bounds of 80-125%. Based on these data, GS-7977/GS-5885 FDC has been selected for Phase 3 clinical development.

Based on a preliminary safety data review of Cohort 1, GS-7977/GS-5885 FDC was generally well tolerated. Twenty-eight subjects were enrolled and completed the study as planned. The most frequently reported AEs in >1 subject were vessel puncture site pain (n=4) and headache (n=3). AEs were transient and mostly mild in severity. A pregnancy was reported during the end of study follow-up visit in a 36 year old, African American female, that later resulted in a SAE of spontaneous abortion. The SAE was not considered by the investigator to be related to study drug. No other SAEs, ≥Grade 2 AEs, or clinically significant laboratory abnormalities were reported in Cohort 1.

The effect of food (moderate-fat or high calorie/high-fat meals) on the pharmacokinetics of GS-7977/GS-5885 FDC was evaluated in Cohort 2, of study GS-US-337-0101.

Table 5: Study GS-US-337-0101: Preliminary Pharmacokinetic Data for GS-7977, Metabolites (GS-566500 and GS-331007) and GS-5885 on Administration of GS-7977/GS-5885 FDC Fasted or with a Moderate-Fat Meal or with A High-Calorie/High Fat Meal

GS-7977 (n=29)			
Mean (%CV)	**FDC Fasted**	**FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1530 (39.2)	2880 (33.6)	194 (176, 214)
AUC_{last} (ng.hr/mL)	1520 (39.6)	2870 (33.8)	195 (1767, 215)
C_{max} (ng/mL)	1240 (49.6)	1540 (39.4)	126 (109, 147)
	FDC Fasted	**FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1530 (39.2)	2590 (34.1)	178 (161, 197)
AUC_{last} (ng.hr/mL)	1520 (39.6)	2580 (34.4)	178 (161, 197)
C_{max} (ng/mL)	1240 (49.6)	1380 (40.6)	115 (99.0, 134)
GS-566500 (n=29)			
Mean (%CV)	**FDC Fasted**	**FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1520 (41.3)	2490 (21.1)	175 (161, 189)
AUC_{last} (ng.hr/mL)	1470 (43.3)	2440 (21.5)	180 (164, 196)

C_{max} (ng/mL)	352 (42.7)	89 (21.8)	151 (136, 167)
	FDC Fasted	**FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	1520 (41.3)	2550 (22.6)	179 (165, 194)
AUC_{last} (ng.hr/mL)	1470 (43.3)	2500 (23.0)	184 (168, 201)
C_{max} (ng/mL)	352 (42.7)	507 (26.1)	154 (139, 171)
GS-331007 (n=29)			
Mean (%CV)	**FDC Fasted**	**FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	11800 (23.0)	13800 (17.9)	117 (112, 123)
AUC_{last} (ng.hr/mL)	11300 (23.4)	12800 (18.3)	114 (108, 121)
C_{max} (ng/mL)	865 (26.6)	696 (19.7)	82.0 (76.0, 88.0)
	FDC Fasted	**FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	11800 (23.0)	12900 (19.0)	112 (107, 118)
AUC_{last} (ng.hr/mL)	11300 (23.4)	12200 (19.4)	110 (103, 116)
C_{max} (ng/mL)	865 (26.6)	597 (23.3)	70.0 (65.0, 76.0)
GS-5885 (n=27)			
Mean (%CV)	**FDC Fasted**	**FDC Moderate-Fat Meal**	**% GMR (90% CI) [Moderate-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	9610 (52.3)	10100 (33.8)	120 (103, 141)
AUC_{last} (ng.hr/mL)	7940 (51.0)	8220 (30.0)	118 (101, 139)
C_{max} (ng/mL)	310 (45.4)	313 (26.0)	112 (96.0, 131)
	FDC Fasted	**FDC High-Calorie/High-Fat Meal**	**GMR (90% CI) [High-Fat/Fasted]**
AUC_{inf} (ng.hr/mL)	9610 (52.3)	8740 (34.0)	107 (92.0, 126)
AUC_{last} (ng.hr/mL)	7940 (51.0)	7350 (31.3)	107 (91.0, 126)
C_{max} (ng/mL)	310 (45.4)	254 (27.5)	92.0 (79.0, 108)

Data presented as 3 significant figures.

Food slowed the rate of absorption of GS-7977 (median T_{max}: 1.00 vs 2.00 hours) with only modest alteration in the bioavailability, as evidenced by increases of 2-fold or less in GS-7977 and GS-566500 plasma exposure. For GS-331007, an approximately 20-30% lower C_{max} was observed upon GS-7977 administration with food with no change in AUC. The %GMR and associated 90% CI (fed/fasted treatments) for AUC of GS-331007 were within the equivalence bounds of 70% to 143%. Since the decrease in GS-331007 C_{max} was modest and the AUC

parameters met the equivalence criteria, the effect of food on GS-331007 PK was not considered clinically significant. These results are consistent with the data from previous Phase 1 studies (P7977-1318 and P7977-0111), which demonstrated that GS-7977 could be administered without regard to food.

Similar GS-5885 plasma exposures (AUC and C_{max}) are achieved upon administration of GS-5885 as the FDC under fasted or fed conditions. The %GMR and associated 90% CIs (fed/fasted treatments) were within the equivalence bounds of 70-143%. While a "negative" food effect was previously observed on GS-5885 (single agent), the pharmacokinetics of GS-5885 administered within the FDC does not appear to be altered by food.

As such, GS-7977/GS-5885 FDC may be administered without regard to food.

1.3.1.2.1 GS-US-337-0127

Study GS-US-337-0127 was an open-label, 2-cohort, single and multiple-dose, crossover Phase 1 study in healthy subjects. Cohort 1 evaluated the potential for a drug-drug interaction between GS-7977/5885 fixed-dose combination (FDC) tablet and HIV antiretroviral agents (ARVs). The effect of acid reducing agents on the pharmacokinetics of FDC was evaluated in Cohort 2.

In Group 1 (Cohort 1), eligible subjects received FDC once daily (QD) alone followed by FDC plus EFV 600 mg/FTC 200 mg/ TDF 300 mg QD (Atripla®; ATR) or ATR alone followed by FDC plus ATR, for 14 days each. All study drugs were administered under fasted conditions, in accordance with the prescribing information for ATR.

In Group 2 (Cohort 1), eligible subjects received FDC QD alone followed by FDC plus Rilpivrine 25 mg/FTC 200 mg/TDF 300 mg QD (Complera®; COMP) or COMP alone followed by FDC plus COMP, for 10 days each. All study drugs were administered with a moderate-fat meal, in accordance with the prescribing information for COMP.

Preliminary pharmacokinetic (PK) and safety results for Cohort 1 are available and are presented in Table ~~Table~~ and Table T~~able 6,~~ respectively.

Effect of ARV on FDC:

The PK of GS-7977 and its predominant circulating nucleoside metabolite GS-331007 were not altered upon co-administration of GS-7977/5885 with ATR or COMP, as evidenced by the 90% confidence intervals (CIs) for the geometric mean ratios (GMR) for GS-7977 and GS-331007 PK primary parameters (AUC_{tau}, C_{max} and C_{tau}) being contained within the protocol pre-defined lack of PK alteration boundaries of 70-143%.

GS-5885 PK was unaltered by COMP. A modest reduction (~ 35%) in 5885 systemic exposures was observed following administration of GS-7977/5885 with ATR. GS-5885 exposures continued to remain within the range of values associated with maximum efficacy (E_{max} model from GS-US-256-0102). Of note, GS-5885 C_{tau} in combination with ATR is

approximately 190-fold above the protein adjusted EC_{90} (0.91 ng/ml) for genotype 1 HCV.

The effect of ATR on GS-5885 PK has been previously examined (GS-US-344-0102) within the context of GS-5885 90 mg (single-agent). The results from both studies are in agreement. ATR modestly decreases GS-5885 administered either as a single agent (~ 20-30% reduction in exposure) or within the fixed dose combination with GS-7977 (~ 35% reduction).

Table 6. Study GS-US-337-0127: Preliminary Pharmacokinetic Data for GS-7977, GS-331007, and 5885 on Administration of GS-7977/5885 Alone or in Combination with ATR or COMP

GS-7977 (N=14)			
Mean (%CV)	**FDC**	**FDC+ATR**	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	1670 (27.8)	1600 (30.7)	95.5 (81.6, 112)
C_{max} (ng/mL)	1530 (32.2)	1530 (20.3)	103 (86.7, 123)
C_{tau} (ng/mL)	NA	NA	NA
GS-7977 (N=17)			
Mean (%CV)	**FDC**	**FDC+COMP***	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	3130 (32.7)	3510 (40.2)	110 (100, 120)
C_{max} (ng/mL)	1520 (38.0)	1640 (37.7)	104 (91.6, 118)
C_{tau} (ng/mL)	NA	NA	NA
GS-331007 (N=14)			
Mean (%CV)	**FDC**	**FDC+ATR**	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	11100 (15.0)	10100 (21.0)	89.6 (82.9, 96.9)
C_{max} (ng/mL)	1060 (20.6)	917 (25.4)	85.7 (76.2, 96.3)
C_{tau} (ng/mL)	232 (21.7)	252 (26.7)	107 (102, 113)
GS-331007 (N=17)			
Mean (%CV)	**FDC**	**FDC+COMP***	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	11200 (16.2)	12900 (20.7)	115 (111, 119)
C_{max} (ng/mL)	868 (15.3)	916 (16.1)	106 (101, 111)
C_{tau} (ng/mL)	340 (22.2)	394 (24.7)	118 (113, 124)
5885 (N=14)			
Mean (%CV)	**FDC**	**FDC+ATR**	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	8080 (38.8)	5270 (35.8)	66.4 (58.6, 75.3)
C_{max} (ng/mL)	480 (34.4)	315 (32.1)	66.1 (57.1, 76.5)
C_{tau} (ng/mL)	265 (42.0)	173 (41.4)	66.4 (58.9, 74.9)
5885 (N=17)			
Mean (%CV)	**FDC**	**FDC+COMP***	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	10900 (27.0)	12000 (30.2)	108 (102, 115)
C_{max} (ng/mL)	647 (26.3)	660 (30.5)	116 (108, 125)
C_{tau} (ng/mL)	391 (29.2)	462 (34.3)	100 (94.4, 107)

* N=15; Data presented as 3 significant figures.

Effect of FDC on ARV:

Efavirenz (EFV), rilpivirine (RPV) and emtricitabine (FTC) pharmacokinetics were not altered upon co-administration of ATR or COMP with FDC. The 90% CIs for the GMR for EFV, RPV and FTC AUC_{tau}, C_{max} and C_{tau} remained within lack of PK alteration bounds of 70-143%.

Modest increases in TDF AUC_{tau}, C_{max} and C_{tau} of approximately 2.0-, 1.8- and 2.7-fold, respectively, were observed following dosing of ATR with FDC. Similarly, increases in TDF AUC_{tau}, C_{max} and C_{tau} of approximately 1.4-, 1.3- and 1.9-fold, respectively, were observed upon dosing of COMP with GS-7977/5885.

The effect of GS-7977 and GS-5885, administered as single agents, on TDF PK has been previously evaluated in study GS-US-334-0131 and GS-US-344-0102, respectively. GS-7977, administered as a single agent increased TDF C_{max} by ~ 25% without any changes in other PK parameters. GS-5885 (single agent) increased TDF AUC_{tau} and C_{tau} (~ 38% and ~55% higher, respectively) without a change in TDF $C_{max.}$ As seen above, GS-7977/5885, administered as a fixed dose combination tablet, additively affected all TDF primary parameters, evidenced by increases in AUC_{tau}, C_{max} and C_{tau}.

Renal clearance of TDF was similar following administration of FDC alone or with ATR and slightly (~ 15%) lower upon addition of COMP relative to FDC alone. FDC interaction with TDF appears to be predominantly pre-systemic and may be mediated by the effect of FDC on the absorption of TDF (AD-337-2001).

Overall, TDF plasma exposures following co-administration of FDC and ATR or COMP are similar to TDF exposures achieved with HIV protease inhibitors, which did not warrant dose adjustment. Accordingly, FDC may be co-administered with ATR, COMP or the standard of care backbone FTC/TDF without dose adjustment.

Table 7. Study GS-US-337-0127: Preliminary Pharmacokinetic Data for EFV, RPV, FTC and TDF on Administration of ATR or COMP Alone or in Combination with FDC

EFV (n=15)			
Mean (%CV)	**ATR**	**FDC+ATR**	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	63800 (49.2)	58100 (55.8)	90.1 (84.3, 96.3)
C_{max} (ng/mL)	3980 (41.8)	3500 (41.6)	88.4 (79.7, 98.2)
C_{tau} (ng/mL)	2070 (57.8)	1890 (63.9)	91.4 (83.7, 99.8)
RPV (n=14)			
Mean (%CV)	**COMP**	**FDC+COMP**	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	2640 (41.6)	2640 (39.6)	102 (93.6, 111)
C_{max} (ng/mL)	186 (43.6)	177 (40.0)	97.0 (87.9, 107)
C_{tau} (ng/mL)	104 (45.2)	115 (44.0)	112 (103, 121)
TDF (n=15)			
Mean (%CV)	**ATR**	**FDC+ATR**	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	2270 (29.0)	4400 (27.1)	202 (180, 226)
C_{max} (ng/mL)	307 (35.8)	527 (29.9)	182 (159, 208)
C_{tau} (ng/mL)	43.6 (27.6)	113 (33.0)	268 (237, 303)
TDF (n=14)			
Mean (%CV)	**COMP**	**FDC+COMP**	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	3400 (27.5)	4780 (28.6)	140 (131, 150)
C_{max} (ng/mL)	373 (25.7)	490 (24.1)	132 (125, 139)
C_{tau} (ng/mL)	60.9 (22.4)	118 (26.4)	191 (174, 210)
FTC (n=15)			
Mean (%CV)	**ATR**	**FDC+ATR**	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	9760 (21.1)	9890 (17.3)	106 (99.2, 112)
C_{max} (ng/mL)	1760 (31.2)	1800 (22.0)	111 (00.2, 123)
C_{tau} (ng/mL)	73.9 (27.6)	76.7 (22.8)	104 (97.9, 111)
FTC (n=14)			
Mean (%CV)	**COMP**	**FDC+COMP**	**%GMR (90%CI)**
AUC_{tau} (ng·hr/mL)	10500 (25.1)	10900 (24.7)	105 (102, 108)
C_{max} (ng/mL)	1770 (23.8)	1800 (19.4)	102 (97.9, 106)
C_{tau} (ng/mL)	89.0 (27.9)	93.6 (25.7)	106 (97.1, 115)

1.3.1.3 Ongoing Phase 2 Studies

1.3.1.3.1 GS-US-337-0118 (LONESTAR)

Study GS-US-337-0118 is evaluating GS-7977/5885 as a fixed dose combination tablet ± RBV in treatment-naive and treatment-experienced genotype 1 HCV-infected subjects. Subjects were enrolled into one of 5 treatment groups. All 60 subjects in Groups 1-3 were treatment-naive and non-cirrhotic. Fifty-eight out of the 60 subjects treated in this cohort achieved SVR_{12}. One subject in Group 1 (FDC for 8 weeks) relapsed at the Post-Treatment Week 8 assessment. In Group 3 (FDC for 12 weeks), one subject withdrew consent after achieving SVR_8. All 40 subjects in Groups 4 and 5 previously failed treatment with a PI+PEG+RBV regimen; in each group, approximately 50% of subjects have cirrhosis. In Group 4 (FDC for 12 weeks), 95% were HCV RNA < LLOQ (Lower Limit of Quantification) at post-treatment Week 12. In Group 5 (FDC + RBV for 12 weeks), 100% were HCV RNA < LLOQ at post-treatment Week 12. Of the 22 cirrhotic subjects in Groups 4 and 5, one subject (Group 4) experienced virologic failure; the remainder achieved SVR_{12}. This data confirms the efficacy of GS-5885 as part of a fixed dose combination tablet with GS-7977, both with and without RBV, in both treatment naïve and treatment experienced subjects, with and without cirrhosis.

Preliminary PK data showed generally similar plasma exposures of GS-7977, its metabolites GS-566500 and GS-331007, and GS-5885 in treatment-naive or treatment-experienced HCV-infected subjects irrespective of treatment duration or presence/absence of RBV. The PK for GS-7977, its metabolites, and GS-5885 was also comparable in treatment-experienced subjects with or without cirrhosis, consistent with Phase 1 hepatic impairment data (P2938-0515 and GS-US-248-0117).

1.3.1.4 Ongoing Phase 3 Studies

Study GS-US-337-0102 (ION-1) is a Phase 3, multicenter, randomized, open-label study investigating efficacy and safety of GS-7977/5885 FDC ± RBV for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection. Enrollment is complete and the study is ongoing.

Study GS-US-337-0109 (ION-2) is a Phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of GS-7977/5885 FDC ± RBV for 12 and 24 weeks in treatment-experienced subjects with chronic genotype 1 HCV infection. Enrollment is complete and the study is ongoing.

Study GS-US-337-0108 (ION-3) is a Phase 3, multicenter, randomized, open label study to investigate the efficacy and safety of GS-7977/5885 FDC ± RBV for 8 weeks and GS-7977/5885 FDC for 12 weeks in treatment-naive subjects with chronic genotype 1 HCV infection. Enrollment is complete and the study is ongoing.

1.3.1.5 Serious Adverse Events Reported as Related to FDC from All Studies

Two serious adverse events have been reported from the ION study as having relationship to FDC. One subject experienced mesenteric venous thrombosis and dosing was interrupted. Another developed salpingitis but continued with dosing. One subject on FDC in the

ELECTRON-2 study developed abdominal pain, which resolved in 10 days. No change was made in study drug dosing. No SAE was reported by more than one subject.

1.4 Rationale for the Current Study Design

This is a Phase 2 study designed to evaluate the efficacy and safety of the GS-7977/GS-5885 FDC tablet, for treatment durations of 12 weeks, in IFN-naïve, chronic genotype 1 HCV/HIV infected subjects.

There is a significant unmet medical need for IFN-free all oral regimens for the treatment of chronic HCV infection in HIV/HCV coinfection patients, given the toxicity and tolerability issues associated these medications, the unwillingness of many patients to be treated with PegIFN and/or RBV, as well as the substantial numbers of patients who cannot receive PegIFN and/or RBV due to contraindications [20-24].

The pivotal studies for PegIFN+RBV indicate that the rate of treatment discontinuation due to side effects ranges from 14% to 21%; however, the actual discontinuation rate is significantly higher in clinical practice. In addition to these toxicity and tolerability issues, a number individuals cannot receive IFN and/or RBV due to co-morbidities and/or contraindications [22]. In a retrospective review of genotype 1 HCV infected subjects at a US Veterans Affairs hospital, only 32% were considered eligible for PegIFN therapy, with 19% and 12% of subjects deemed ineligible due to a history of severe mental illness or major depression [23]. In a prospective study of 237 GT-1 HCV infected subjects identified as potential candidates for PegIFN and RBV, only 28% were treated. The authors identified medical contraindications [24] as the primary reason for non-treatment in approximately one third of those not treated.

In a study of dual therapy with GS-7977 and BMS-790052, an NS5A inhibitor in HCV monoinfected GT-1 treatment naïve individuals, 100% achieved an SVR after 24 weeks of treatment regardless of RBV dose [17]. A different study of GS-7977 and a different NS5A inhibitor (GS-5885) with RBV in HCV monoinfected patients has also now been shown to be effective with SVR_4 rates of 100% [19]. In both studies, regimens suppressed HCV RNA quickly, with all treated subjects having an HCV RNA less than the level of detection by week 4. Currently there is a FDC consisting of GS-7977 with GS-5885, 2 well-tolerated, highly active, once-daily antiviral agents in late clinical development. This GS-7977/GS-5885 FDC has the potential to be a simple and effective all-oral, once daily treatment regimen for chronic genotype 1 HCV infection. Preliminary results from the use of this regimen in a fixed dose combination (FDC) with and without RBV for 8 weeks in treatment-naïve subjects without cirrhosis showed SVR_8 rate of 95% in either arm. As such, a PegIFN and potentially RBV-free treatment would obviate the toxicity and tolerability issues as well as the contraindications associated with these medications, thereby increasing the number of individuals eligible for treatment. Furthermore, as a potential one-pill-once-a-day therapy, this simplified FDC regimen will reduce pill burden and is therefore anticipated to increase adherence [25] and decrease the risk of the emergence of drug resistant mutations. In the HIV literature, it has been shown that a single-tablet regimen (one pill, once a day) is associated with higher adherence [26] and higher viral suppression [27].

In conclusion, there is a high unmet medical need for the development of an all-oral treatment

regimen without PegIFN and/or RBV for chronic HCV infection. An all-oral regimen would represent a paradigm shift in the global management of HCV infection as it would expand access to a significant proportion of the HCV-infected population that currently lack or cannot tolerate current treatment options. Furthermore, improvements in treatment compliance that will likely result from an IFN-free, all oral regimen, especially if formulated as a single tablet, may be expected to result in higher SVR rates.

1.5 Rationale for Studying HIV/HCV Coinfected Subjects

HIV/HCV coinfected subjects have lower rates of SVR when treated with combination therapy using PegIFN/RBV when compared to HCV monoinfected subjects. HIV/HCV coinfected patients also have faster rates of progression and a higher likelihood of development of end stage liver disease and decompensated liver failure [7, 8]. DAAs that do not rely on host immune system exclusively to abrogate HCV replication may be an effective approach among HIV/HCV coinfected subjects regardless of race and IL28B genotype.

Furthermore, use of RBV in HIV/HCV coinfected subjects is associated with an increased incidence of anemia that requires dose reductions, interruptions and or treatment with erythropoietin. All these increase the cost and adverse event profile of the therapeutic regimen. The development of a treatment regimen without PegIFN/RBV for genotype 1 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. Safety, tolerability and efficacy of the protease inhibitors/PEG/RBV appear comparable between the HIV/HCV coinfected and HCV monoinfected subjects supporting the evaluation of similar regimens to those under evaluation in HCV monoinfection. Furthermore, certain studies suggest that patients with a robust immune status respond better to HCV therapy [28].

1.6 Rationale for Dose Selection of GS-7977

The GS-7977 dose selected for further development in Phase 3 studies is 400 mg once daily. This dose was associated with higher SVR rates in genotype 1 HCV infected subjects as compared to the 200 mg once daily dose when given in conjunction with PegIFN plus RBV for 24 weeks in P7977-0422. Safety and tolerability appeared similar across both dose levels and was similar to the PegIFN plus RBV control arm. In addition, when GS-7977 400 mg once daily plus RBV was given to genotype 2 or 3 HCV infected subjects, 100% SVR_{24} was observed.

GS-7977 400 mg is also being studied in P7977-0724 (ATOMIC), which is assessing treatment durations of 12 and 24 weeks in genotypes 1, 4, 5, and 6 HCV infection. Evaluation of GS-7977 400 mg once daily is also currently ongoing in the following Phase 3 clinical studies: FISSION (P7977-1231) and POSITRON (GS-US-334-0107) in genotype 2 and 3 HCV-infected, treatment-naïve, IFN ineligible, intolerant and unwilling adult subjects; FUSION (GS-US-334-0108), in genotype 2 and genotype 3 HCV-infected treatment experienced adult subjects; and NEUTRINO (GS-US-334-0110), in genotype 1, 4, 5 and 6 HCV-infected treatment naïve subjects. These Phase 3 studies evaluating GS-7977 will enroll over 1,200 subjects.

1.7 Rationale for Dose Selection of GS-5885

The Phase 1 multiple-ascending dose study GS-US-256-0102 established the anti-HCV activity of GS-5885. In this study, the maximum median HCV RNA $\log_{10}$ reduction was 3 or greater for all cohorts dosed with ≥ 3 mg of GS-5885. An E_{max} PK/PD model indicates that the exposures achieved following administration of the 30 mg dose provides > 95% of maximal antiviral response in genotype 1a HCV infected subjects. It was also observed that 30 mg or greater of GS-5885 likely provided coverage of some drug related mutations that doses less than 30 mg did not, based on an analysis of NS5A mutants that arose in response to exposure to GS-5885. Therefore, 30 mg and 90 mg of GS-5885 were selected for further clinical evaluation.

In IFN-free Study GS-US-248-0120, 30 mg of GS-5885 (Arm 1) is being compared to 90 mg of GS-5885 (Arm 2), on a background of 3 other antivirals, GS-9451, GS-9190, and RBV. When comparing these 2 arms, it is notable that the breakthrough (BT) rate (number of patients with HCV RNA > lower limit of quantification (LLOQ) after having achieved vRVR/total number of patients who achieved vRVR), is higher in Arm 1 (BT = 33%, 11/33; 30 mg GS-5885), than Arm 2 (BT = 12%, 9/74; 90 mg GS-5885). Therefore, the 90 mg dose of GS-5885 may confer greater anti-viral coverage that prevents viral breakthrough. For this reason, 90 mg has been selected as the dose of choice for further development in Phase 3 studies. More than 400 patients have been dosed with 90 mg of GS-5885 for over 12 weeks.

1.8 Rationale for Selection of Allowed Concomitant ARV Regimens

The protocol-approved ARV regimens are:

FTC/TDF plus:

- efavirenz (EFV); or
- rilpivirine (RPV); or
- raltegravir (RAL)

The doses of the allowed concomitant ARV medications (EFV/FTC/TDF 600/200/300 mg QD, RPV/FTC/TDF 25/200/300 mg, FTC/TDF 200/300 mg QD, FTC 200 mg, TDF 300 mg QD, EFV 600 mg, RPV 25 mg QD, RAL 400 mg BID) are the recommended doses of the marketed products to be used alone as a single tablet regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection. FDC and ARVs (FTC, TDF, EFZ, RPV, or RAL) are not involved in any clinically significant drug interactions [GS-US-337-0127 (Reference protocol Section 1.2.1.1.1); GS-US-344-0102, GS-US-334-0131 (Reference IB)].

1.9 Overall Risk/Benefit Assessment

The GS-7977/GS-5885 FDC product combines a potent HCV nucleotide inhibitor and a potent

HCV NS5A inhibitor, and has the potential to be a once-daily regimen for the treatment of chronic genotype 1 HCV infection.

The potential benefits of GS-7977/GS-5885 FDC product for the treatment of chronic HCV are:

- Greater antiviral efficacy (i.e., rapid and durable eradication of HCV) compared to the current standard of care
- A reduction in the AEs currently associated with the use of PegIFN, RBV, and/or available protease inhibitors (telaprevir, boceprevir)
- Shortened duration of therapy
- Increased adherence to therapy with the convenience of a once daily, all oral, FDC

The combination of GS-7977 400 mg and GS-5885 90 mg has been administered in on-going Phase 2 and Phase 3 studies to over 2,500 subjects, of which 2,239 were subjects with HCV. A review of the safety data from completed studies shows that treatment with GS-7977 and GS-5885 or FDC has been generally well tolerated. No deaths or discontinuations of study drug due to AEs have been reported. No Grade 4 or clinically relevant Grade 3 laboratory abnormalities have been reported. No trends in vital sign changes have been observed following administration. The favorable safety and efficacy profiles of support further evaluation of this combination and doses in clinical development.

In summary, there is no current approved all-oral treatment available for HIV/HCV coinfected and HCV-infected patients and no therapy available for those with chronic HCV who are IFN-intolerant or are medically ineligible to receive IFN and/or RBV. If high rates of SVR can be obtained with a short, IFN-free and RBV-free regimen, the anticipated improvements in safety and tolerability would offer a favorable risk-benefit determination for individuals with HCV infection in most populations including HIV coinfection.

1.10 Rationale for the use of Interferon-free, all Oral Regimen

HIV-infected subjects seem to have lower responses to HCV treatment using interferon based regimens. Since HIV infection is by itself an immunoregulatory disease, it is believed that these patients will have less optimal responses to immune based therapies. However, use of non-immune based directly acting antiviral therapies that do not rely on host immunity excessively, seem to work very well in HIV infected subjects. For example, HIV infected subjects respond to antiretroviral therapy regardless of baseline CD4 T cell counts. Hence, it is expected that HIV-infected subjects would have better rates of SVR when treated with non-immune based, directly acting agents for HCV. Second, we have previously demonstrated that HIV-infected subjects who control HIV replication by themselves without the aid of ART seem to have faster clearance than those subjects with similar CD4 T cell counts, but requiring ART to suppress HIV replication [28]. Third, we are using an extended treatment duration for these subjects (12 weeks over 8 weeks that was reported to result in high rates of SVR in LONESTAR study). We believe this would allow us to maximize the rates of SVR for HIV

infected subjects as the first clinical trial using a directly acting HCV agent only treatment for HCV in HIV-infected subjects.

1.11 Justification for Exploratory Endpoints

Previously we have identified several factors, such as race, IL28B haplotype, interferon stimulating gene expression, HCV viral kinetics and proteomic profiling patterns as predictors of SVR in HIV-infected subjects receiving interferon alfa-based treatment. It is clear that HIV-infected subjects have modest responses to interferon alfa signaling and adversely effect therapeutic responses. However, the determinants of SVR in a non-immune based therapeutic regimen in HIV-infected subjects have not yet been explored. In this study, we plan to accomplish the following. First, we would like to demonstrate GS-7977/GS-5885 fixed drug combination is a safe, well tolerated and highly effective therapeutic regimen for treating HCV in HIV-infected subjects. Second, we would like to identify host and viral factors that are associated with and predictive of SVR in this population. Third, we would like to explore the effects of eradication of HCV on the immune system pertaining to the control of HIV replication using comprehensive immunological techniques. These bench-based studies are pivotal in expanding our understanding of biological correlates of SVR of HCV in HIV-infected subjects. Such valuable information will enhance our understanding of why and how DAA treatment result in SVR and unravel the mechanism(s) of virologic relapse, if any.

2 OBJECTIVES

2.1 Primary Objective

To assess the safety, tolerability, and efficacy of a fixed dose combination of GS-7977/ GS-5885 for 12 weeks in HIV/HCV GT-1 coinfected subjects who are IFN-treatment naïve.

2.2 Secondary Objectives

1. To compare the immunologic, virologic and host genetic/proteomic predictors of response to treatment with a fixed dose combination of GS-7977/ GS-5885 in subjects treated for 12 weeks.

2. To compare HCV quasispecies evolution from baseline and throughout 12 weeks of treatment (especially during relapse or viral breakthrough) and assess the influence on virologic response to treatment in HIV/HCV GT-1 coinfected patients.

3. To assess the fitness of NS5A/B viral mutants in vivo in the presence or absence of a fixed dose combination of GS-7977/ GS-5885 in vitro by performing NS5A/B site directed mutagenesis.

4. To evaluate the effect of HCV viral clearance on host immunity to HIV as well as HIV viral kinetics.

5. To determine the pharmacokinetics of a fixed dose combination of GS-7977/GS-5885 in HIV infected patients not on ARVs.

6. To determine the decline in extra hepatic HCV reservoir in PBMCs and its role in predicting relapse or SVR_{12}.

7. To evaluate the kinetics of plasma HCV RNA during treatment and after treatment discontinuation.

8. To evaluate the effect of a fixed dose combination of GS-7977/GS-5885 treatment on HIV VL and CD4 T cell counts.

9. To determine whether suppression of HIV has an influence on SVR_{12} with a fixed dose combination of GS-7977 and GS-5885.

10. To assess the change from baseline of serum creatinine at the end of treatment and at Post-Treatment Week 12 and 24

3 STUDY DESCRIPTION

This is an open-label Phase 2a study evaluating the safety, tolerability, efficacy, early viral kinetics, viral mutants, HCV quasispecies, and immunologic, virologic, and host genetic/proteomic predictors of response in treatment naïve HIV/HCV coinfected subjects with HCV GT-1 infection following 12 weeks of treatment with a fixed dose combination (FDC) of GS-7977/GS-5885. A total of 50 subjects will be enrolled.

Participants taking ARVs must be classified as HIV-infected with CD4 >100 and HIV RNA level less than the level of detection (according to the local assay being used). Participants not on ART must not have been on ARVs for > 8 weeks from dosing, must have CD4 $\geq$500 cells/mm^3 OR have an HIV viral load less than 500 copies/mL and stable CD4 count for at least 3 months.

Starting with Day 0, all subjects will receive FDC for 12 weeks. The total amount of time required to complete all the study visits is approximately 68 weeks from the screening period through the end of the follow-up visits:

- 8-week screening period.
- 12-week treatment period.
- 12- and 24-week post-treatment follow-up visits (SVR_{12} and SVR_{24}).
- 48-weeks post-treatment visit to assess late viral relapse.

Subjects identified to have mutations leading to GS-7977 or GS-5885 resistance following sequencing and phenotypic analysis will be requested to return at 12-week intervals for up to 60 weeks to determine the time required for the resistant virus to return to background levels.

3.1 Viral Kinetics & Pharmacokinetics Substudy for Both Treatment Arms

Up to 20 subjects will be invited to participate in a viral and pharmacokinetics substudy at the NIH. These subjects will be admitted at the NIH Clinical Center (CC) for research blood collection for 36 hours following the first dose of the study drugs. The PK of the ARV regimen may be analyzed as appropriate.

3.2 Treatment Failure / Drug Discontinuation

See visit schedule for subjects who stop study medications early or who are found to have treatment failure. Also see Criteria for premature withdrawal of subjects (Section 14.2).

Criteria Requiring Discontinuation of GS-7977/GS-5885 FDC
Subjects will be considered treatment failures and will discontinue GS-7977/GS-5885 FDC if they meet any of the following criteria while taking study drugs:

- Serum HCV RNA greater than LLOQ after 2 prior consecutive HCV RNA values less than the LLOQ
- Greater than a 1 $\log_{10}$ increase in serum HCV RNA from nadir
- Less than a 2 $\log_{10}$ decline in HCV RNA after 4 weeks of treatment
- Serum HCV RNA $\geq$ LLOQ after 8 weeks of treatment

If any of these should occur in a patient who is currently on study drugs, the subject should return within one week for a confirmatory test. If the confirmatory test also meets the same criteria, the subject will be considered a treatment failure and should be discontinued from therapy. The anticipated clinical impact of discontinuation should be discussed in advance with the Sponsor Medical Monitor if possible, particularly if discontinuation is thought to pose a risk to the overall clinical wellbeing of the subject. Those who are discontinued will continue to follow the general study schedule of assessments unless unwilling to do so, in which case they may be seen at least every 12 weeks for safety and research labs until the end of the study. Subjects will be followed closely for resolution of active laboratory abnormalities or adverse events which are considered related to the study agents prior to starting the revised schedule.

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

- Elevation of ALT >5x OR AST >5x Day 0, confirmed by immediate repeat testing
- Abnormal elevation of ALT >3 x Day 0 *and* total bilirubin >2 x ULN, confirmed by immediate repeat testing
- Elevation of ALT >15 x ULN confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 event assessed as related to treatment with GS-7977 or GS-5885

3.2.1 Treatment Failure Criteria After Stopping GS-7977/GS-5885 FDC

- Have detectable HCV RNA during the post-treatment period (after having

achieved HCV RNA <LLOQ at end of treatment).

3.3 Rescue Therapy for Treatment Failures

For all subjects who experience a treatment failure as described**,** rescue therapy will be offered with an HCV protease inhibitor [Telaprevir or Boceprevir] + PegIFN/RBV. The rescue therapy will be initiated no sooner than 6 weeks after the study drug discontinuation.

All subjects who decline to go on rescue therapy will be followed as described. Those subjects who decide to go on rescue therapy may do so under the consult arm of NIAID protocol # 04-I-0086 ("Evaluation of Clinical, Virologic and Immunologic Factors that Contribute to the Pathogenesis of Chronic Hepatitis C and Its Complications"; HCVRES2).

3.4 HIV Virologic Rebound Criteria for Subjects on ARVs

Subjects on ARVs who have at least 2 consecutive post-Day-0 visit plasma HIV-1 RNA levels ≥ 400 copies/mL (at least 2 weeks apart) will be considered to have HIV virologic rebound.

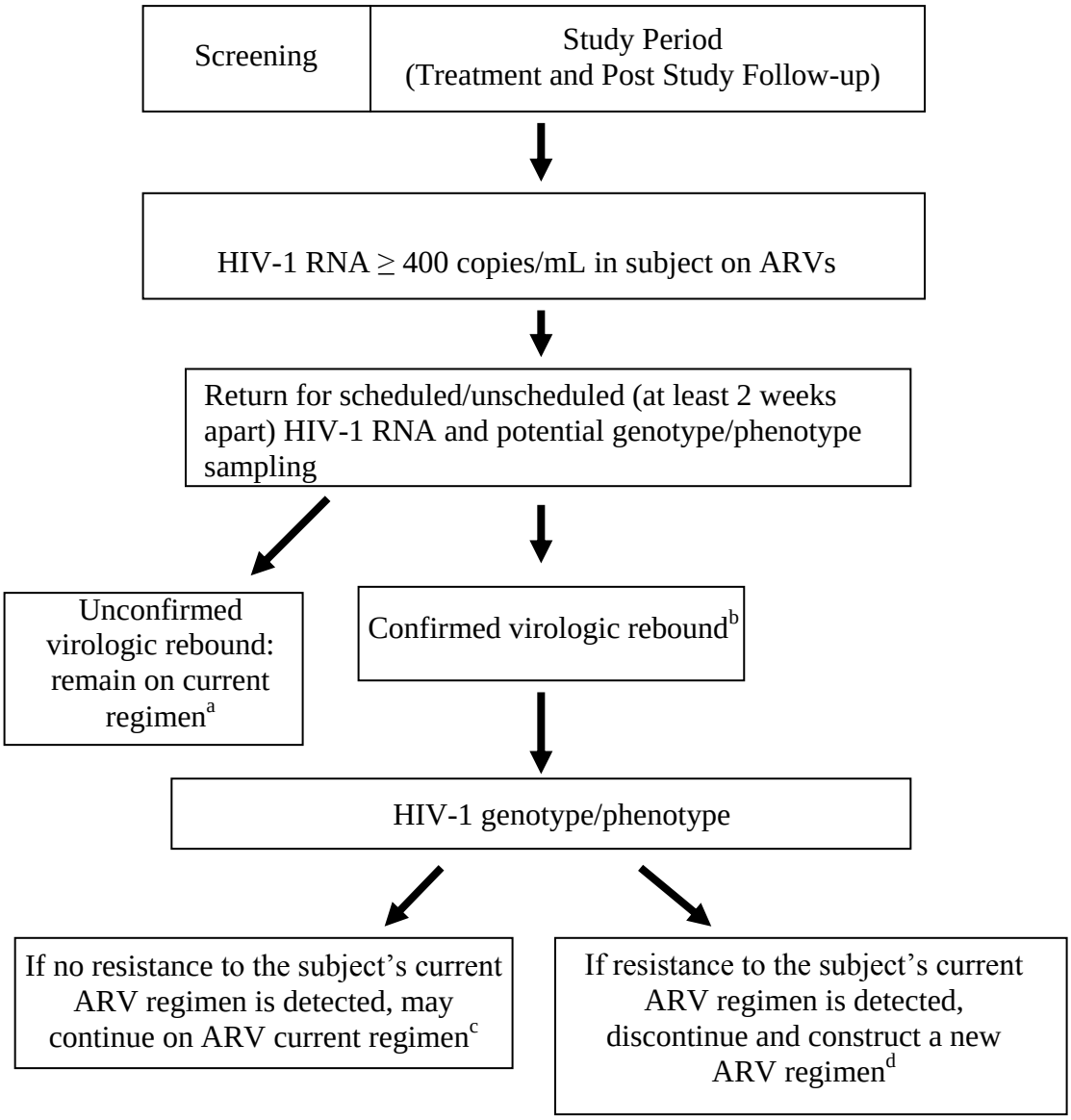
Following an initial HIV-1 RNA result of ≥ 400 copies/mL, subjects on ARVs will be asked to return to the clinic after 2 weeks for a scheduled or unscheduled blood draw for confirmation of HIV virologic rebound. If HIV virologic rebound is confirmed, the blood samples from this visit will be used for HIV-1 genotype/phenotype testing. If no resistance to the subject's current ARV regimen is detected, the subject may continue on current ARV regimen.

HCV study drug should be continued unless safety events warrant the discontinuation of these study drugs, as outlined in Sections 3.2.1, 14.2 of the protocol.

Please refer to

-Figure 2 ~~manage~~ment of subjects who meet the criteria for HIV virologic rebound.

Figure 2: HIV Virologic Rebound Schema



a If virologic rebound is not confirmed, the subject should 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.

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 may be configured at the discretion of the Investigator.

d A new ARV regimen should be configured or the ARV regimen held for the duration of FDC dosing at the Investigator's discretion

3.5 Monitoring for Potential Nephrotoxicity

TDF levels, when given with FDC, are anticipated to be close to or may exceed the exposures seen when TDF is given with boosted HIV protease inhibitors. For this reason, the following renal monitoring will be implemented for all subjects taking ARVs:

1. Serum uric acid (in addition to glucose, potassium, phosphate, bicarbonate and creatinine collected as part of acute care and mineral panels) will be completed at Screening, Day 0, Weeks 1, 2, 3, 4, 6, 8, 12, 14, 16, 20, 24 and 36.

2. Urinalysis at Screening, Day 0, Weeks 1, 2, 3, 4, 6, 8, 12, 14, 16, 20, 24 and 36.

3. Fasting urine beta-2 microglobulin, at Day 0, Weeks 2, 4, 12, 16, 24 and 36 visits. If the subject does not arrive at the clinic fasting, they can return anytime in the next 72 hours to provide a fasting urine sample.

4. Estimated glomerular filtration rate (eGFR) will be calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at screening as well as Day 0, Weeks 1, 2, 3, 4, 6, 8, 12, 14, 16, 20, 24 and 36.

5. In subjects who develop signs or symptoms of potential renal impairment or tubulopathy there wil be monitoring of the fractional excretion of phosphate every month or more frequently if indicated.

4 STUDY ENDPOINTS

4.1 Primary Endpoints

- Proportion of patients achieving SVR_{12} (HCV RNA <LLOQ 12 weeks after completion of treatment)

4.2 Secondary Endpoints

- Correlation of the slope of HCV viral load decline (early viral kinetics) with sustained virologic response at 24 weeks post-treatment (SVR_{24})
- RVR_4, (RVR_4: HCV RNA<LOD at Week 4): Correlation of early viral kinetics with the percentage of patients achieving RVR_4.
- End of treatment response (ETR: HCV RNA<LOD at end of treatment). Correlation of early viral kinetics to the percentage of patients who achieve ETR.
- Correlation of early viral kinetics to the percentage of patients who achieve SVR_{12}.
- Viral relapse: Correlation of early viral kinetics with the percentage of patients who develop viral relapse.
- Differential interferon sensitive gene (ISR) response to therapy in patients treated for 12 weeks who do and do not attain RVR_4 and SVR.
- Host genetic and proteomic factors in patients with differential RVR_4 and SVR HCV quasispecies evaluation at baseline and during therapy to determine emergence of resistance patients who attain RVR_4, and those who achieve SVR.
- HIV and HCV immunologic (adaptive and innate) correlates of SVR and RVR
- Predictive ability of extra hepatic HCV reservoirs on relapse to GS-7977 + GS-5885.
- Change in liver histology before and after liver biopsy

5 STATISTICAL ANALYSIS

5.1 Sample Size

In terms of safety, a sample size of 50 is sufficient to have high probability of observing at least 1 adverse event of probability 10% or more. If the true event probability is 10% or more, there is about a 96% chance of observing at least 1 such adverse event Consequently, if no one has a given type of AE, we can be confident that its true probability is under 10%. This trial will provide preliminary evidence on the safety and efficacy of GS-7977 in combination with GS-5885 in coinfected participants. A previous study in subjects with genotype 1 led to a sustained virologic response at Week 12 (SVR_{12}) in all participants. We therefore expect the suppression rate in this study to 80% or higher. If the true suppression rate is 80%, we will be able to estimate the probability of suppression to within approximately $\pm 1.96\{(.8)(1-.8)/30\}^{1/2}=.14$ ((Table 8).

Table 8: Sample Size
For sample sizes shown in row 1, row 2 gives the accuracies of the estimates of the proportion of patients suppressed to below the limit of detection (based on a 95% confidence interval).

n=30	n=40	n=50
±.14	±.12	±.11

Table 9: Adverse Event Probability Table
For AE probabilities shown in row 1, row 2 gives the probabilities of observing at least 1 participant with the AE among 50 total participants.

.01	.05	.10	.15
26%	79%	96%	99%

5.1.1 Primary Endpoint
The primary efficacy endpoint is SVR_{12} (HCV RNA <LLOQ 12 weeks after cessation of therapy).

5.1.2 Secondary Endpoints
Secondary efficacy endpoints include: HCV RNA < LLOQ at 4 and 24 weeks after discontinuation of therapy (SVR_4 and SVR_{24}); viral breakthrough; and relapse.

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

5.1.3.1 Other Endpoints of Interest
Additional efficacy evaluations may include HCV RNA change from Day 0; ALT normalization; and viral kinetic parameters.

5.1.4 Analysis Sets

5.1.4.1 Efficacy

The analysis set for antiviral activity analyses will include subjects who were enrolled into the study and received at least one dose of study drug.

5.1.4.2 Safety

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

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

5.1.4.3 Pharmacokinetics

The PK analysis set will include all subjects who are enrolled and have received at least one dose of study medication. The PK analysis set will be used for analyses of general PK. The intensive PK analysis will include the 20 participants who were enrolled in the sub study.

5.2 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 time points on, or following, the date of discontinuation. If no HCV RNA values are obtained after the last dose of study medication, the subject will be considered a treatment failure for the SVR endpoints.

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

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

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

Values for missing vital signs data will not be imputed; however, a missing Day 0 result will be replaced with a screening result, if available.

5.3 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, and additional endpoints as necessary.

5.4 Efficacy Analysis

5.4.1 Primary Analysis

The primary efficacy endpoint is SVR_{12} (HCV RNA <LLOQ 12 weeks after cessation of therapy.)

In the primary efficacy analysis the SVR_{12} rate will be compared to the assumed spontaneous rate of 5% using two-sided exact one-sample binomial test at a significance level of 0.05.

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

5.4.2 Secondary Analysis

The proportion of subjects with HCV RNA below the LLOQ over time (including SVR endpoints) will be presented.

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.

6 SAFETY ANALYSIS

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

6.1 Adverse Events

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 will be provided.

6.1.1 Laboratory Evaluations

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

6.1.2 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 GS-5885 and metabolite(s)] using descriptive statistics. Details of the analysis plan will be provided in the pharmacokinetic reporting and analysis plan.

7 PATIENT POPULATIONS

It is anticipated that approximately 100 HIV/HCV GT-1 coinfected subjects (including screening drop-outs) will be screened for this study. We will be enrolling subjects from ongoing NIH clinical studies as well as new recruits.

7.1 Subject Selection

Inclusion Criteria

1. Eighteen years of age or older at screening.
2. HCV treatment-naïve, as defined as no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent.
3. Participants must be willing to practice either:
    a. Abstinence from sexual intercourse or
    b. At least 2 forms of contraception including one barrier method from 2 weeks prior to Day 0 through 30 days after the last dose is received.
        i. Female partners of male study subjects may rely upon hormonal contraception as one of the 2 methods; however female study subjects may not.
4. Chronic hepatitis C infection defined as one of the following:
    a. Positive for anti-HCV antibody, HCV RNA, or an HCV genotype at least 6 months before screening, and positive for HCV RNA and anti-HCV antibody at the time of screening or

    b. Positive for anti-HCV antibody and HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed

before enrollment with evidence of chronic hepatitis C disease, such as the presence of fibrosis).

5. HIV treatment status:

   a) Documented HIV infection, ARV untreated for >8 weeks preceding dosing and having either:

      1) a CD4 T-cell count ≥ 500 cells/mm^3 within 8 weeks of Day 0 or

      2) an HIV viral load less than 500 copies/mL with a stable CD4 count for at least 3 months.

   b) Documented HIV infection on a stable, protocol-approved, ARV regimen for ≥ 8 weeks prior to dosing and is expected to continue the current ARV regimen through the end of study with all of the following:

      1) a CD4 T-cell count >100 cells/mm^3

      2) a documented plasma HIV-1 RNA level less than the level of detection for at least 8 weeks preceding dosing. If the lower limit of detection of the local HIV-1 RNA assay is <50 copies/mL (e.g., <20 copies/mL), the Screening plasma HIV-1 RNA level cannot exceed 50 copies/mL.

      3) HIV ARV agents including only combination regimens consisting of medications from the following list: tenofovir (TDF), emtricitabine (FTC), efavirenz, raltegravir, and rilpivirine administered according to their manufacturer's prescribing information. (reference Section 10.3 for additional information)

6. Documentation of hepatitis C genotype 1a, 1b or mixed 1a/1b.

7. Absence of cirrhosis, defined as one of the following:
   a. A liver biopsy performed within 36 calendar months of screening showing absence of cirrhosis.
   b. FibroTest® score of <0.48 AND APRI of <1 performed during the 8 weeks preceding dosing (In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy is required).

8. Able to effectively communicate with the Investigator and other center personnel.

9. Willing to give written informed consent and comply with the study restrictions and requirements.

10. If opioid-dependent, subjects must be participating in a supervised treatment.

11. Participants must have a primary medical provider outside of OP8 and the NIH for medical management.

Exclusion Criteria

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

1. Current or prior history of any of the following:
   a. Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol;

subjects currently under evaluation for a potentially clinically-significant illness (other than HCV) are also excluded.

b. Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug.
c. Poor venous access interfering with required study blood collection.
d. Clinical hepatic decompensation (i.e., ascites, encephalopathy or variceal hemorrhage).
e. Solid organ transplantation.
f. Significant pulmonary disease, significant cardiac disease or porphyria.
g. Unstable psychiatric disease (Subjects with psychiatric illness that is well-controlled on a stable treatment regimen or currently not requiring medication may be included).
h. Any malignancy or its treatment that in the opinion of the PI may cause ongoing interference with host immunity; subjects under evaluation for malignancy are not eligible.
i. Significant drug allergy (such as anaphylaxis or hepatotoxicity).
j. Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency, cholangitis).
k. Patients with renal impairment or uncontrolled medical problems that could place them at high risk for developing renal impairment.

2. Positive test at screening for either HBsAg or quantifiable HBV DNA (completed only if necessary to rule out chronic HBV).
3. Current use of non-protocol approved ARVs.
4. A new AIDS-defining condition diagnosed within 30 days prior to screening or active, serious infection (other than HIV or HCV) requiring parenteral antibiotics, antivirals or antifungals within 30 days prior to Day 0.
5. Cirrhosis of the liver.
6. Screening or baseline ECG with clinically significant ECG findings.
7. Abnormal hematological and biochemical parameters, including:
    a. Neutrophil count <750 cells/mm^3
    b. Hemoglobin <9 g/dL. If Hgb < 11g/dL in women and < 12 g/dL in men other causes of anemia should be excluded as medically indicated.
    c. Platelet count ≤50,000 cells/mm^3
    d. Estimated GFR (calculated by the CKD-EPI equation) <50 mL/min/per 1.73 m^2 if not on ARV or <60 mL/min if on ARVs
    e. ALT or AST ≥10 times ULN
    f. Serum lipase ≥1.5 times ULN (at screening or during the screening period)
    g. Direct bilirubin ≥1.50 times ULN
    h. Albumin ≤3.0 g/dL
    i. INR ≥ 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR.
8. Donation or loss of more than 400 mL blood within 8 weeks prior to first dose administration.

9. Poorly controlled diabetes mellitus, indicated by hemoglobin A1C > 10% at screening for known diabetics.
10. Known hypersensitivity to, GS-5885, GS-7977, or formulation excipients.
11. Pregnant/Breastfeeding women.
12. Co-enrollment in other clinical trials is restricted, and requires approval of the Investigator. Study staff should be notified of co-enrollment status.
13. Need for use of the following medications from 21 days prior to the start of study drugs through the end of treatment:
    a. Hematologic stimulating agents (e.g. erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)
    b. Chronic systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonal antibodies (e.g., infliximab)
    c. Investigational agents or devices for any indication
    d. 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.

    Concomitant use of certain medications or herbal/natural supplements per PI expected to result in pharmacokinetic interactions resulting in increases or decreases exposure of study drug(s) as listed in

e. **Table** ~~of this~~ of this protocol.

SCHEDULE OF VISITS AND PROCEDURES

Screening and study visits may take place at the NIH Clinical Center, OP8 and other applicable departments. Screening and study visits may also occur at the Washington, DC Community Clinics, usually where participants receive their HIV or HCV care (if applicable).

NIH Study Team Roles at the Washington, DC Community Clinics: Members of the study team have been actively involved in patient care at the 3 community clinics (Unity's DC General, Walker-Jones, and Family and Medical Counseling Service). These clinics have signed an NIH IRB Reliance Agreement. The study team Investigators will act in a supervisory capacity for the site Primary Investigators (site PIs) and the research operations at the sites. The site PIs may see subjects at non-study visits and will communicate findings to NIH study team. The research coordinators will also oversee research operations in the clinics and at the NIH Clinical Center. The NIH/contractor study staff will see participants for scheduled visits, dose modifications, and study withdrawal.

If subjects are seen at The DC Clinics: All phlebotomy will be done by a phlebotomist working in the clinic or clinic staff. A specimen bag and specimen tubes will be prepared by NIH/contractor staff and will be labeled with the participant's first 3 initials of last and first name and study number. All laboratory studies will be performed by NIH and will be reviewed by NIH/contractor staff on a weekly basis. Copies of results will be sent to the primary care provider and scanned into the electronic medical record at the participating clinic.

Clinic staff will not participate in study-related visits unsupervised by NIH/contractor study staff. Participants will be given a calendar of scheduled study visits and will be informed that any clinic visits outside of scheduled study visits may be either unscheduled visits or non-study visits. All visits related to the treatment of HCV will be considered study related. Any other medical problems will be addressed by the participant's primary provider. Participants will receive this information when given the visit calendar.

The primary responsibility of the site AI's/ site collaborating investigators and the community clinics is to provide timely and effective communication regarding any potential adverse events if a subject/patient is seen for care outside of the normal study visit. Study visit notes will be documented in CRIMSON database or the electronic clinical database in the clinic.

8.1 Screening

Each patient will provide informed consent of his/her free will prior to commencement of any study procedures according to ICH and Code of Federal Regulations (CFR). Each patient will be provided a copy of the signed informed consent form.

After a patient has provided informed consent, the Investigator and other study personnel will determine if the patient is eligible for participation in the study. Screening may begin up to 8

weeks prior to dosing to allow for a possible liver biopsy if one has not been performed within 36 months prior to the first dose of study drug (Day 0), as specified in the inclusion criteria. An optional research liver biopsy will be offered to subjects during screening (and at end of treatment) with the aim of having paired research samples on up to 20 subjects on the study.

Screening will include a review of the inclusion/exclusion criteria and completion of all screening procedures as outlined in the Schedule of Tests. Screening tests within the last 8 weeks that have been done as part of other NIH studies (all labs) or at an outside facility (with the exception of chemistries, hCG, CBC with differential, coagulation studies) can be used if within the acceptable time frame.

The standard consent includes permission for HIV testing, liver biopsy, HLA testing, and storage of blood and tissue samples. HLA testing is necessary for this study if not on file, because this information will be invaluable for the evaluation of HIV and HCV-specific immune responses.

Screening procedures do not need to be repeated within the 8 week screening window unless clinically indicated.

8.2 History and Physical

All subjects will have a History and Physical during the screening process as part of final determination of protocol eligibility. Physical exams will be performed with study point visits at Week 4, Week 8 or 12, Week 24 and Week 48.

8.3 Starting GS-7977/GS-5885 FDC (Day 0)

The participant will be started on GS-7977/GS-5885 FDC on Day 0. Blood will be drawn for HCV viral loads, GS-7977 and GS-5885 levels, immunologic studies, and for storage prior to dosing. A pregnancy test will be done for females with childbearing potential and the pregnancy test must be negative prior to dosing with study drugs. Subjects will be asked to fill out a baseline adherence questionnaire and an electronic pill bottle cap, which records pill bottle openings will be placed on all study drug bottles. Assistance will be provided filling out the questionnaire as needed. The Day 0 procedures are summarized in Schedule of Tests (see 11.1).

8.4 Clinic Visits

On arrival at the clinic for study visits (does not include Day 1, 3, 5, 10, Week 3, Week 6, or Week 14 which are for lab collection only), subjects will have their vital signs obtained and females of childbearing potential will undergo a pregnancy test (if appropriate per visit day, see Schedule of Tests, clinical laboratories drawn, and a review of the study restrictions).

At each scheduled study visit (does not include Day 1, 3, 5, 10, Week 3, Week 6, or Week 14 which are for lab collection only), subjects will be asked about their state of health and use of any concomitant medication since the previous study visit. They will also be questioned about

AEs and their adherence with study restrictions. Subjects will be asked to fill out a follow-up adherence questionnaire and pill bottle openings will be recorded from the electronic bottle cap at Day 7, Week 4, Week 8 and Week 12. Assistance will be provided filling out the questionnaire as needed. Physical exams will be performed at Week 4, 8 or 12, 24 and 48. A complete list of study procedures and lab tests to be performed is in the Schedule of Tests.

In addition, subjects may be seen at unscheduled visits for a grade 3 or 4 AE or any unexpected AE (adverse event) or potential toxicity.

Some of the visits have a small amount of flexibility regarding when they need to occur. The visits in the first 12 weeks of the study have limited flexibility since they occur so frequently, so a visit skipped during this period will be considered a missed visit (unless the subject will be available/willing to come in for the visit). The window period for visit schedules is as follows:

- Days 0, 1, 3 (no window)
- Days 5, 7, 10, 14 (+/- 2 days)
- Weeks 3, 4 (+/- 3 days)
- Weeks 6, 8, 12 (+/- 7 days)
    - Optional Week 12 Liver Biopsy (+/-14 days)
- Weeks 14, 16, 20, 24, 36, 48, 60 (+/- 10 days)

8.5 Beck Depression Inventory

This questionnaire will be performed on Day 0, Week 2 and then Weeks 4, 8, 12, 16, 20, 24, 36, 48, and 60 to allow for comparisons with previous treatment regimens.

8.6 Week 4 Visit

During this visit, serum HCV RNA will be obtained to determine if virologic-response based treatment stopping criteria have been met. Subjects who fail to achieve >2 $\log_{10}$ HCV RNA drop at this time (unless >2 log drop would be below LLOQ) will be discontinued from therapy unless a review by the PI/LAI/Sponsor Medical Monitor determines otherwise (See Section 3.2)

8.7 Week 8 Visit

During this visit, serum HCV RNA will be obtained to determine if virologic-response based treatment stopping criteria have been met. Subjects who have serum HCV RNA ≥ LLOQ at this time will be discontinued from therapy.

8.8 Week 12 / End of Treatment Visit

Week 12 will mark the last dose of GS-7977/GS-5885 FDC to be administered. In addition, if a patient's participation terminates prior to Week 12, the Week 12 assessments may be performed at any end-of-treatment visit. An optional liver biopsy will be performed at this time. The additional liver biopsy data will serve to explore hepatic HCV RNA sequence

analysis. If subjects are undergoing the optional research liver biopsy, they will have safety labs completed prior to the procedure and imaging as medically indicated.

8.9 Week 24 Visit

All subjects will be assessed for sustained virologic response (SVR_{12}) at this visit.

8.10 Follow-up Visits after Study Drug Discontinuation

After discontinuation of the study drug, subjects will be followed at Weeks 14, 16, 20, 24, 36, 48, and 60. A serum pregnancy test will be done with each visit up to every 4 weeks, as appropriate. (Week 14 will include only collection of labs).

8.11 Viral Kinetic and Pharmacokinetic Sub Study Visits

Up to 20 subjects who enroll in the more intensive VK/PK study will be admitted to the Clinical Center for 36 hour sampling after study drug dosing. Samples will be stored, batched, and evaluated at a later date. Controlled administration and documentation of participant's drugs, at a minimum all HCV therapeutics, will be part of these visits.

Study subjects will undergo one sampling period for determination of plasma GS-7977 and GS-5885 concentrations as well as viral kinetics. Sampling will occur on Days 0-1 following administration of GS-7977/GS-5885 FDC. Subjects will have a hep-lock inserted for this blood sampling. Initial (pre-dose) blood samples will be collected prior to dosing. Subjects will then receive a tablet containing GS-7977/GS-5885 FDC. Blood samples will then be collected at 1, 2, 4, 8, 12, 24, and 36 hours after GS-7977/GS-5885 FDC dosing. All blood samples will be centrifuged and the plasma will be harvested and stored at -80°C until time of analysis.

8.12 Failures, Early Termination and Early Treatment Discontinuation

Participants who prematurely discontinue study agents due to toxicity will be followed closely for resolution of symptoms, until final outcome is known or until the end of the study follow-up period.

Participants requiring discontinuation as well as those who elect to discontinue study drugs prior to treatment completion for medical or personal reasons will continue to follow the general study schedule of assessments unless unwilling to do so, in which case they may be seen at least every 12 weeks for safety and research labs until the end of the study. The participant should have an end of treatment visit scheduled as soon as possible after all therapy is discontinued if willing. Any subject continuing in the study will be followed closely for resolution of active laboratory abnormalities or adverse events which are considered related to the study agents. Participants with undetectable HCV RNA at the end of treatment should continue to follow the scheduled SVR_2, SVR_4, SVR_8, SVR_{12}, and SVR_{24} visits following the date of their last dose of therapy while remaining undetectable.

Participants who have detectable HCV RNA at the end of treatment or who relapse post-treatment will be asked to return for additional visits at least every 12 weeks after the end of treatment for up to a total of 48 weeks to determine the persistence of any HCV populations with treatment-emergent substitutions conferring resistance to GS-7977 or GS-5885. Any subject continuing in the study will be followed closely for resolution of active laboratory abnormalities or adverse events which are considered related to the study agents. Assessments should be performed in accordance with the Schedule of Tests.

Subjects who meet any of the criteria for treatment failure will be offered treatment including an HCV protease inhibitor [Telaprevir or Boceprevir] + PegIFN/RBV.

Samples collected will be used to determine the durability of response or the dynamics of any changes in resistance conferring mutations. The reason for any early termination should be documented.

9 STUDY AGENT INTERVENTION

9.1 Disposition and Dispensation

Study agents will be distributed via the NIH Central Pharmacy according to standard pharmacy procedures.

All drug products will 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 will be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions will be followed to avoid direct eye contact or exposure through inhalation when handling study drugs.

9.2 Packaging and Labeling of Study Drugs

Each bottle will be individually labeled with the patient ID number, dosing instructions, recommended storage conditions, the name and address of the manufacturer, Investigational Use Statement ("Caution: New Drug – Limited by Federal [USA] Law to Investigational Use") and that the agent should be kept out of reach of children.

9.2.1 Formulation

GS-7977/GS-5885 fixed dose combination (FDC) tablets are blue or orange, diamond-shaped, film-coated tablets containing 400 mg of GS-7977 and 90 mg of GS-5885. The tablets are debossed with "GSI" on one side and "7985" on the other side. The GS-7977/GS-5885 FDC tablets contain the following inactive ingredients: lactose monohydrate, copovidone, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol, FD&C blue # 1/brilliant blue FCF aluminum lake or FD&C yellow # 6/sunset yellow FCF aluminium lake.

9.2.2 Packaging and Labeling

GS-7977/GS-5885 FDC tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains approximately 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.

Sufficient quantities of GS-7977/GS-5885 FDC tablets to complete the entire study will be shipped from Gilead Sciences Materials & Logistics (or its designee).

9.2.3 Storage and Handling

GS-7977/GS-5885 FDC bottles should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

All drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored prior to dispensing in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling GS-7977/GS-5885 FDC.

10 TREATMENT OF SUBJECTS

All subjects will receive 12 weeks of treatment with GS-7977/GS-5885 FDC.

GS-7977/GS-5885 FDC will be administered as a single pill at dose of 400 mg and 90 mg respectively orally once a day. The 1st dose will be taken at the study site on Day 0.

10.1 Dose Modifications / Toxicities

Maximal suppression of HCV replication is most likely accomplished by sustained delivery of antiviral agents at their current recommended doses. Dose reduction, however, would compromise this goal and predispose to the emergence of drug-resistant viral variants. Hence, no dose reduction will be allowed for GS-7977/GS-5885 FDC. If FDC is stopped due to toxicity, it must not be restarted.

10.1.1 Dose Modification for GS-7977/GS-5885 FDC

Dose modifications will not be permitted. If a subject forgets to take the medication at the correct time, it may be taken later in the day; however, no more than a single dose should be taken on any calendar day. The subject should resume the standing dosing schedule on the next day. Any treatment interruption or discontinuation will be recorded including the reason for the interruption or discontinuation.

10.2 Concomitant Medications

Concomitant medications taken within 30 days of screening through 30 days following discontinuation of study treatment need to be recorded in the source documents.

The following medications are prohibited from 21 days prior to the Day 0 visit through the end

of treatment:

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

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

- Investigational agents or devices for any indication

- Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e., P-gp) with study drug(s) may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug(s). Examples of representative medications which are prohibited from 21 days prior to Day 0 through the end of treatment are listed below:

  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.

Table 10: Disallowed and Concomitant Medications to be Used with Caution

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

a H2-receptor antagonists must not exceed a dose of 20 mg of famotidine or equivalent. Antacids that directly neutralize stomach pH (i.e. Tums, Maalox) may not be taken within 4 hours (before or after) of study drugs administration. The 21 day washout period does not apply to PPIs, which can be taken up to 7 days before the start of dosing.
b May result in an increase in the concentration of study drugs and/or concomitant medications
c May result in a decrease in the concentrations of study drugs.
d Use with study drugs may result in an increase in the concentration of the HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis

10.3 Acceptable HIV Antiretroviral Regimens

Acceptable antiretroviral (ARV) regimens at study enrollment include combination regimens consisting of medications from the following list: tenofovir (TDF), emtricitabine (FTC), efavirenz, raltegravir, and rilpivirine. Medications must be administered according to their manufacturer's prescribing information.

ARV regimens not on the above list are excluded from this study at enrollment, but may be allowed in the cases of HIV virologic breakthrough during the study period if approved by the PI and Sponsor Medical Monitor. HIV medications will not be supplied.

Specifically regarding ARVs, the following are recommended:

a) Rilpivirine in combination with emtricitabine and tenofovir should be administered with food if given as a fixed dose combination tablet.
b) Rilpivirine should be administered with a meal if administered as a separate tablet.
c) Efavirenz should be administered on an empty stomach and dosing is recommended at bedtime.

11 STUDY TESTS

Table : ~~C~~linical Laboratory Assessments from Blood Samples

Serum Chemistry	Hematology	Other
Alanine aminotransferase (ALT)* Albumin [#] Alpha fetoprotein (AFP) Alkaline phosphatase * Aspartate aminotransferase (AST) * Bicarbonate [+] Bilirubin, total, direct * Calcium [#] Chloride [+] Creatine Phosphokinase (CPK) C-reactive protein, highly sensitive Glucose [+] GGT Hemoglobin A1C Iron studies Lactate dehydrogenase (LDH) Lipase Lipids Magnesium [#] Phosphorus [#] Potassium [+] Sodium [+] Urea nitrogen [+] Creatinine [+]	Hematocrit Hemoglobin MCV MCH MCHC Platelet Count Red Blood Cell (RBC) Count White Blood Cell (WBC) Count Differential Neutrophils Lymphocytes Monocytes Eosinophils Basophils INR/PT/PTT	ANA HLA **Virology Panel:** HBsAg, Screening Anti-HBc Ab HBV DNA Quantitative Anti-HCV Ab HCV Genotype Assay Plasma HCV RNA Serum HCV RNA Pregnancy Test: Urine or serum Urinalysis Serum Uric Acid Fasting urine renal biomarker Beta-2 microglobulin (urine) **HIV** HIV-1/2 Multispot Western Blot Plasma HIV RNA levels Flow Cytometry (WhBl)

* *included in hepatic panel*
[+] *included in acute care panel*
[#] *included in mineral panel*

11.1 Schedule of Tests

Laboratory Studies
Screening tests that have been done as part of other NIH studies within the last 8 weeks or at an outside facility (with the exception of safety labs chemistries, hCG, CBC with differential, coagulation studies) can be used if within the 8 weeks prior to Day 0.

Serum Chemistry and Hematologic Profiles
Acute Care Panel, Hepatic Panel, Mineral Panel, Serum Uric acid, and CBCs (with differential) will be performed to monitor clinical status, document drug-related benefits and detect

potential drug-related toxicities. These may be done on screening, days 0, 7, 14, and every scheduled visit thereafter through Week 60. Additionally, non-fasting lipids may be done for research at Day 0, weeks 2, 4, 12, 24, 48, and 60 based upon blood volume availability by patient. Highly sensitive C-reactive protein may also be done at Days 0, 3, 7, weeks 2, 4, 8, 12, 24 and 36 again dependent upon blood volume availability by patient.

Prothrombin Time and Partial Thromboplastin Time
Measured by standard assay on screening, Weeks 12, prior to liver biopsy and Week 48.

Creatine Kinase, Lactate Dehydrogenase, Lipase, Amylase.
Measured by standard assay on screening and Weeks 4, 12, and 24.

Alpha Fetoprotein, Iron/Transferrin, Ferritin, ANA, GGT, Hepatitis Serologies, HCV genotype, Hemoglobin A1C, Urinalysis, HIV testing and HLA screening.
Measured by standard assay as part of screening (Historic HCV genotype, HIV testing if positive and HLA testing are acceptable). Hemoglobin A1C will be repeated at Day 0, Weeks 12, 24, 48 and 60.

Serum/Urine Pregnancy Test
Measured by standard assay on screening, on Day 0, and then every 4 weeks while on treatment and at every visit post treatment completion for women of childbearing potential. (Will not be done at Week 14).

Urinalysis
Including: Appearance, Blood, Color, Glucose, Leukocyte esterase, pH, Protein, Urobilinogen. Reflex to microscopic urinalysis if dipstick result is abnormal. This will be done at screening for all subjects and at Weeks 1, 2, 3, 4, 6, 8, 12, 14, 16, 20, 24 and 36 for those on ARVs

Special Urine Testing for Renal Monitoring
Fasting urine renal biomarker: beta-2 microglobulin will be performed at Day 0, weeks 2, 4, 12, 16, 24, and 36.

GS-7977 level / PSI-6206 (collected pre-dose) & GS-5885 level (collected pre-dose)
Measured at Days 0 and each scheduled study visit continuing through the End of Treatment visit. This will be drawn as trough levels at pre-dose prior to administering the morning dose of drugs. Blood samples for drug levels and pharmacokinetic analyses will be collected in provided tubes. Plasma samples will be analyzed for PSI-6206 or GS-7977 level using a validated method. Actual date and time of PK sample collection will be recorded.

Plasma HCV RNA Levels (HCV Viral Loads)
This will be done at screening, Day 0 and every scheduled visit subsequently. Measured by Abbott real-time PCR assay at screening with sample prep done by the Abbott M2000 SP allowing for a limit of quantification of 12 international units/mL.

Serum HCV RNA Levels (HCV Viral Loads)
Serum levels using the COBAS TaqMan HCV test v 2.0 (TaqMan HCV; Roche Molecular Systems, Inc., Branchburg, NJ, USA) are performed on the COBAS TaqMan 48 Analyzer with a lower limit of quantification of 4.3 international units/mL. This will be performed at screening, Week 4, Week 8, Week 12, and Week 24.

HCV Genotype Assay
This Siemens LiPA v2.0 assay will be performed using probes from both the 5' untranslated region and the core region allowing distinction between subtypes a and b of genotype 1, and between HCV G1 and G6c-l. It will be measured at screening if not on file.

HIV Antibody Screening
This screening will be performed using the BioRad Multispot HIV-1/-2 assay if no positive results are on file.

Plasma HIV RNA Levels
At screening, Days 0, 1, 3, 5 and 7, Weeks 2, 4, 8, and 12, and then every 12 weeks. This will be done using the Abbott m2000 real-time PCR assay with a lower limit of detection of 40 copies/mL.

Virological Tests
If HIV-1 virologic rebound is confirmed, HIV-1 genotype/phenotype will be determined using the available phenotype or genotype assays.

Phenotypic Flow Cytometry Analysis including CD4 Absolute (WhBL)
At screening, Day 7, Weeks 2, 4, 8, and 12 then every 12 weeks.

VK/PK Sub Study
Subjects will have blood drawn at time points 0, 1, 2, 4, 8, 12, 24, and 36 hours after administration of drug to assess drug levels, plasma HIV RNA levels, and HCV viral load levels. HIV RNA levels may be processed outside of real-time. (Timepoints 0 and 24 are collected for all study subjects).

Research tests
HCV Virologic Studies
Full length HCV genome pyro sequencing may be performed using the protocol as described and compared for variability of sequences [29].

DNA Methylation Studies
Promoter methylation status for candidate genes or at a whole genome level using methylation–specific PCR may be performed on tissue samples [30].

rs12979860 (IL28B) Genetic Variant
IL28B genetic variants have been shown to predict HCV treatment induced clearance [31]. The IL28B assay is a real-time PCR assay that utilizes 5-prime nuclease activity of a thermostable

polymerase and unique primers and SNP-specific probes to determine the genotype. Test results will not be used as inclusion or exclusion criteria, or to randomize subjects into treatment groups.

Immune Responses to HCV and HIV
Both humoral and cellular immunity against HCV and HIV will be estimated before and during treatment to assess the effect of HCV treatment on host immune response against HCV. We may also perform multiplex PCR assays to detect ISGs before and during treatment.

HCV Genotypic and Phenotypic Resistance Monitoring
Serum samples for genotypic and phenotypic monitoring will be collected

Resistance monitoring will be completed in all subjects who received study drug and were virologic failures as defined.

Subjects who are determined by sequencing and phenotypic analysis to have had mutations leading to GS-7977 resistance will be requested to return at 12 week intervals for up to 48 weeks after the last dose of study drug to determine the time for the resistant virus to return to background levels.

Genome-wide Transcriptional Profiling (Affymetrix Exon Array)
Exon arrays provide the most comprehensive coverage of the genome, including empirically supported and predicted transcribed sequences, enabling the discovery of previously unidentified novel events. We plan to design a low-density PCR array of 20-30 genes of most interest that are highly representative of the analysis group for validation.

Protein Profiling
We may screen sera and urine of all subjects for differential expression of protein peaks that may be associated with response to IFN sparing therapy using a high-throughput MALDI-5 approach and using multiplex cytokine arrays, which has the capability of detecting 600 different cytokines and other biologically relevant proteins [32] Simultaneously, we may employ classical proteomic analysis using Mass Spectra that will enable us to detect unknown proteins that may be associated with therapeutic response.

Extra Hepatic HCV Reservoir Quantitation
Extra hepatic HCV levels may be quantified using previously described assays developed in our laboratory. Serial measurement of PBMC associated HCV RNA will be determined and used to predict HCV relapse versus SVR_{12}.

Lucipherase Immunoprecipitation (LIPS) Assay
LIPS assay may be used to determine changes in qualitative and quantitative antibody responses to HCV and HIV antigens at baseline and while undergoing treatment. These titers have been previously described to have predictive ability for relapse during PegIFN/RBV treatment. We will use this assay to validate the effectiveness of this assay as a predictor of relapse.

Ultracentrifugation for HCV RNA
Low levels of HCV RNA may be present during therapy that cannot be detected by conventional assays. We will perform ultracentrifugation and concentration of serum for detection of HCV RNA in order to detect low levels of HCV RNA and may serve as a predictor of relapse [33].

12 HAZARDS/DISCOMFORTS/RISKS

12.1 Drugs

12.1.1 GS-7977 (sofosbuvir)
As of July 15, 2012, a total of 1,765 participants with HCV have been dosed with this drug as part of a study. When GS-7977 was used with interferon and RBV, it was well tolerated. Some patients taking GS-7977 with RBV & interferon experienced fatigue (seen in 6-14%), headache (6-13%), dizziness (6%), and nausea (6-27%). When GS-7977 was used with only RBV, the side effects were similar to what would be expected when using RBV by itself. For example, a few patients experienced anemia or a drop in red blood cell count, which is a known side effect from RBV. There may be additional side effects of GS-7977 that are not yet known.

12.1.2 GS-5885 (ledipasvir)
In studies done on those with HCV using GS-5885, more than 2 people experienced mild to moderate headache (20%), frequent daytime urination (20%), and upper respiratory infection. Other side effects seen less frequently were drowsiness, nausea and dizziness, which were seen in the same frequency as the group taking a placebo (sugar pill). In healthy volunteers, the following mild side effects were seen in more than two participants: headache, chest pain, feeling hot, constipation, rash with itching, and upper respiratory infection. One participant had more serious abdominal pain, but also had a history of abdominal pain prior to the study. No significant laboratory changes occurred in either group requiring any type of intervention. There may be additional side effects of GS-5885 that are not yet known.

One death occurred within 30 days of stopping study treatment in a 59 year old participant taking GS-5885 plus another study drug, GS-9451, along with interferon and ribavirin. This subject had a number of risk factors for a hemorrhagic stroke (bleeding in the brain) including a history of high blood pressure, male sex and age more than 55. This subject had a hemorrhagic stroke in a part of the brain usually associated with strokes caused by high blood pressure. However, as the timing of the stroke occurred during the study, it is considered as being related to each of the 4 drugs. This patient did not have abnormal lab values at the time of the stroke.

12.1.3 Resistance
An additional possible risk is the development of class resistance to NS5B inhibitors and NS5A inhibitors. Development of such resistance could affect future therapeutic options. However all efforts will be made to manage the development of class specific mutations that

could lead to cross resistance to other NS5B and NS5A inhibitors. This risk will be reduced by the detailed rescue plan outlined.

12.2 Procedures

12.2.1 Phlebotomy

The primary risks of phlebotomy include occasional bleeding or bruising of the skin at the site of needle puncture, and the sensation of transient lightheadedness or rarely, fainting and infection. The amount of blood drawn will be within the limits allowed for adult subjects by the NIH CC (Medical Administrative Policy 95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://internal.cc.nih.gov/policies/list_policies.asp?index=med_chrono).

12.2.2 Chest X-ray

A chest X-ray may be performed if medically indicated at the CC Radiology Department during the screening visit.

12.2.3 Electrocardiogram

This will be performed at screening for all participants and if medically indicated while on study. Subjects may experience itching, redness or irritation at the site of the electrodes.

12.2.4 Liver Biopsy

Liver biopsies performed within 36 months prior to Day 0, either the CC or outside institutions, will be acceptable as inclusion criteria based upon the written pathology report.

If a liver biopsy is required for inclusion, it can be performed at the CC of the NIH as part of the screening process, or may be performed as part of another NIH study (such as screening protocol 04-I-0086). Liver biopsies completed at NIH will be performed by interventional radiology (depending on availability).

A separate procedure consent will be obtained prior to each liver biopsy. An ultrasound of the liver or other imaging will only be performed if medically indicated prior to biopsies. Subjects will be admitted and released after the procedure according to the site policies for subjects receiving conscious sedation. The adverse effects of liver biopsy include both early and late manifestations. All side effects will be recorded and classified as minor and major complications. The minor complications include pain and vasovagal reaction. The major complications include clinically significant hemorrhage, bowel perforation, infection, pneumothorax, and rarely death. All subjects will be followed as outpatients after discharge from the site so as to detect any major late manifestations of complications associated with liver biopsy.

Participants will be asked to consider an optional research biopsy during the screening process, and again at the end of treatment. These biopsies would be for the purpose of obtaining paired research tissue samples from study participants.

13 HUMAN SUBJECT PROTECTIONS

Subjects will be fully counseled prior to entry into the study as to the potential risks of the study. Subjects who, in the opinion of the study team, do not fully comprehend these potential risks will not be offered participation in the study. Subjects will be monitored closely during their participation in the study.

13.1 Rationale for Subject Selection

The study will be advertised and posted on the NIH web site. All advertisements will be IRB approved before use. Untreated individuals with high CD4 counts will be selected to be treated as the likelihood of developing an indication that requires ART initiation for these subjects within a 3 month time period is very slim.

13.2 Gender, Ethnicity, and Race Considerations

Subjects will not be excluded based on gender. This study is designed to target an understudied demographic of the HCV epidemic in the United States in which current therapy has had poor results. The NIAID/DC-PFAP (DC Partnership for AIDS Progress) program is targeted largely to minority subjects in the District of Columbia in order to improve their access to clinical trials.

13.3 Children and Pregnant Women

This study will be limited to adults aged 18 years or older. Insufficient data are available to evaluate the safety and efficacy of GS-7977 or GS-5885 in the pediatric population. The risks of GS-7977 or GS-5885 during pregnancy have not been evaluated; therefore, pregnant or nursing women will be excluded from this study. Any woman of child-bearing potential must have a negative pregnancy test on Day 0 prior to receiving the first dose of GS-7977 and GS-5885 and use effective contraception throughout the study.

13.4 Contraception

Male subjects, as well as female subjects who are potentially capable of becoming pregnant, will be required to use at least 2 forms of contraception, including one barrier method, from 2 weeks prior to Day 0 until 30 days following the last dose of study drug. Female partners of male study subjects may rely upon hormonal contraceptives as one of the 2 forms, however female study subjects may not. As both drugs in the fixed dose combination are investigational study agents, prevention of pregnancy, in a subject or partner, during and after treatment is important as the risks are as yet unknown.

14 EVALUATION OF SAFETY

All enrolled subjects who have received GS-7977/GS-5885 FDC will be evaluated for safety. Safety will be assessed by physical examination, vital signs, hematology, and chemistries. The

severity of signs, symptoms, and AEs will be determined by using the 2004 DAIDS Toxicity Severity Scale, with edits made to allow for clinical center normal values.

14.1 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded.

14.2 Criteria for Premature Withdrawal and Stopping Rules

Subjects have the right to withdraw from the study at any time for any reason. Subjects who withdraw early or who are terminated from study by the Investigator will not be replaced unless they have received no study drugs. In addition to the criteria for stopping subject treatment described in 3.2 the Investigator or designee also has the right to withdraw subjects from the study for any of the following:

1. Development of life-threatening infection (requiring withdrawal of study drugs for more than 6 weeks) or malignancy.
2. CD4 count drops below 100 cells/mm^3
3. Participant's desire to leave study.
4. Pregnancy or breastfeeding.
5. Participant's non-compliance. If a subject misses 5 or more total study visits or > 3 weeks of study drug, the subject will be removed from the protocol by the study team.
6. Termination of study.
7. Development of liver decompensation with elevated Child Turcotte –Pugh's score of 8 or more.
8. If GS-7977/GS-5885 FDC is permanently discontinued by the pharmaceutical company.
9. Development of a medical condition, such as hepatocellular carcinoma, that in the opinion of the Investigator, it is in the subject's best interest to discontinue study drug even if criteria requiring drug discontinuation have not been met.
10. Request of the primary care provider or Investigator if s/he thinks the study is no longer in the best interest of the subject.
11. Clinical reasons believed life threatening by the physician.
12. If the subject is judged by the Investigator to be at significant risk.
13. Subjects may decide at any point not to have their samples stored. This will be treated as a withdrawal of the consent and in this case, the Principal Investigator will assure the destruction of all known remaining samples and report what was done to both the subject and to the IRB. This decision will affect the subject's participation in this protocol but may not affect participations in any other protocols at NIH.

15 BENEFITS/COMPENSATION/ALTERNATIVES

15.1 Benefits

Subjects may have the benefit of suppression and in some cases eradication of hepatitis C virus. Study drugs and study-related routine clinical monitoring tests will be provided free of charge to all subjects. The results of any specialized tests performed as part of the study will be made available to interested study subjects and their physicians.

In the event of injury occurring as a result of participation in this research study, subjects will be advised to seek immediate necessary medical care from their home physician and to contact the PI. Short-term medical care will be provided, as needed, for such injury. There is no provision for long-term free medical care or for monetary compensation from any injury from the physicians conducting this study, from the National Institute of Allergy and Infectious Diseases (NIAID), or from the Clinical Center of the NIH.

15.2 Alternatives

Subjects can receive hepatitis C treatment through their private physician or decide not to be treated at this time. Standard of care treatment would include weekly pegIFN with twice-daily RBV.

15.3 Compensation

Subjects will receive remuneration for the immediate costs associated with their study-related expenses like travel expenses, lodging, etc. as provided by the NIAID travel policy. Subjects will also receive financial compensation for the additional time associated with study related procedures such as research blood draws for the PK/VK sub study and liver biopsy. Subjects will be financially compensated according to the NIH Normal Volunteer Guidelines given the inconvenience of the procedures necessary to obtain the samples. The compensation will be as follows:

- Liver Biopsy with research specimens: $250 per biopsy (maximum of 2)
- VK sub study: $200 for each sampling day for total of $400
- Scheduled Study Visits: $20 grocery gift card

16 ADVERSE EVENT REPORTING AND TOXICITY MONITORING

16.1 Definitions

Adverse Event (AE): An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Adverse Reaction (AR): An adverse event that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR): An adverse event for which there is a reasonable possibility that the investigational agent caused the adverse event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which implies a high degree of certainty.

Serious Adverse Event (SAE):
A Serious Adverse Event is an AE that results in one or more of the following outcomes:

- death
- a life-threatening (i.e., an immediate threat to life) event
- an inpatient hospitalization or prolongation of an existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- a medically important event*

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but they may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected Adverse Event: An AE is unexpected if it is not listed in the Investigator's Brochure or Package Insert (for marketed products) or is not listed at the specificity or severity that has been observed. It is the responsibility of the IND Sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR): A SUSAR is a Suspected Adverse Reaction that is both Serious and Unexpected.

Unanticipated Problem (UP): An Unanticipated Problem is any event, incident, experience, or outcome that is:

1. unexpected in terms of nature, severity, or frequency in relation to:
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
   b. the characteristics of the subject population being studied; and
2. possibly, probably, or definitely related to participation in the research; and
3. places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (Per the IND Sponsor, an AE with a serious outcome will be considered increased risk.)

Unanticipated Problem That Is Not An Adverse Event (UPnonAE): An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study or significantly impact the integrity of the research data. Such events would be considered a non-serious UP.

For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

Protocol Deviation: Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as:

1. Those that occur because a member of the research team deviates from the protocol.
2. Those that are identified before they occur, but cannot be prevented.
3. Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as

1. Serious: Non-compliance that
    a. Increases risks, or causes harm, to participants
    b. Decreases potential benefits to participants
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

16.2 Investigator Assessment of Adverse Events

If a diagnosis is clinically evident, the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

All AEs occurring from the time of ingesting one dose of the medications through the end of study will be documented, recorded, and reported. The Investigator will evaluate all AEs with respect to **Seriousness** (criteria listed above), **Severity** (intensity or grade), and **Causality** (relationship to study agent and relationship to research) according to the following guidelines.

16.2.1 Severity Grading

The investigator will grade the severity of each AE according to the "Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse Events" (Version 1.0, December, 2004; Clarification August 2009), which can be found at: http://rsc.tech-res.com/document/safetyandpharmacovigilance/table_for_grading_severity_of_adult_pediatric_adverse_events.pdf

Some Grade 1 lab parameters on the DAIDS Toxicity Table (Fibrinogen, Potassium (low), Uric Acid (males only, elevated)) fall within the NIH lab reference range for normal values. These normal values will not be reported as grade 1 adverse events. The grade 1 values for these tests will be reported as follows (according to Section on Assessing Adverse Events, above):

- Fibrinogen: 100 - 176 mg/dL
- Potassium (low): 3.0 – 3.3 mmol/L
- Uric Acid (males): 8.7 – 10.0 mg/dL

Please note that changes in hemoglobin will be graded only by the absolute value for this study and not by change from baseline.

Adverse Events not found in the Toxicity Table will be assessed for severity and classified into one of the categories below:

- **Grade 1 (Mild)**: Event requires minimal or no treatment and do not interfere with the participant's daily activities.
- **Grade 2 (Moderate)**: Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 (Severe)**: Event interrupts a subject's usual daily activity or functioning and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- **Grade 4 (Potentially Life threatening)**: Events causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.
- **Grade 5 (Death)**

16.2.2 Causality

Causality (likelihood that the event is related to the study agent) will be assessed from the time study dosing begins until 30 days following the last dose considering the factors listed under the following categories:

Definitely Related
- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related
- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related
- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related
- does not have a reasonable temporal relationship

OR

- good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship

OR

- definitely due to an alternative etiology

Note: Other factors (e.g., dechallenge, rechallenge) should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The Investigator may revise the causality assessment as additional information becomes available.

16.3 Investigator Reporting Responsibilities to the Sponsor

16.3.1 Adverse Events

Line listings, frequency tables, and other summary AE data will be submitted to the IND Sponsor when needed for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

16.3.2 Serious Adverse Events

SAEs (regardless of relationship and whether or not they are also UPs) must be reported on the Safety Expedited Report Form (SERF) and sent to the Sponsor Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life threatening SAEs must be reported to the CSO within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness. SPONSOR CLINICAL SAFETY OFFICE CONTACT INFORMATION:

RCHSPB Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone 301-846-5301
Fax 301-846-6224
E-mail: rchspsafety@mail.nih.gov

16.3.3 Unanticipated Problems

Unanticipated Problems that are also adverse events must be reported to the CSO and sent by fax or e-mail attachment no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the Sponsor CSO. All UPs that are also adverse events will be reported to the CSO on the NIH Problem Report Form.

A copy of the RCHSPP Safety Expedited Report Form will also be sent by the site to the Gilead Sciences.

16.4 Documenting, Recording, and Reporting Adverse Events

Adverse events will be collected from the time the subject signs the informed consent document through the end of the study follow-up period.

At each contact with the subject as outlined above, information regarding AEs will be elicited by appropriate questioning and examinations and will be:

- immediately documented in the subject's medical record/source document. Source documents will include: progress notes, laboratory reports, consult notes, phone call summaries, survey tools and data collection tools. Source documents will be reviewed in a timely manner by the research team. The onset date, the end date, the severity of each reportable event, and the Investigator's judgment of the AEs relationship to GS-7977 and GS5885 will also be recorded.
- Recorded in the electronic database,

  and
- Reported as outlined below

16.5 Follow-up of Adverse Events and Serious Adverse Events

Adverse events that occur following enrollment of the subject (by signing the informed consent) will be followed at a minimum until a final outcome is known (resolution of the AE or a return to baseline laboratory value) or until the end of the study follow-up period (Week 60).

SAEs that occur after the study follow-up period that are reported to and are assessed by the Investigator to be possibly, probably, or definitely related must be reported to the CSO, as described above.

16.6 Reporting Procedures to the NIAID IRB

16.6.1 Expedited Reporting to the NIAID IRB

Serious and non-serious Unanticipated Problems, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. Serious Adverse Events that are possibly, probably, or definitely related to the research will be reported to the NIAID IRB within 7 days of investigator's awareness, regardless of expectedness.

16.6.2 Waiver of Reporting Anticipated Protocol Deviations, Expected UPnonAEs and Deaths to the NIAID IRB

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected adverse events will not be reported to the IRB unless they occur at a rate greater than that known to occur in Hepatitis C and HIV. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported as though they are unanticipated problems. Deaths related to the natural history of hepatitis C and HIV will be reported at the time of continuing review.

16.6.3 Annual Reporting to the NIAID IRB

The following items will be reported to the NIAID IRB in summary at the time of continuing Review:

- Serious and non-serious unanticipated problems
- Expected serious adverse events that are possibly, probably, or definitely related to the research
- Serious adverse events that are not related to the research
- All adverse events except expected AEs and deaths granted a waiver of reporting.
- Serious, continuing, and minor non-compliance
- Serious and Non-serious protocol deviations which in the opinion of the Investigator should be reported
- Any trends or events which in the opinion of the Investigator should be reported

Reporting a Pregnancy

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be SAEs. Pertinent obstetrical information of all pregnancies will be reported to the CSO via fax or email within 3 business days from site awareness of the pregnancy. Study drug must be stopped immediately. The participant will be advised to notify her obstetrician of study agent exposure.

Pregnancy outcome data (e.g., delivery outcome, spontaneous, or elective termination of the pregnancy, presence of absence of birth defects, congenital abnormalities, or other complications) will be reported to the CSO within 3 business days of the site's awareness on a protocol-specified form.

16.7 Sponsor's Reporting Responsibilities

Serious and unexpected suspected adverse reactions (SUSARs) as defined in 21 CFR 312.32 and determined by the IND Sponsor will be reported to FDA and all participating Investigators as IND Safety Reports.

The IND Sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

AEs that are also UPs will be summarized by the IND Sponsor and distributed to Investigators.

16.8 Safety Oversight

16.8.1 Safety Review and Communications Plan (SRCP) and Transfer of Regulatory Obligations (TORO)

A Safety Review and Communication Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the Principal Investigator and the IND Sponsor Clinical Safety Office (CSO), which delineates the safety oversight responsibilities of

the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

The IND Sponsor and the PI have signed a formal TORO/SRCP which documents that the PI has accepted the responsibility for periodic safety surveillance assessments as outlined in § 21CFR312.32(b).

16.8.2 Sponsor Medical Monitor

A Medical Monitor, representing the IND Sponsor (RCHSPB), has been appointed for oversight of safety in this clinical study. The Sponsor Medical Monitor will be responsible for performing safety assessments as outlined in a Safety Review and Communications Plan (SRCP).

16.9 Safety Monitoring Plan

Ongoing Safety Monitoring by the Study Team: Cumulative safety data will be monitored by the study team (PI, Lead Associate Investigator (AI) and study coordinator (SC)) as per the SRCP. Upon recognition of any safety concerns, a teleconference may be held with the SMM to discuss the concern. The PI will notify the Safety office when enrollment begins and will provide verification of safety assessments to the SMM as per the SRCP.

Additionally, the PI will be responsible for submitting the NIAID IRB Continuing Review package and will provide the necessary safety data for the FDA IND Annual Report as directed by the IND Sponsor Safety Office.

16.10 Specific Criteria to Pause Enrollment for Virologic/Therapeutic Failure and for Resistance

16.10.1 Virologic/Therapeutic Failure Criteria to Pause Enrollment

- Criteria 1: 5 participants experience treatment failure while receiving treatment (see 3.2.1)

16.10.2 Resistance Criteria to Pause Enrollment

- Criteria 2: 5 subjects have new detectable resistance to GS-7977 at viral breakthrough or at viral rebound after treatment or
- Criteria 3: 5 subjects have new detectable resistance to GS-5885 at viral breakthrough or at viral rebound after treatment

If enrollment is paused due to virologic failure or resistance as outlined above, further dosing will necessitate FDA review and approval.

16.11 Specific Criteria to Halt Enrollment for Safety

Enrollment will also be halted if the study Sponsor or PI decides to stop or cancel the study or if the IRB or the FDA requests that the study be stopped. New patient accrual will be temporarily halted and a full report sent to the IRB in the event of the occurrence of any one of

the following listed below. If a halting requirement is met, a description of the event(s) or safety issue must be reported by the PI within one business day to the Sponsor CSO by fax or email.

We will evaluate and consider stopping enrollment of the study if posterior probability that the regimen toxicity (Grade 3 or 4 toxicity) is greater than 20% exceeds 0.90. Stopping means that serious consideration will be given to modifying or terminating the protocol. Evaluation boundaries are given in the table below. Beta prior distributions are used for these calculations with parameters alpha, beta = 1.2, 4.8.

Table 6~~12~~Group Sequential Monitoring Plan

No. of subjects	Evaluation if number of subjects with Grade 3 toxicity reaches or exceeds:
8	4
16	6
25	9

The monitoring plan was evaluated by simulation. Based on 10,000 repetitions, if the true regimen failure rate is 0.2, we will stop about 12% of the time. However if the true regimen failure rate is 0.4, we will stop about 80% of the time. This is acceptable performance for a stopping rule. New subject accrual will also be temporarily stopped if one death definitely, probably, or possibly related to the study drugs is observed at any time. The decision to restart enrollment will be made by the PI with input from the Sponsor Medical Monitor. The Investigator will notify the IRB of the decision to resume the study.

Dosing will be discontinued if 3 or more subjects develop a definitely or probably related Grade 4 toxicity (excluding ALT and AST elevations). Further dosing will require review and approval from the FDA. Grade 4 toxicities that result from patient non-compliance with medications for unrelated events will not be considered toward discontinuation.

16.12 If Criteria to Pause Enrollment are Met

If criteria 1, 2, or 3 are met, the viral kinetic, pharmacokinetic and resistance data will be reviewed with the study team and sponsor, and a decision will be made as to whether to continue further enrollment.

Participants receiving study drugs at this time will continue receiving treatment and follow-up visits through Week 60.

For all subjects who meet criteria 1, 2, or 3 the cause of treatment failure will be evaluated by viral sequencing and GS-7977 and GS-5885 drug levels. Subjects who meet any of the criteria for treatment failure will be offered treatment including an HCV protease inhibitor [Telaprevir or Boceprevir] + PegIFN/RBV.

16.13 Management of Potential Nephrotoxicity in Subjects on ARVs

All subjects with eGFR < 50 mL/min must have serum creatinine and subject weight measured again as soon as feasible within 5 calendar days of receipt of results. If a subject has confirmed eGFR < 50 mL/min the ARV regimen should be modified as necessary per product label (e.g. dose modification for TDF).

All subjects with a change from baseline serum creatinine of ≥ 0.4 mg/dL must have a serum creatinine repeated with a concurrent urinalysis within two weeks of result. Upon confirmation of change from baseline serum creatinine, a plan will be promptly documented and reported to the Sponsor Medical Monitor.

All subjects with a negative or trace proteinuria at baseline that develops ≥1+ proteinuria on urinalysis must have a concurrent urinalysis repeated within two weeks of result. Upon confirmation of new proteinuria, a plan will be promptly documented and reported to the Sponsor Medical Monitor.

17 STUDY SITE MONITORING

This is an open label study using an investigational agent. The study will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP), and any applicable regulatory requirement(s). The Investigator (and/or designee) will make study documents (e.g., consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB, the FDA and monitors under contract to the NIAID/RCHSPB.

As per ICH-GCP 5.18 and 21 CFR 312.50, "clinical protocols are required to be adequately monitored by the study sponsor." This study monitoring will be conducted according to the *NIAID Intramural Clinical Monitoring Guidelines*. Monitors under contract to the NIAID/RCHSPB will visit the clinical research site to monitor all aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information (including CRIMSON data abstracts) with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure Investigators' compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (FDA and Office for Human Research Protections [OHRP]) and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the Investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

A specific protocol monitoring plan will be discussed with the Principal Investigator and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status and regulatory obligations.

18 STORED SAMPLES AND FUTURE RESEARCH

Extra blood and tissue samples will be stored using a code name that only the study team can link back to the subjects. These samples will be stored for future research. Other Investigators may want to pursue additional research using these stored samples. If so, the NIH study team will seek IRB approval prior to sharing of any samples. After approval, the NIH study team may send these samples to them, along with the coded label. Investigators will use stored samples only for research. At the completion of the protocol, samples and data will either be destroyed, or after IRB approval, will be transferred to another existing protocol. The IRB will be notified in writing of any loss or destruction of stored samples.

18.1 Research Use of Stored Human Specimens and Data

Samples and data collected under this protocol may be used to study mechanisms involved in the hepatitis C treatment response among subjects. Genetic testing may be performed.

Access to research samples will be limited using a locked freezer. Samples and data will be stored using codes assigned by the Investigators' designees. Data will be kept in a password-protected computer. Only Investigators and their designees will have access to the samples and data. Samples will be stored and tracked utilizing the NCI-FCRF Repository operated by SAIC-Frederick.

In the future, other Investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples. Any clinical information shared about the sample with or without patient identifiers would similarly require prior IRB approval. The research use of stored, unlinked or unidentified samples may be exempt from the need for prospective IRB review and approval. Exemption requests will be submitted in writing to the NIH Office of Human Subjects Research, which is authorized to determine whether a research activity is exempt.

Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that meets the definition of Protocol Deviation and/or compromises the scientific integrity of the data collected for the study, will be reported to the NIAID IRB

Any loss or unanticipated destruction of >25% samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) will be reported to the IRB.

Additionally, subjects may decide at any point not to have their samples stored. This will be treated as a withdrawal of the consent and in this case, the Principal Investigator will assure the destruction of all known remaining samples and report what was done to both the subject and to the IRB. This decision will affect the subject's participation in this protocol but may not affect participation in any other protocols at NIH.

19 DATA MANAGEMENT PLAN

All research data and results will be carefully recorded using data collection forms and/or the NIAID CRIMSON system to be saved and allow for continuous access. Further, all collected data will be saved to a password-protected computer spreadsheet (Microsoft Excel) for analysis and review. All research data, including the primary experimental results, will be retained for a minimum of 5 years to allow for analysis and repetition by others of published material resulting from the data.

Corrections to electronic data systems shall be tracked electronically (password protected or through an audit trail) with time, date, individual making the correction, and what was changed. The Investigator is responsible for assuring that the data collected is complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected**,** and must be signed and dated by the person recording and/or reviewing the data. Source documents include all recordings of observations or notations of clinical activities, and all reports and records necessary for the evaluation and reconstruction of the clinical trial. Source documents include, but are not limited to, the subject's medical records, laboratory reports, x-rays, radiologist's reports, biopsy reports, ultrasound photographs, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study. Data for the CRIMSON Data System will be collected directly from subjects during study visits, or will be abstracted from subjects' medical records. The subject's medical record must record his/her participation in the clinical trial and study treatment (with doses and frequency) and any other medical interventions or treatments administered, as well as any adverse reactions experienced during the trial.

Demographic information (ethnicity, sex, etc.) and standard laboratory results (serum chemistries, etc.) will be collected in an electronic database on an ongoing basis as volunteers are enrolled. Other experimental data including IL28B genotyping, and serum drug concentrations will be analyzed and reported in batches. Standard laboratory results will be accessed from CRIS by the PI, LAI, the study coordinator, certain Associate Investigators, and the clinic staff caring for the patient only. All non-clinical results and stored samples will be recorded and maintained using only the subject's code for identification purposes. Primarily the PI and Study Coordinator will perform data collection and monitoring.

Data management, including the decision to publish, will be the responsibility of the PI. After publication, all research data that form the basis of that communication will be made available promptly and completely to all responsible scientists seeking further information. Exceptions include those requests that would infringe on confidentiality of clinical data or if unique materials were obtained under agreements that preclude their dissemination.

20 STUDY RECORDS RETENTION

The Investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study subjects is to be maintained by the Investigators in a secure storage facility for a minimum of 3 years per NIAID policies. The FDA requires study records to be retained for up to 2 years after

marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB/EC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by federal, state, and local law.

Should the Investigator wish to assign the study records to another party and/or move them to another location, the Investigator must provide written notification of such intent to RCHSPB/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. NIAID must be notified in writing and written NIAID/RCHSPB permission must be received by the site prior to destruction or relocation of research records.

21 ANONYMITY AND CONFIDENTIALITY

As each volunteer provides consent and is then enrolled, he or she will be allocated a unique study number. To ensure subject confidentiality, these numeric codes will substitute for personal identifiers on non-clinical research results and stored samples. The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted is prohibited. The results of the research study may be published, but participants' names or identities will not be revealed. Records will remain confidential. To maintain confidentiality, the PI will keep records in locked cabinets and the results of tests will be coded to prevent association with subject names. It is expected that this data will be reported in scientific journals and scientific meetings. Confidentiality of participants will be maintained in all forms of reporting. Participants will be informed in general terms of the results as soon as practical.

22 CONSENT PROCEDURES

Consent forms will be provided to the participant for review and the protocol will be discussed verbally between the participant and one of the Investigators or their designee during the screening visit. No screening procedures or tests for this study will be done before the consent process is completed. The participant will be given ample opportunity to discuss any questions. The subject will be given a copy of the signed document.

Illiterate English Speaking Participants

As the majority of the patient populations from which the study participants are drawn are literate, written consent will typically be provided. However, this population does have a significant rate of illiteracy, and oral consent will be obtained for illiterate participants as consistent with NIH MAS Policy M77-2 without separate IRB approval for each specific use. At Continuing Reviews, the NIAID IRB will be informed of the number of illiterate participants who provided consent verbally.

Non-English Speaking Participants

If a non-English speaking participant is unexpectedly eligible for enrollment, the participant will be provided with the CC Short Written Consent Form for Non-English Speaking Research

Participants in the participant's native language and a verbal explanation of the purpose, procedures and risks of the study as described in MAS Policy M77-2, 45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. Preferably, the interpreter will be someone who is independent of the participant (i.e., not a family member). Interpreters provided by the CC will be used whenever possible. The interpreters will translate the IRB-approved English consent form verbatim and facilitate discussion between the participant and investigator.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the participant to take home.

The investigator obtaining consent will document the consent process in the participant's medical record (CRIMSON), including the name of the interpreter. Further, all instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language within an IRB approval period, this will be reported to the IRB immediately.

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