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RESOLVE Protocol

Safety, Tolerability and Efficacy of Sofosbuvir, Velpatasvir, and Voxilaprevir in Subjects with previous DAA experience

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ABBREVIATIONS

Abbreviation	Term
3TC	Lamivudine
ABC	Abacavir
AE	Adverse event
AI	Associate investigator
ALT	Alanine aminotransferase
APRI	AST to platelet ratio index
AR	Adverse Reaction
ARV	Antiretroviral therapy
AST	Aspartate transaminase
BMI	Body mass index
c	Cobicistat
CBC	Complete blood count
CFR	Code of federal regulations
CSO	Clinical safety office
CyTOF	Cytometry by time-of-flight
DAA	Direct acting antiretroviral
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DRV	Darunavir
EBR	Elbasvir
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ESAs	Erythropoiesis stimulating agents
ETR	End of Treatment Response
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed dose combination
GCP	Good Clinical Practices
GCSF	Granulocyte colony stimulating factor
GS	Gilead Sciences, Inc.
GT-1, -2, and -3	Genotype 1,2, and 3
GZR	Grazoprevir
HbA1c	Hemaglobin A1C
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigator's Brochure

IL28B	Interleukin 28B
IND	Investigational new drug application
IFN	Interferon
IRB	Institutional Review Board
ISR	Interferon sensitive gene
LDV	Ledipasvir
LIL	Liver infiltrating lymphocytes
MM	Medical Monitor
NS3/4	Non-structural proteins 3 and 4, protease
NS5A	Non-structural protein 5A
NS5B	Non-structural protein 5B, polymerase
NSAID	Nonsteroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cells
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PPI	Proton pump inhibitor
PrOD	Paritaprevir (co-dosed with ritonavir [paritaprevir/r]), ombitasvir, dasabuvir
RAL	Raltegravir
RAV	Resistance Associated Variants
RBV	Ribavirin
r	Ritonivir
RPV	Rilpivirine
RNA	Ribonucleic acid
SAE	serious adverse event
SAR	Suspected adverse reaction
SC	Study Coordinator
SERF	Safety expedited report form
SIM	Simeprevir
SOF	Sofosbuvir
SUSAR	Serious and unexpected suspected adverse reaction
SVR	Sustained virologic response
SVR_4	HCV RNA < LLOQ 4 weeks after completion of treatment
SVR_8	HCV RNA < LLOQ 8 weeks after completion of treatment
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
TPO	Thrombopoeitin
ULN	Upper limit of normal
UP	Unanticipated problem
UPnonAE	Unanticipated problem that is not an adverse event
VEL	Velpatasvir
VK	Viral kinetics

VOX	Voxilaprevir
WBC	White blood cell

ABBREVIATIONS FOR HCV STUDY AGENTS & FDA APPROVED AGENTS

GS-7977, SOF	Sofosbuvir, nucleotide NS5B inhibitor, an FDA approved treatment for HCV
GS-5816, VEL	Velpatasvir, second generation NS5A inhibitor, an HCV study agent
GS-9857, VOX	Voxilaprevir, second generation NS3/4A protease inhibitor, an HCV study agent
SOF/VEL/VOX FDC, Vosevi	Fixed dose combination of sofosbuvir, an FDA-approved NS-5B nucleotide inhibitor, 400mg; velpatasvir, an FDA-approved NS5A inhibitor, 100mg; and GS-9857, a second generation FDA-approved NS3/4A protease inhibitor, 300 mg
IFN, PegIFN, PEG	Interferon (known as pegylated IFN or pegIFN)
RBV	Ribavirin, an FDA approved standard of care treatment for HCV when used with Interferon and/or an additional agent
Viekira Pak, PrOD	Ombitasvir, paritaprevir (co-dosed with ritonavir [paritaprevir/r]), dasabuvir

PRÉCIS

Chronic hepatitis C virus (HCV) infection is a major public health problem with an estimated 180 million people infected worldwide. In the United States, an estimated 4.1 million people are infected, and HCV is the principal cause of death from liver disease and leading indication for liver transplantation. While treatment with combination directly acting antiviral agents (DAAs) represents a dramatic improvement over previous therapies in safety, tolerability and efficacy, these therapies are not universally effective and some patients fail to achieve sustained virologic response (SVR). As DAA medications become more widely available outside clinical trial settings, it is important to evaluate retreatment strategies in patients who fail combination DAA therapy. As of yet, the ideal retreatment strategy and predictors of response in these patients have not yet been determined. In this trial, we will test the safety, tolerability, and efficacy of treatment with sofosbuvir (an approved NS5B inhibitor), velpatasvir (formerly GS-5816, a second generation NS5A inhibitor) and voxilaprevir (formerly GS-9857, an NS3/4A protease inhibitor) (trade name Vosevi) in HCV infected patients with early and advanced liver disease, including those coinfected with HIV and or hepatitis B, who have failed previous combination DAA therapies. The findings from this study will aid in our understanding of determinants of response to combination DAA regimens in HCV infected patients for subgroups of patients with early as compared to advanced liver disease, in patients with HCV GT 1 subtypes a and b, in patients coinfected with HIVand or hepatitis B, and in patients previously failing different combination DAA therapies**.**

STUDY SUMMARY

Title:	Safety, Tolerability and Efficacy of Sofosbuvir, Velpatasvir and Voxilaprevir in Subjects who failed previous DAA Therapy
Short Title:	RESOLVE Protocol
Clinical Phase:	Phase IIb
IND Sponsor:	IHV/University of Maryland SOM
Principal Investigator:	Eleanor Wilson, MD, MHS
Sample Size:	N=120 N=20 participants in a pharmacokinetic/viral kinetic sub study 10 with and 10 without cirrhosis
Accrual Ceiling:	N=150
Study Population:	HCV, genotype 1, infected subjects, with or without HIV, who have previously been treated with unsuccessful combination DAA-based therapy
Accrual Period:	1 year
Study Design:	Open-label phase IIb study to examine safety, tolerability, and efficacy of SOF/VEL/VOX in subjects with chronic HCV infection who have failed to eradicate HCV despite previous combination DAA therapy. Subjects with cirrhosis and those without cirrhosis will receive 12 weeks of therapy and will be stratified by initial combination DAA therapy.
Study Agents:	SOF/VEL/VOX is a fixed dose combination of sofosbuvir, an FDA-approved NS-5B nucleotide inhibitor, 400mg; velpatasvir, an FDA-approved NS5A inhibitor, 100mg; and voxilapravir, an FDA approved NS3/4A protease inhibitor, 100 mg, dosed once daily.
Treatment Duration:	Subjects with and without cirrhosis will receive 12 weeks of therapy
Primary Objectives:	To assess the safety, tolerability, and efficacy of 12 weeks of SOF/VEL/VOX in subjects with chronic HCV infection who have previously failed FDA approved DAA-based therapy, with compensated cirrhosis and without cirrhosis, with and without HIV coinfection.
Secondary Objectives:	1. To evaluate the immunologic, virologic, and host genetic/proteomic predictors of response to therapy with SOF/VEL/VOX in HCV infected subjects who have failed previous combination DAA-based therapy. 2. To compare HCV quasispecies and resistance associated variants (RAVs) at baseline and throughout treatment, especially in the case of relapse or

breakthrough, and assess the influence of past DAA experience on evolution of RAVs and virologic response to treatment
3. To determine the kinetics of plasma HCV RNA during treatment and after treatment discontinuation
4. To evaluate the effect of SOF/VEL/VOX on peripheral markers of T cell activation
5. To evaluate the proportion of subjects whose alanine aminotransferase (ALT) levels normalize between baseline and $SVR_{4,12,24}$.
6. To delineate the precise effects of specific HCV lifecycle inhibitors on host immune recovery in patients receiving single (SPARE), or combination DAA-based therapy (RESOLVE).

Primary Endpoints:

The incidence of grade 3 and 4 adverse events (AEs) following 12 weeks of treatment with SOF/VEL/VOX in HCV infected subjects who have previously failed FDA approved DAA-based therapy.

The proportion of subjects who achieve sustained virologic response 12 weeks after completion of treatment, SVR_{12}.

Secondary Endpoints:

1. Correlation and comparison of the slope of HCV viral load decline (early viral kinetics) with end of treatment response (ETR) and sustained virologic response 4, 12, and 24 weeks post treatment in patients with early and advanced stage liver disease, in patients with HCV GT 1 subtypes a and b, and in patients who previously failed different combination DAA therapies.

2. Comparison of HCV viral kinetics (VK) and pharmacodynamic (PD) parameters in subjects who achieve SVR and those who do not.

3. Percentage and comparison of subjects who achieve ETR, SVR_4 and SVR_{24} in patients with early and advanced stage liver disease, in patients with HCV GT-1 subtypes a and b, and in patients failing different combination DAA therapies.

4. Comparison of pharmacokinetics (PK) of SOF/VEL/VOX in subjects who achieve SVR and those who do not.

5. Comparison of differential interferon sensitive gene (ISR) response to therapy in patients who do and do not attain SVR, as well as in subgroups of patients with early as compared to advanced liver disease, in patients with HCV GT-1 subtypes a and b, and in patients failing different combination DAA therapies.

6. Detection of host genetic/proteomic factors associated with differential response to SOF/VEL/VOX overall and in subgroups of patients with early and advanced stage liver disease, in patients with HCV GT-1 subtypes a and b, and in patients failing different combination DAA therapies.

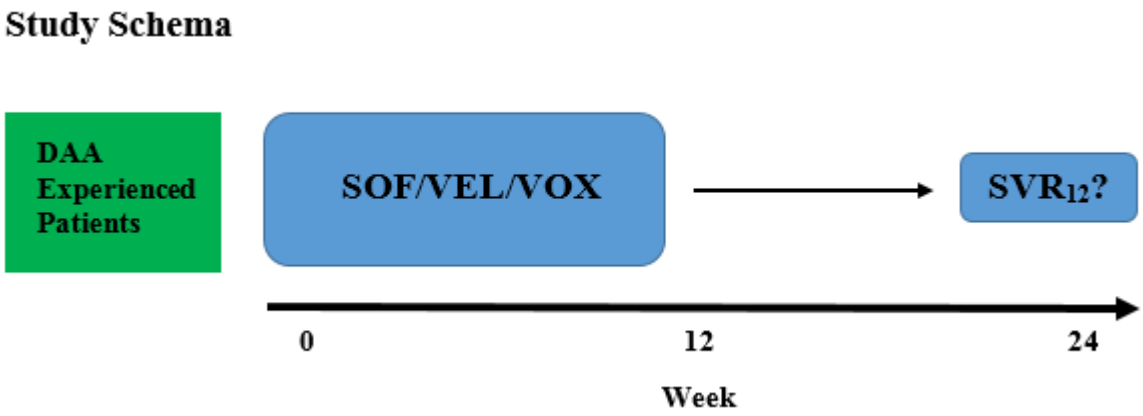
7. Evaluation of HCV quasispecies fitness at baseline, during therapy, and at the time of viral relapse to determine the emergence of resistant HCV and immunologic (adaptive and innate) correlates of SVR.

8. Changes in HCV specific CD8 responses in patients with cirrhosis and not with cirrhosis.

9. Changes in HCV specific immune responses in patients treated with single (NS5B) DAA versus dual (NS5B + NS5A) versus triple combination DAA (NS5B + NS5A + NS30) using samples from SPARE, SYNERGY, and this study

Study Duration: Subjects will be evaluated by 10 clinic visits over approximately 38 weeks.

STUDY SCHEMA



1 INTRODUCTION AND RATIONALE

1.1 CHRONIC HEPATITIS C INFECTION: BACKGROUND

Chronic hepatitis C virus (HCV) infection is a major public health problem with an estimated 180 million people infected worldwide[1]. In the United States, an estimated 2.7 million people are infected[2]. HCV is the principal cause of death from liver disease and leading indication for liver transplantation in the Western world[3,4]. According to the CDC, in 2013, over 19,000 deaths were attributed to HCV infection and its complications, although this is likely an underestimate, by as much as five fold by some reports[5]. HCV now surpasses human immunodeficiency virus as a cause of death within the United States[6]. Of those patients with chronic HCV infection, as many as 20% are estimated to go on to develop complications including cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC)[7]. Until recently, standard of care treatment with pegylated interferon (pegIFN) and ribavirin (RBV) was associated with low response rates[8,9], from 27-39%, depending on the patient population, but was associated with complicated drug interactions and high rates of toxicity, including psychiatric illness, constitutional side effects, and cytopenias.

Recent advances in therapy have dramatically improved the prognosis of those with chronic HCV infection. The development of directly-acting antivirals (DAAs) represents a major advance in HCV treatment. Modern combination DAA-based regimens are shorter in duration, better tolerated, and result in higher sustained virologic response (SVR) rates than prior therapies. The safety and efficacy of combination DAA-based regimens has been demonstrated in patients with a broad range of disease stages from patients naïve to HCV therapy with minimal fibrosis to patients with advanced fibrosis and cirrhosis who have failed previous interferon-based therapies[10-15]. Even patients failing early single DAA therapies have shown high response rates to combined therapy with a fixed-dose combination (FDC) of ledipasvir (LDV) and sofosbuvir (SOF)[16], with excellent safety and tolerability profiles [17,18].

1.2 RATIONALE FOR NEW COMBINATION DAA THERAPIES

Despite the high efficacy of currently approved combination DAA therapies, some patients do not successfully clear HCV, either due to non-adherence, viral resistance, virologic breakthrough, or virologic relapse. The ideal strategy for pursing HCV clearance in these patients remains uncertain, and careful clinical trials assessing the safety and efficacy of retreatment strategies in these patients need to be conducted. While some groups have demonstrated high response rates (>90%) after previous failure of a short course regimen[19], despite the presence of resistance associated HCV variants (RAVs), others have reported low treatment response rates, in some cases less than 50%, related to treatment emergent NS5A RAVs[20]. In these small studies, it is unclear whether viral, treatment or host factors drive the low response rates. This study seeks to address this question and determine whether a universal "salvage" regimen would be safe, tolerable, and effective in patients failing a diverse array of combination DAA-based therapies.

Sofosbuvir, a nucleotide analogue chain terminating inhibitor of the NS5B HCV viral polymerase, was approved by the FDA in December 2013, and of note, treatment emergent resistance to NS5B inhibitors has not been observed in patients failing SOF-based regimens[21]. The investigational agents Velpatasvir (VEL, formerly GS-5816) which inhibits the NS5A protein, and Voxilapravir, the NS3/4 viral protease, have shown promise in early clinical studies[22-24], including efficacy of approximately 90% in patients who had previously failed

combination DAA-based therapy[25, 30,31]. In patients who have previously failed combination DAA therapy, including LDV/SOF, paritaprevir/ritonavir/ombitasvir/dasabuvir (PrOD), and elbasvir/grazoprevir (EBR/GZR)-based combination DAA regimens, we hypothesize that retreatment with at least two novel drugs will be safe and effective, overcoming baseline or treatment emergent viral resistance and inhibiting viral replication.

1.3 RATIONALE FOR SELECTION OF ALLOWED CONCOMITANT ARV REGIMENS

HIV ARV regiments allowed in this study include emtricitabine (FTC)/tenofovir alafenamide (TAF), FTC/tenofovir disoproxil fumarate (TDF) , or abacavir (ABC)/lamivudine (3TC) plus:

- Ritonavir (r) and darunavir (DRV), or
- Raltegravir (RAL), or
- Elvitegravir (EVG)/Cobicistat (c), or
- Rilpivirine (RPV)

Fixed dose combinations of approved regimens (ie, FTC/TAF [Descovy], EVG/c/FTC/TAF [Genvoya], RPV/FTC/TAF [Odefsey], FTC/TDF [Truvada] EVG/c/FTC/TDF [Stribild], RPV/FTC/TDF [Complera]) will be allowed as part or all of an approved ARV regimen. Alternative ARV regimens will be considered on an individual basis, based on available drug-drug interaction (DDI) data at the discretion of the principal investigator.

Protocol-approved ARV regimens were selected based on the results from the DDI studies that demonstrated co-administration of these ARVs with SOF/VEL/VOX would not require dose adjustment to any of these agents (Study GS-US-367-1657 [Section **Error! Reference source not found.**]; Study GS-US-380-1999 [Section **Error! Reference source not found.**]. The protocol-approved ARV regimens must be administered as indicated in the prescribing information of the package insert for the treatment of HIV infection.

1.4 SOFOSBUVIR

Sofosbuvir (SOF) is an FDA-approved nucleotide analog that is a potent and selective inhibitor of the NS5B HCV polymerase and was approved for the treatment of HCV infection by the FDA in December of 2013 as a component of an antiviral treatment regimen. Please refer to the product insert for additional information.

1.5 SOF/VEL

Epclusa (SOF/VEL) in an FDA-approved fixed dose combination (FDC) of SOF and the NS5A inhibitor Velpatasvir (VEL). This combination was approved by the FDA in June 2016 for the treatment of HCV infection both with and without cirrhosis. Please refer to the product insert for additional information.

1.6 SOF/VEL/VOX

1.6.1 Voxilaprevir

Voxilaprevir (Gilead product no. GS-9857) is a novel macrocyclic HCV NS3 protease inhibitor with potent in vitro antiviral activity against genotypes 1 to 6 HCV, broad coverage of NS3 protease polymorphs, and an improved resistance profile compared with PIs approved by the Food and Drug Administration (FDA) or currently in clinical development. Please refer to the IB for SOF/VEL/VOX for additional information on Voxilaprevir including:

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

1.6.2 Summary of Clinical Experience with SOF/VEL/VOX

Data from three Phase 2 studies, GS-US-337-1468 (LEPTON), GS-US-367-1168, and GS-US-367-1169, support the efficacy of 12 week therapy with SOF/VEL/VOX in subjects with DAA experience. In the LEPTON study, 67% (20/30) subjects who had previously failed 2 DAAs and then received 6 weeks of SOF/VEL+VOX achieved SVR12. In Study GS-US-367-1168, 100% (63/63) genotype 1 subjects that had previously failed DAAs and received 12 weeks of SOF/VEL+VOX achieved SVR12. In study GS-US-367-1169, 98.5% (64/65) subjects infected with genotypes 2-6 HCV who were treatment experienced, including 38 subjects who had failed a DAA, and received 12 weeks of SOF/VEL+VOX achieved SVR12. Treatment was safe and generally well tolerated. No safety signal associated with the administration of these agents was identified.

1.6.3 FDA-approval

The fixed dose combination with SOF/VEL/VOX was approved in the U.S. by the FDA on 17 July 2017 and is indicated for the treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have:
• genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.
• genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

1.6.4 Phase 3 Studies with Vosevi

The efficacy of VOSEVI was evaluated in two Phase 3 trials (GS-US-367-1171 [POLARIS-1], GS-US-367-1170 [POLARIS-4] in DAA-experienced subjects with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis. In these studies, 445 subjects received SOF/VEL/VOX (400/100/100 mg). The results from these studies are described within the Package Insert, but across all POLARIS studies, the efficacy of SOF/VEL/VOX ranged from 95-97%. The most common (at least 10%) adverse reactions were headache, fatigue, diarrhea, and nausea.

1.7 PHARMACOKINETICS OF SOF/VEL/VOX

Please refer to the Vosevi (SOF/VEL/VOX) package insert for information on the pharmacokinetics of these agents.

1.8 SAFETY OF SOF/VEL/VOX

To date, over 2600 subjects have received SOF/VEL+VOX clinical studies and there have been no clinical safety issues identified. There is no expectation of significant overlapping or new, unexpected toxicities upon coformulation of SOF/VEL with VOX as an FDC; data from study GS-US-367-1176 comparing SOF/VEL+VOX with SOF/VEL/VOX- were consistent with this. However, a potential risk of the study includes the identification of previously undetected adverse effects.

There is a potential risk for subjects to develop multiclass resistance if treatment in this study is unsuccessful. However, VOX has the highest reported barrier to resistance among NS3/4A PIs and so the anticipated clinical risk of developing drug-resistant mutants with VOX is anticipated to be lower than that associated with first and second generation NS3/4A PIs [26]. Accordingly, there was a lack of any viral breakthrough during therapy with VOX in the 3-day monotherapy study. Mutants generated in vitro to be resistant to VOX remain sensitive to SOF and VEL, supporting the clinical use of VOX in combination with other classes of HCV inhibitors. Lastly, this risk is balanced by the high efficacy shown in evaluations of SOF/VEL+VOX in Phase 2 studies and a very low rate of emergent resistance among subjects who relapsed.

Please see the Investigators Brochure for SOF/VEL/VOX for further information about SOF/VEL/VOX.

1.9 RATIONALE FOR DOSE SELECTION OF SOF/VEL/VOX

Sofosbuvir 400 mg, once daily is the approved marketed dose of SOF for the treatment of HCV infection.

Velpatasvir 100 mg has been administered in combination with SOF for 12 weeks to more than 1500 subjects infected with HCV genotypes 1-6 in Phase 2 and 3 studies. The favorable safety and efficacy profile of this combination support selection of SOF 400 mg and VEL 100 mg for co-formulation into an FDC with VOX.

Voxilaprevir 100 mg dose was selected for co-formulation with SOF 400 mg and VEL 100 mg based on the anti-HCV activity of VOX established in the phase 1 study GS-US-338-1121 (50 – 300 mg VOX dose evaluated).

Results from the relative bioavailability study GS-US-367-1176 show that the SOF/VEL/VOX FDC formulation achieves similar exposures of the relevant analytes to those observed with SOF/VEL+VOX. Additionally, the favorable safety and efficacy profile of SOF/VEL+VOX from Phase 2 studies support further evaluation of the combination of SOF/VEL/VOX 400/100/100 mg.

1.10 OVERALL RISK/BENEFIT ASSESSMENT

The potential benefits of SOF/VEL/VOX for the treatment of chronic HCV for patients included in the current study population are:

- Addressing the unmet medical need of the growing population of patients who have failed prior therapies, particularly those including DAAs such as SOF;
- Provision of a once-daily, single tablet, pangenotypic therapy for patients who have failed prior therapies and have no current treatment options.

Based on the well-characterized nonclinical toxicology profile of SOF, VEL, and VOX, and the clinical experience with SOF, VEL, and VOX, there is no expectation of significant overlapping or new, unexpected toxicities upon administration of SOF/VEL/VOX.

There is a potential risk for subjects to develop previously undetected adverse events or multiclass resistance. However, the development of resistance is anticipated to be low due to the high efficacy rate of the SOF/VEL + VOX combination therapy, as seen in Phase 2 studies, and the high resistance barrier of VOX.

In summary, this treatment is approved for HCV-infected patients who have failed therapy with DAAs other than first-generation PIs in combination with Peg-IFN+RBV. If high rates of SVR can be obtained with a 12-week pangenotypic regimen, the anticipated value of achieving an SVR for patients with no current therapeutic options, with a safe and tolerable regimen, offers a favorable risk-benefit determination.

2 STUDY DESIGN AND METHODS

This is a Phase IIb, open-label, study to evaluate the safety, tolerability, and efficacy of SOF/VEL/VOX in subjects with chronic HCV infection who have failed to eradicate HCV in response to combination DAA-based therapy, including subjects coinfected with HIV. We will also evaluate the viral mutants, HCV quasispecies, as well as immunologic, virologic, and host genetic/proteomic predictors of response to SOF/VEL/VOX in study subjects.

We hypothesize that the combination SOF/VEL/VOX will result in high SVR rates in patients with chronic HCV infection who are treatment-experienced after previous combination DAA-based therapy with an FDA-approved regimen, including LDV/SOF and Viekira Pak 3D regimen consisting of paritaprevir (co-dosed with ritonavir [paritaprevir/r]), ombitasvir, dasabuvir (PrOD), dosed with or without ribavirin (RBV).

All participants will receive 12 weeks of SOF/VEL/VOX. Patients will be followed for approximately 44 weeks from the screening period through the end of follow up visits:

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

Subjects that experience virologic failure or relapse and identified to have mutations leading to

SOF, VEL, and/or VOX resistance, following sequencing and phenotypic, analysis will be requested to return at 12-week intervals for this or a natural history protocol for up to 44 weeks to determine the time required for the resistant virus to return to background levels.

2.1 PRIMARY OBJECTIVE

- To assess the safety, tolerability, and efficacy of 12 weeks of SOF/VEL/VOX in subjects with chronic HCV infection who have previously failed FDA approved DAA-based therapy, with compensated cirrhosis and without cirrhosis, with and without HIV coinfection.

2.2 SECONDARY OBJECTIVES

- To evaluate the immunologic, virologic, and host genetic/proteomic predictors of response to therapy with SOF/VEL/VOX in HCV infected subjects who have failed previous combination DAA-based therapy
- To compare HCV quasispecies and resistance associated variants (RAVs) from baseline and throughout treatment, especially in the case of relapse or breakthrough, and assess the influence of past DAA experience on evolution of RAVs and on virologic response to treatment.
- To determine the kinetics of plasma HCV RNA during treatment and after treatment discontinuation.
- To evaluate the effect of SOF/VEL/VOX on peripheral markers of T cell activation.
- To evaluate the proportion of subjects whose alanine aminotransferase (ALT) levels normalize between baseline and $SVR_{4,12,24}$.
- To delineate the precise effects of specific HCV lifecycle inhibitors on host immune recovery in patients receiving single (SPARE), or combination DA therapy (RESOLVE).

2.3 EXPLORATORY OBJECTIVES

- Characterize immunologic, virologic, and host genetic/proteomic predictors of response
- Viral kinetic investigations, including early viral kinetics, resistance associated variants, HCV quasispecies
- To determine the impact of liver cirrhosis in SVR when treated with potent combination DAA therapy
- To delineate the precise effects of specific HCV lifecycle inhibitors on host immune recovery in patients receiving combination DAA therapy
- To compare the immunophenotypic responses of patients receiving SOF/VEL/VOX who have previously failed double and triple DAA therapy.

2.3.1 Rationale for Immunologic studies

We propose to study the B and T cell immune responses most associated with chronic HCV eradication after DAA therapy, in order to more fully understand the utility of new ultra short duration therapies for those chronically infected with HCV. We will define T cell immune responses associated with protective immunity in chronic HCV infection and further advance our understanding about host immunity that is associated with SVR. Studies on

B and T cell responses in HCV or HCV/HIV dual infection and the relationships to treatment outcomes require large numbers of patients and extensive clinical trials of DAA therapy. Our research team is making a major impact on the clinical understanding of DAA. We have collected and maintain a large specimen repository that is sufficient for our initial characterization of B and T cells and how they are related to protective immunity.

Chronic HCV infection is characterized by dysfunction of the adaptive immune system. DAA therapy is successful in resolving HCV infection and provides cure in up to 99% cases, except for late stage disease. Whether cure is associated with reconstituted immune regulation and what role the adaptive immune system plays in viral clearance is not known. Faster resolution of secondary infection after spontaneous clearance of HCV in humans and in chimpanzees points to a role for immunological memory in HCV control. Defining the immune correlates of DAA mediated sustained virologic response will help understand the immune defects that may be associated with treatment failure.

Hypothesis

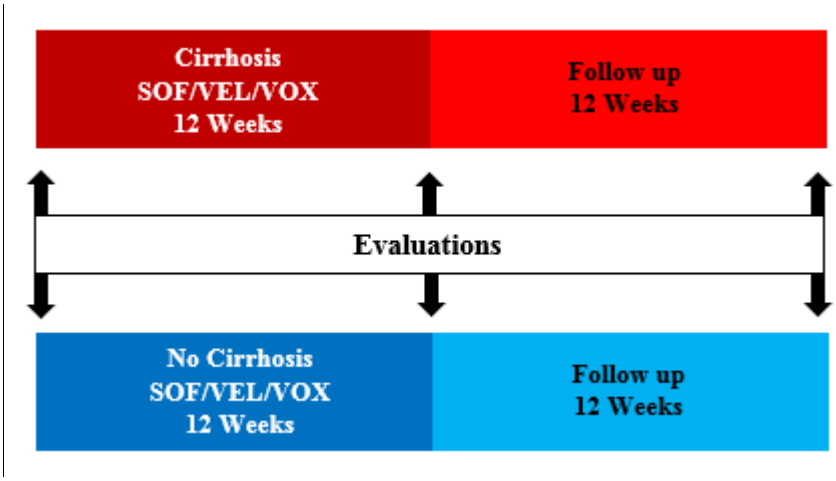
Hypothesis #1: Augmentation of HCV specific cellular immune responses with DAA therapy is associated with SVR.

Hypothesis #2: Healthy (non cirrhotic) liver is critical in mounting HCV specific cellular immunity in DAA treated patients

Hypothesis #3: Specific inhibition of stages of HCV lifecycle leads to precise immune recovery in chronic HCV infected patients treated with combination DAA therapy.

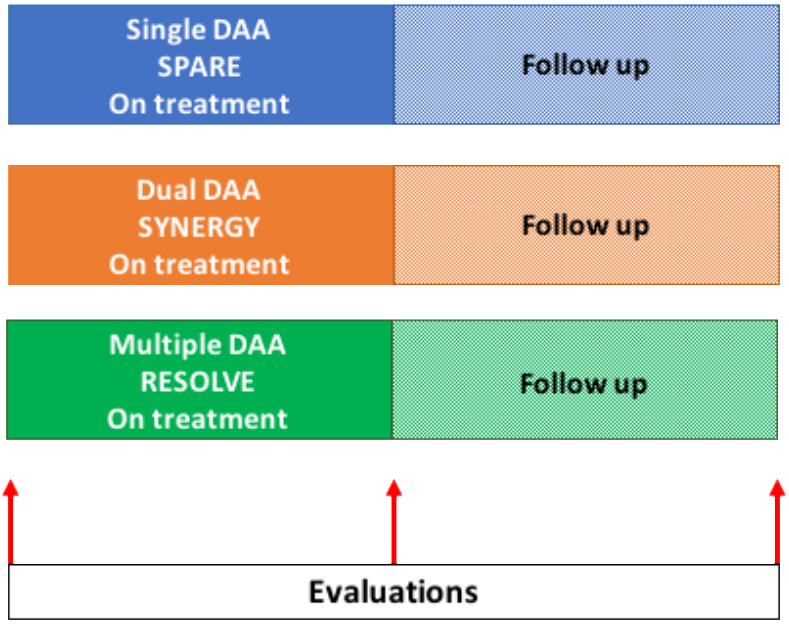
Study Design and Analysis

To achieve these objectives, we will analyze peripheral and intrahepatic cellular immunity in patients who are cirrhotic and those who are not, as described in detail below. The responses/changes observed over time with DAA therapy will be compared between the two groups to evaluate first objective.



To address the second objective, we will utilize samples collected from previous studies that used either single DAA (SPARE), dual or multiple DAA therapy (present study) to determine the

differential effect of specific HCV lifecycle inhibitors (NS5B alone, NS5B with NS5A and NS5B with NS5A and NS3 inhibitors). The assays that will characterize peripheral and intrahepatic cellular immunity are described in detail below. The changes from baseline to the end of therapy (or full viral suppression) will be compared in all patients receiving various regimens to determine the differential effect of added suppression of NS5A and or NS3.



2.4 STUDY POPULATION

It is anticipated that approximately 150 HCV infected subjects, including screening failures and drop-outs, will be screened for this study. The target population is chronic HCV patients who are treatment-experienced with combination DAA therapy and failed to achieve SVR_{12} in the United States. 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. There will be no racial, ethnic, religious, or gender discrimination. Persons in jail or prison are not eligible for this study. We will be enrolling participants from ongoing clinical trials with collaborators, as well as recruiting referrals. Healthy adults will be recruited through Institutional Review Board (IRB)-approved advertising to HCV providers and screened to confirm eligibility requirements for participation.

The following eligibility criteria will be used:

2.4.1 Inclusion Criteria

A subject must meet all of the following criteria:

1. At least 18 years of age or older at screening.

2. Available for clinical follow-up through Week 44 after enrollment.

3. Recurrent HCV GT-1 infection as documented by ≥ 1 measurement of serum HCV RNA ≥ 1,000 IUM/mL during screening and documented history of receiving prior HCV treatment.

4. Exposure to combination DAA therapy, including, but not limited to, the following regimens:
    a. LDV/SOF ± RBV
    b. Viekira Pak ± RBV
    c. EBR/GZR± RBV

5. Ability to communicate effectively with the study investigator and other key personnel.

6. Opioid-dependent individuals must be participating in a supervised treatment program or considered stable at the discretion of the investigator.

7. Subjects must have a primary care doctor for their medical management.

8. Able and willing to complete the informed consent process.

9. Willing to donate blood for sample storage to be used for future research.

10. Female study participants with childbearing potential (as defined below) and all male study participants must be willing to practice either:

- Complete abstinence from sexual intercourse with a member of the opposite sex
  OR
- At least one form of effective contraception from the list below, in addition to correct use of either a male or female condom with spermicide, throughout dosing and for a defined period following the last dose (30 days for women, 14 days for men) of study medication.:
    i. Intrauterine device with a failure rate of <1% per year
    ii. Tubal sterilization
    iii. Bilateral tubal occlusion
    iv. Vasectomy in a male partner
    v. Female barrier method (diaphragm or cervical cap) with spermicide
    vi. Hormonal methods
        1. Oral contraceptives
        2. Injectable progesterone
        3. Implants of levonorgestrel or etonorgestrel
        4. Transdermal contraceptive patch
        5. Contraceptive vaginal ring

11. Hepatitis B coinfected participants, must have evidence of chronic infection and controlled on treatment.

12. HIV coinfected participants only must have HIV status of one of the following:

    a. HIV untreated for ≥8 weeks prior to Screening

i. CD4 T-cell count >500 cells/mm^3 at Screening

ii. No intention of initiating ARV therapy for the duration of trial

OR

b. HIV suppressed on a stable, protocol-approved, ARV regimen for ≥ 4 weeks prior to Screening

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

ii. CD4 count >100 cells/mm^3 at Screening

iii. HIV antiretroviral (ARV) agents allowed in this study include

- FTC/TAF [Descovy®], FTC/TDF [Truvada®], or ABC/3TC [Epzicom®]

plus

- Ritonavir (r) and darunavir (DRV), OR
- Raltegravir (RAL), OR
- Elvitegravir (EVG) ± Cobicistat (c), or
- Rilpivirine (RPV)

Or

Fixed dose combinations as below

- FTC/RPV/TAF [Odefsey®]
- FTC/RPV/TDF [Complera®]
- EVG/c/TAF/FTC [Genvoya®]
- EVG/c/TDF/FTC [Stribild®]

Alternative ARV regimens will be considered on an individual basis, based on available DDI data at the discretion of the principal investigator

iv. The subject is expected to continue the current ARV regimen for the duration of the trial

Cirrhosis Criteria:

13. Liver fibrosis staging as determined by an AASLD/IDSA guideline-approved

measurement, within three years of Screening, including any one of the following:

a. Imaging
b. Liver biopsy
c. Transient elastography
d. Noninvasive markers

Liver imaging within 6 months of Day 0 to exclude hepatocellular carcinoma (HCC) is required in patients with cirrhosis.

2.4.2 Exclusion Criteria

A subject will be excluded if one or more of the following conditions apply:

1. Combination DAA therapy was completed or discontinued less than 8 weeks prior to enrollment.
2. Current or prior history of any of the following:

    a. Clinically significant illness (other than HCV) or any other major medical disorder that may, in the opinion of the investigator, interfere with the subject treatment, assessment of compliance with the protocol; subjects currently under evaluation for a clinically-significant illness (other than HCV) are also excluded
    b. Gastrointestinal disorder with post-operative condition that could interfere with the absorption of the study drugs
    c. Poor venous access interfering with required study blood collection
    d. Hepatic impairment or decompensation (e.g., Child-Pugh class B [moderate] or Child-Pugh class C [severe])
    e. Solid organ transplantation
    f. Significant pulmonary disease, significant cardiac disease, or porphyria.
    g. Unstable psychiatric disease, including hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within 2 years prior to Screening (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. Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency, cholangitis)
3. Abnormal hematological and biochemical parameters at screening, unless the test has been repeated and at least one subsequent result is within the acceptable range prior to study drug administration, including:

    a. Neutrophil count <750 cells/mm^3
    b. Hemoglobin level <10 g/dL
    c. Platelet count ≤50,000 cells/mm^3
    d. Estimated glomerular filtration rate, calculated by the chronic kidney disease epidemiology collaboration formula: <30 mL/min/1.73 m^2
    e. ALT or AST level ≥10 times upper limit of normal (ULN)
    f. Serum lipase level ≥1.5 times ULN at screening or during the screening period in a patient with symptoms of pancreatitis

g. Total bilirubin level ≥2.0 times ULN, except in subjects with Gilbert's syndrome or other clinical explanation at the discretion of the PI.
h. Albumin level <3 g/dL

4. Poorly controlled diabetes as indicated by a screening glycosylated hemoglobin (HbA1c) >10

5. Known hypersensitivity to any of the study medications

6. Screening ECG with clinically significant findings

7. Need for the use of the following medications from 21 days prior to the start of study drugs through the end of treatment:

    a. Hematologic stimulating agents, erythropoiesis stimulating agents (ESAs), granulocyte colony stimulating factor (GCSF), thrombopoeitin (TPO) mimetics
    b. Chronic systemic antineoplastic or immunomodulatory treatment including supraphysiologic doses of immunosuppressants such as corticosteroids (e.g., prednisone equivalent >10 mg/day for >2 weeks), azathioprine or monoclonal antibodies (e.g., infliximab)
    c. Investigational agents or devices for any indication
    d. Use of certain medications and herbal/natural supplements per PI discretion, expected to result in increases or decreases in exposure to study or non-study medications as listed in section 3.5 (Table 3-1).

8. Any medical, psychiatric, social condition, occupational reason or other responsibility that, in the judgment of the investigator, is a contraindication to protocol participation or impairs a volunteer's ability to give informed consent.

Female-specific criteria:

9. Woman who is breast-feeding or planning to become pregnant during the first 24 weeks after study drug administration.

2.5 PHARMACOKINETIC AND VIRAL KINETIC SUBSTUDY

Participants, N=20 (10 participants with cirrhosis and 10 without cirrhosis) that meet the above criteria and who are willing to participate will be eligible for a voluntary 24 hour and 72 hour pharmacokinetic (PK) and viral kinetic (VK) substudy.

2.6 RECRUITMENT PLAN

The study will be advertised and posted using flyers. All advertisements will be IRB approved before use.

2.7 HUMAN SUBJECTS PROTECTIONS

Subjects will be fully counseled prior to entry into the study as to the potential risks of the study and consenting using good clinical practice. 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.

2.7.1 Gender, Ethnicity, and Race Considerations

Subjects will not be excluded based on gender. This study is designed to target an underrepresented demographic of the HCV epidemic in the United States with poor representation in clinical trials, and in which current therapy has had poor results.

2.7.2 Rationale for the Exclusion of 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 SOF, VEL and VOX in the pediatric population. The risks of SOF or VEL or VOX 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 SOF/VEL/VOX and use effective contraception throughout the study.

2.7.3 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, one method must be correct use of a condom with spermicide, from 2 weeks prior to Day 0 until after completing study drug (30 days post completion for women, 14 days for men 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 study drugs are investigational agents, prevention of pregnancy, in a subject or partner, during and after treatment is important as the risks are as yet unknown.

Definitions:
a. Definition of Childbearing Potential: For the purposes of this study, a female born subject is considered of childbearing potential from menarche until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a post-menopausal state when they are $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility: For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchiectomy or medical documentation.

2.8 CLINICAL PROCEDURES AND SCHEDULE OF EVALUATIONS

This section describes the clinical procedures for evaluating study participants and follow-up after administration of study drug.

Study visits, including screening, will occur at the UMB Institute of Human Virology clinic or one of the clinics mentioned in the study roster based upon scheduling availability to accommodate each treatment group. Participants in the pharmacokinetic or viral kinetic substudy will be seen at the University of Maryland Medical Center.

UMB Study Team Roles at Washington, DC community clinics: Members of the study team have been actively involved in patient care at the community clinics (Unity's Parkside and Walker-Jones). Unity will sign a UMB Reliance Agreement prior to initiating any study activities. The site AI and collaborating investigator may see subjects at non-study visits and will communicate findings to UMB study team. The UMB research coordinators will also oversee research operations in the clinics and at the UMB IHV clinic. The UMB study staff will see participants for all scheduled and unscheduled visits and study withdrawal.

If subjects are seen in the Community: 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 UMB staff and will be labeled with the participant's first three initials of last and first name and study number. All laboratory studies will be performed by UMB and will be reviewed by UMB 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 UMB 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 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.

2.8.1 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) and is indicated for disease staging 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, Section 5.1. Screening tests within the last 8 weeks prior to screening visit that have been done as part of routine medical care or at an outside facility (with the exception of chemistries, hCG, HIV, CBC with differential, coagulation studies) can be used if within the acceptable time frame. Known HIV infected participants will not have an HIV test, but will have HIV RNA and CD4 T-Cell count testing.

The standard consent includes permission for HIV testing (in those not previously known to be infected), optional liver biopsy, and storage of blood and tissue samples. HLA testing may be tested for this study if not on file, because this information will be useful for the evaluation of HCV-specific immune responses.

Screening procedures do not need to be repeated within the 8 week screening window unless clinically indicated. Once the screening window has elapsed, patients may be rescreened at the discretion of the PI.

2.9 RANDOMIZATION AND BLINDING

This is an open-label, phase IIB clinical trial, and will be without blinding. Randomization will not be employed, as all participants will be allocated to 12 weeks of the same therapy.

2.10 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 Day 0, Week 4, Week 12 and Post-treatment Weeks 12 and 24. Directed physical exam will be done as needed at other study points. On arrival at the clinic for study visits, 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, Section 5.1), clinical laboratories drawn, and a review of the study restrictions. 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, their adherence with study restrictions, and their adherence to study drug administration. A complete list of study procedures and lab tests to be performed is in the Schedule of Tests, Section 5.1.

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 flexibility regarding when they need to occur. The window period for visit schedules is as follows:

- Days 0, 3(PK/VK participants only), no window
- Optional Week 1 (+/- 3 days)
- Weeks 2, 4 (+/- 3 days)
- Weeks 8 and 12 (+/- 7 days)
    - Optional End of therapy Liver Biopsy (+/-14 days)
- Post Therapy Weeks 4, 12, 24 (+/- 10 days)

2.11 STARTING SOF/VEL/VOX (DAY 0)

The participant will be started on SOF/VEL/VOX on Day 0. Blood will be drawn for HCV viral loads, 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. The subject will undergo a history and physical exam on Day 0, prior to starting study medications.

2.12 OPTIONAL PK/VK SUBSTUDY

Participants who are eligible and interested in participating in the optional PK/VK substudy will undergo timed blood draws at baseline, 1, 2, 4, 8, 24, and 72 hours after initiating study medication.

2.13 WEEK 1 VISIT

Participants will either have a telephone phone follow up visit to assess for adverse events and adherence or they will come to the clinic for an in person study visit that will include clinical and research blood draw.

2.14 WEEK 2 VISIT

In addition to scheduled study events, the second bottle of study medication will be dispensed.

2.15 WEEK 4 VISIT

During this visit, 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/Medical Monitor (MM) determines otherwise, and the last bottle of study medication will be dispensed.

2.16 WEEK 8 VISIT

During this visit, HCV RNA will be obtained to determine if virologic-response based treatment stopping criteria have been met.

2.17 WEEK 12 / END OF TREATMENT VISIT

Week 12 will mark the last dose of SOF/VEL/VOX 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.

2.18 FOLLOW-UP VISITS AFTER STUDY DRUG DISCONTINUATION

After discontinuation of the study drug, subjects will be followed at Weeks 4, 12, and 24 after completion of therapy. All subjects will be assessed for sustained virologic response (SVR_{12}) at the post-treatment week 12 visit, to occur at study week 24. A serum pregnancy test will be done

with each visit up to 30 days after stopping study drug, in women of childbearing potential, as appropriate.

2.19 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 that are considered related to the study agents. Participants with undetectable HCV RNA at the end of treatment should continue to follow the scheduled SVR_4, 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 24 weeks or on a separate natural history protocol to determine the persistence of any HCV populations with treatment-emergent substitutions conferring resistance to SOF or GS-5885 or VOX. Any subject continuing in the study will be followed closely for resolution of active laboratory abnormalities or adverse events that are considered related to the study agents.

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.

2.20 EVALUATION OF SAFETY

All enrolled subjects who have received SOF/VEL/VOX 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.

2.20.1 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.

2.20.2 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 Dose Modification and Treatment Failure Sections, 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. Participant's desire to leave study.
3. Pregnancy or breastfeeding.
4. 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 at the discretion of the Investigator or designee.
5. Termination of study.
6. Development of liver decompensation with elevated Child-Turcotte-Pugh score of 8 or more.
7. If SOF/VEL/VOX FDC is permanently discontinued by the pharmaceutical company.
8. 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.
9. Request of the primary care provider or Investigator if s/he thinks the study is no longer in the best interest of the subject.
10. Clinical reasons believed life threatening by the physician.
11. If the subject is judged by the Investigator to be at significant risk.
12. 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 UMD.

3 STUDY AGENTS

3.1 DISPOSITION AND DISPENSATION

Study agents will be distributed via the IHV 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.

3.2 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.

3.2.1 Formulation

SOF/VEL/VOX fixed dose combination (FDC) tablets are beige, capsule-shaped, film-coated tablets containing 400 mg of sofosbuvir, 100 mg of VEL, and 100 mg of VOX. The tablets are debossed with "GSI" on one side and "3" on the other side. In addition to the active ingredients, the tablets contain the following inactive ingredients: copovidone, microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, croscarmellose sodium and magnesium stearate. The tablet film-coating material also contains polyvinyl alcohol, titanium dioxide, macrogol/PEG 3350, talc, iron oxide yellow, iron oxide red, ferrosoferric oxide.

3.2.2 Packaging and Labeling

SOF/VEL/VOX FDC tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 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 SOF/VEL/VOX FDC tablets to complete the entire study will be shipped from Gilead Sciences Materials & Logistics (or its designee).

3.2.3 Storage and Handling

SOF/VEL/VOX 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 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 will 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 SOF/VEL/VOX FDC.

3.3 TREATMENT OF SUBJECTS

All subjects will receive 12 weeks of treatment with SOF/VEL/VOX.

SOF/VEL/VOX FDC will be administered orally once a day. The 1st dose will be taken on Day 0.

3.4 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 would compromise this goal and predispose to the emergence of drug-resistant viral variants. Hence, no dose reduction will be allowed for SOF/VEL/VOX.

3.4.1 Dose Modification for SOF/VEL/VOX

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.

3.4.2 Treatment Failure / Drug Discontinuation

See also Criteria for premature withdrawal of subjects (2.20.2). Subjects will be considered treatment failures and will discontinue SOF/VEL/VOX FDC if they meet any of the following criteria while taking study drugs:

- HCV RNA greater than LLOQ after 2 prior consecutive HCV RNA values less than the LLOQ
- Greater than a 1 $\log_{10}$ increase in HCV RNA from nadir
- Less than a 2 $\log_{10}$ decline in HCV RNA after 4 weeks of treatment (unless >2 log drop would be below LLOQ)
- HCV RNA ≥ 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 Medical Monitor (MM) 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 SOF/VEL/VOX FDC
- Pregnancy

3.4.3 Treatment Failure Criteria After Stopping SOF/VEL/VOX

- Have detectable HCV RNA during the post-treatment period (after having achieved HCV RNA <LLOQ at end of treatment). If virus is detected after subject achieves SVR12, will confirm with repeat viral testing, and then evaluate for reinfection versus relapse with viral subtyping and sequencing.

3.4.4 Viral Co-infection Rebound Schema

For HIV suppressed subjects taking ARVs, at least two consecutive and uptrending post-baseline visit plasma HIV RNA levels ≥ 400 copies/mL (at least two weeks apart) will be considered HIV virologic rebound.

Following an initial HIV RNA result of ≥ 400 copies/mL, subjects will continue to take their current ARV regimen and be asked to return to the clinic after 2 weeks for a scheduled or unscheduled blood draw for confirmation of HIV virologic rebound. If HIV virologic rebound is confirmed at the scheduled or unscheduled visit, the blood samples from this visit will be used for HIV 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 or HCV response based stopping criteria warrant the discontinuation of the study drug, as outlined in Section 3.4 of the protocol.

For those with chronic HBV infection taking chronic suppressive therapy, if HBV flare does occur, monitoring and treatment plan will be discussed with medical monitor on an individual basis.

3.5 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 28 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.

- Should subjects have a need to initiate treatment with any disallowed concomitant medication, the medical monitor must be consulted prior to initiation of the new medication

Table 3-1: Disallowed and Concomitant Medications to be Used with Caution

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing Agents[a]		Proton-Pump Inhibitors, H2-Receptor Antagonists, Antacids
Anticoagulants		Dabigatran Etexilate[d]
Anticonvulsants [b]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials [b]	Rifabutin, Rifapentine, Rifampicin	
Cardiac Medications	Amiodarone [c]	Digoxin[d]
Herbal/Natural Supplements[b]	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[e]	Rosuvastatin	Pravastatin

a Proton-pump inhibitors (PPIs) comparable to omeprazole 20 mg once-daily may be taken. H2 receptor antagonists must not exceed the equivalent of 40 mg of famotidine twice daily. Antacids that directly neutralize stomach pH (i.e. Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/VEL/VOX FDC administration.
b May result in a decrease in the concentrations of study drugs.
c May result in symptomatic bradycardia. Mechanism is not currently known. The use of amiodarone is prohibited from **60 days prior to Day-1** through the end of treatment.
d May result in an increase in the concentration of study drugs and/or concomitant medications
e 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. Pravastatin may be administered with SOF/VEL/VOX FDC at a dose that does not exceed pravastatin 40 mg.

4 STATISTICAL CONSIDERATIONS

This study is a single-center trial to assess the safety and tolerability of SOF/VEL/VOX.

4.1 SAMPLE SIZE

We anticipate enrolling approximately 60 patients with cirrhosis and 60 patients without cirrhosis, for a total of 120 HCV, genotype 1, infected subjects who have previously been treated with unsuccessful combination DAA-based therapy.

An anticipated sample size of approximately 120 patients will provide a 97% power to detect at least an absolute 15% improvement in SVR_{12} from the conservative estimate of 70%[20] by using a 2-sided, exact, 1-sample binomial test at a significant level of 0.05 (See Table 4-1).

Table 4-1 Power calculations for observed SVR12 rate compared to Historical rate of 70%

H_o SVR12	H_a SVR12	Sample Size	Power
70%	80%	120	0.641
70%	85%	120	0.968
70%	90%	120	>0.999
70%	95%	120	>0.999

In terms of safety, a sample size of 120 is sufficient to have high probability of observing at least 1 adverse event of probability 5% or more. If the true event probability is 5% or more, there is about a 99.8% 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 5%. This trial will provide preliminary evidence on the safety and efficacy of SOF/VEL/VOX. A previous study of SOF/VEL FDC in subjects with genotype 1 led to a sustained virologic response at Week 12 (SVR_{12}) in all participants. We therefore expect SVR to 80% or higher. If the true suppression rate is 80%, we will be able to estimate the probability of suppression to within approximately $\pm 1.96[(.8)(1-.8)/120]^{1/2}=.07$ (Table 4-2). 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).

Table 4-2: Sample Size

n=50	n=75	n=100	n=120
±.11	±.09	±.08	±.07

AE probabilities are shown in Table 4-3, wherein for a given N, the probability of observing at least 1 participant with the AE among study participants. We selected at least 100 participants based on the ability to detect adverse event rates of a frequency of 1% and 5% with 63% and 99% probability, respectively.

Table 4-3: Adverse Event Probability Table

	Probability of Adverse Event			
	0.01	**0.05**	**0.10**	**0.15**
N=75	52%	98%	>99.9%	>99.9%
N=100	63%	99%	>99.9%	>99.9%
N=120	70%	99.8	>99.9%	>99.9%

4.1.1 Primary Endpoint

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

The primary statistical hypothesis for efficacy is that SVR_{12} rate is higher than the conservative estimate of 70%[20].

- H_o: SVR12 = 70%
- H_a: SVR12 ≠ 70%

The primary analysis will be intention-to-treat, including all enrolled subjects into the study and received at least one dose of study drug, performed after all enrolled subjects have been followed through 12 weeks post-treatment or discontinued from study.

4.1.2 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.

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. Changes in HCV specific CD8 responses in patients with cirrhosis and not with cirrhosis. Changes in HCV specific immune responses in patients treated with single (NS5B) DAA versus dual (NS5B + NS5A) versus triple combination DAA (NS5B + NS5A + NS3) using samples from SPARE and this study

4.1.3 Safety Endpoints

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

4.1.3.1 Other Endpoints of Interest

Additional efficacy evaluations may include HCV RNA change from Day 0; ALT normalization; and viral kinetic parameters.

4.1.4 Analysis Sets

4.1.4.1 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.

4.1.4.2 Safety

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

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.

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.

4.1.4.3 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.

4.2 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.

4.3 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 (BMI), presence or absence of cirrhosis, HCV RNA level ($\log_{10}$ IU/mL), HCV genotype, and additional endpoints as necessary.

4.4 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.

5 STUDY TESTS

5.1 SCHEDULE OF TESTS

Laboratory Studies

Screening tests that have been done as part of other studies or standard of care 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. HIV test does not need to be done in participants known to be HIV infected. Similarly, HBV serologic testing does not need to be done in participants known to be chronically HBV infected who are on suppressive therapy.

Serum Chemistry and Hematologic Profiles

Acute Care Panel, Hepatic Panel, Mineral Panel, 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 post-treatment Week 24. Highly sensitive C-reactive protein may also be done at Days 0, weeks 1 (optional), 2, 4, 12 (end of therapy), as well as post-treatment weeks 12 and 24, again dependent upon blood volume availability by patient.

Prothrombin Time and Partial Thromboplastin Time

Measured by standard assay on screening, end of therapy (Week 12), prior to liver biopsy and post-treatment Week 24.

Creatine Kinase, Lactate Dehydrogenase, Lipase, Amylase.

Measured by standard assay on screening and Weeks 4, end of therapy (Week 12) and post-treatment Week 12.

Alpha Fetoprotein, HCV genotype, Hemoglobin A1C, HIV testing.

Measured by standard assays as part of screening. Hemoglobin A1C will be repeated at Day 0, End of therapy: (Weeks 12), and post-treatment Weeks 12 and 24.

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.

SOF/VEL/VOX level

Measured at scheduled study visit continuing through the End of Treatment visit. Actual date and time of PK sample collection and study drug administration will be recorded.

HCV RNA Levels (HCV Viral Loads)

This will be performed at the following study points: screening; day 0; weeks 1 (optional visit), 2, 4, 8; end of therapy (week 12); post treatment weeks 4, 12, and 24.

HCV Genotype Assay

This will be performed at screening if not on file. A result from an outside lab can be used if it was completed after documented treatment failure.

HIV RNA Test
This will be performed in HIV coinfected individuals at the following study points: screening, day 0, weeks 4, 8, 12 and post-treatment week 12.

CD4 Test
This will be performed in HIV coinfected individuals at the following study points: screening, week 12 and post-treatment week 12.

HBV DNA Test
This will be performed in chronically HBV-infected individuals at the following study points: day 0, on-treatment weeks 4, 8, and 12 and post-treatment weeks 4 and 12.

VK/PK Sub Study
Subjects will have blood drawn at time points 0, 1, 2, 4, 8, 24 and 72 hours after administration of drug to assess drug levels and HCV viral load levels.

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[27].

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[28].

rs12979860 (IL28B) Genetic Variant
IL28B genetic variants have been shown to predict HCV treatment induced clearance[29]. 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.

Immune Responses to HCV
Both humoral and cellular immunity against HCV 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 where virologic failures as defined.

Subjects who are determined by sequencing and phenotypic analysis to have had mutations leading to SOF 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.

Immunophenotyping for T cells

We will study the effectiveness of DAA therapy for normalizing effector T and B cell populations. Peripheral or hepatic lymphocytes will be evaluated using flow cytometry for different activation and exhaustion markers. Lymphocytes will be stained with conjugated-antibodies against CD3, CD4, CD8, CD56, CD45RA, CCR7, CD69, CD25, HLA-DR, CD38, Ki67, FoxP3, CTLA4, Tim-3, PD-1 and CD57. The percentage of cells expressing each and multiple markers will be determined by flow cytometry (BD FACSAria). Data will be analyzed using FlowJo (TreeStar) software.

Determination of HCV specific polyfunctional CD4 and CD8 T cells

For characterization of HCV specific T cell phenotype and function, peripheral T cells will be isolated from PBMCs by Ficoll-paque density gradient separation to be stimulated with pooled HCV genotype specific peptides. For this experiment, we will use HCV 15-18-mer peptides with 11 or 12 amino acid overlaps spanning the entire HCV polyprotein (Mimotopes, Peptide Array, HCV), reconstituted in 5% sterile dimethylsulphoxide (DMSO), pooled consecutively into twenty-one groups and aliquotted until use. The number of HCV-responsive IFN-γ-producing PBMC will be quantified by standard ELISPOT assay (BD Biosciences), in which 96 well ELISPOT plates are coated with anti-IFN-γ biotinylated capture antibody and incubated overnight at 4°C. Plates will be blocked using lymphocyte medium, and PBMC allowed to rest for 6 hours at 37°C. PBMC will be plated between 250,000- 400,000 cells per well with either phytohaemagglutinin (PHA) as a positive control (5 mg/ml), DMSO as a negative control (0.05%), or pooled HCV peptides (3 mg/ml/peptide). All cultures will be performed in duplicate. After incubating for 12 hours at 37°C, cells will be removed, and plated with streptavidin detection antibody, enzyme conjugate, and substrate. The plates will then be air dried in the dark overnight, and developed spots will be enumerated using an ELISPOT plate reader.

Further testing of HCV responsive T cells will be conducted by flow cytometric analysis. To identify HCV responsive cell populations, carboxyfluoresceinsuccinimidyl ester (CFSE) dilution will be utilized. PBMC will be washed and incubated with 2.5mM CFSE (Invitrogen) at 37°C for 6 minutes, quenched with PBS + 5% fetal calf serum (FCS), and washed three times with lymphocyte medium. PBMC will be incubated at $5x10^6$ in 1.2 mL with either pools of overlapping HCV peptides spanning the entire proteome (3mg/mL/peptide) or DMSO (1%) and NH_4OH (0.7mM) as a vehicle control for a total of 48 hours. Brefeldin A and monensin will be added at 36 hours to block the Golgi apparatus and allow intracellular cytokine accumulation. Following incubation, PBMC will be harvested and stained with LIVE/DEAD Near-IR (Invitrogen) for 30 minutes on ice. The percentage of live, CFSE+ cells will be assessed by flow cytometry data (FACSAria) and analyzed using FlowJo software (TreeStar) for phenotype and function using the antibodies described previously. To assess secreted cytokine production, 100 µl of supernatant will be collected at 36 hours and frozen at -80°C until used. Samples will be thawed and analyzed for cytokine production using Mesoscale Discovery Human TH1/TH2 10-plex ultra-sensitive kit (catalog #K15010C-1) according to manufacturer's protocol. All samples will be tested in duplicate.

Determination of T cell defects in liver with mass cytometry using CYTOF

Liver infiltrating lymphocytes (LIL) will be isolated from liver biopsy specimen and evaluated for markers of immune exhaustion and activation on effector and memory T cell subsets. Because we are able to obtain limiting number of lymphocytes from liver biopsies (up to 1 million cells per biopsy) it will be critical to use a technology that maximize the spectrum of T cell phenotypes visualized. Although flow cytomtery-based immunophenotyping has been

extensively used to connect polyfunctionality and memory phenotypes of T cells, it is limited by its inability to discern all distinct cellular phenotypes and relate them to one another without the ability to evaluate simultaneously at many phenotypic markers, functional capacity, and antigen specificity in individual cells. Flow cytometry is limited by its ability to evaluate 12–18 parameters because of overlapping excitation and emission spectra between different fluorophores. We plan to use a recently developed single-cell mass spectrometric (cytometry by time-of-flight or CyTOF) approach in which heavy metal isotopes are used to label antibodies and then labeled cells are analyzed by high throughput mass spectrometry to quantify 34 parameters at the single-cell level, with very little crosstalk between channels. This approach will allow us to evaluate more than 30 functional phenotypes represented by distinct CD8+ T cell subsets, a nearly combinatorial diversity in the critical liver infiltrating lymphocyte population. Phenotypic and functional characterization of liver cells will be done on 10 subjects with no liver fibrosis and compared with 10 advanced stage liver fibrosis subjects using mass cytometry analysis. We will test the samples for levels and exhaustion status of their HCV specific polyfunctional T cells. The University of Maryland School of Medicine Cellular Flow Cytometry Core Lab will provide technical assistance in design, data acquisition and analysis of all CyTOF experiments on fee-for-service basis.

Flow cytometry for B cell phenotyping

B cell subpopulations will be phenotyped by flow cytometry at baseline (pre-treatment) and at the end of treatment and compared with samples from healthy volunteers as controls, matched for age and gender. Multicolor flow cytometry analyses will be performed on cryopreserved PBMC. Lymphocyte counts will be determined by a core facility following standard procedures. The frequency of each B cell subpopulation will be determined by flow cytometry. The following fluorochrome-conjugated monoclonal antibodies will be used in the B cell staining strategy: V450 anti-CD3 (BD Biosciences, Carlsabad, CA); PerCP-Cy5.5anti-CD19, PE-Cy7 anti-CD27 (eBioscience, San Diego, CA); FITC anti-CD21 (Beckman Coulter, Brea, CA);allophycocyanin (APC) anti-CD10, APC-H7 anti-CD20 (BD Biosciences, San Jose, CA); PE anti-CD95 (BD Biosciences, Carlsabad, CA). Analyses will be performed on a FACSAria flow cytometer (BD Biosciences,San Jose, CA) with FlowJo software (TreeStar, Ashland, OR). The following B cell subpopulations will be defined: immature/transitional, naïve, resting memory, tissue-like memory, plasmablast, and activated memory.

Determination of antigen specificity of B cells

In previous work, we performed immunophenotyping of B cells, which demonstrated persistence of abnormal phenotype of peripheral B cells in chronic HCV infected subjects undergoing treatment with 3DAAs. In this regard, there was a higher percentage of TLM B cells present in the peripheral blood of patients at the end of antiviral therapy. Using samples stored from patients from previous protocols, we will determine the antibody responses to HCV antigens during and after treatment in this study. Ruc-antigen fusions, including HCV core, have been previously described. We modified the LIPS technology for simultaneously screening protein panels arranged in a 96-well microtiter plate format. For these studies, extracts of Ruc fusions with proteins from HCV, and Influenza were first produced and stored frozen at−80°C to be used to generate an “antigen cell” for each protein. After incubation with serum samples, the serum-Ruc-antigen mixtures from each well of the microtiter plate were transferred to microtiter filter plates containing protein A/G beads. Each 96-well filter plate was then processed in the standard LIPS format for washing and measuring light units (LU) using a plate luminometer. Luciferase immunoprecipitation assays for profiling and quantification of these Ruc-antigens will be

performed in duplicate as previously described at baseline, weeks 4, 12 and 24 using 50 uL of cryopreserved serum per assay. Antibody titers, reported in LU, will be reported as the average of two independent experiments, after correction for background LU values. Changes in antibody titer from baseline and absolute antibody titers will be measured in patients undergoing treatment and compared.

RNA Seq Analysis.
We will perform transcriptional analysis of whole blood (Paxgene) and LILs. Illumina RNAseq libraries will be prepared with the TruSeq RNA Sample Prep kit (Illumina). Between first and second strand cDNA synthesis, the primers and nucleotides will be removed from the samples with NucAway spin columns (Ambion). The second strand will be synthesized with a dNTP mix. Adapters containing 6 nucleotide indexes will be ligated to the double-stranded cDNA. After adapter ligation, the second strand cDNA will be digested with 2 units of Uracil-N-Glycosylase (Applied Biosystems). The DNA will be purified between enzymatic reactions and the size selection of the library will be performed with AMPure XT beads (Beckman Coulter Genomics). The quantity and size of the libraries were assessed on the LabChip GX (Perkin Elmer) and with the Library Quantification Kit for Illumina (Kapa Biosciences)[30]. Analysis of data, including alignment and statistical analysis

6 HAZARDS/DISCOMFORTS/RISKS

6.1 DRUGS

6.1.1 Sofosbuvir

SOF is an FDA-approved medication for the treatment of HCV. As per the package insert, common side-effects of SOF therapy include, but are not limited to fatigue, headache, dizziness, and nausea. There may be additional side effects of SOF that are not yet known. SOF has been administered to over 10,000 subjects in combination with a DAA, Peg-IFN, and/or RBV in Gilead's clinical development programs as of July 2015. No clinical safety issues related to SOF have been identified to date.

6.1.2 Velpatasvir

In early studies done on those with HCV using VEL, participants 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. 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 VEL that are not yet known.

The safety profile of the regimen of SOF 400 mg and VEL 100 mg administered for 12 weeks has been established in approximately 230 subjects enrolled in Phase 2 studies**.** No clinical safety issues specifically related to VEL or SOF+VEL have been identified to date.

6.1.3 Voxilaprevir

To date, over 2600 subjects have received SOF/VEL+VOX in the Phase 1, 2, and 3 studies and there have been no clinical safety issues identified. There is no expectation of significant overlapping or new, unexpected toxicities upon coformulation of SOF/VEL with VOX as an FDC; data from study GS-US-367-1176 comparing SOF/VEL+VOX with SOF/VEL/VOX were consistent with this. However, a potential risk of the study includes the identification of previously undetected adverse effects.

6.1.4 Resistance

There is a potential risk for subjects to develop multiclass resistance if treatment in this study is unsuccessful. However, VOX has the highest reported barrier to resistance among NS3/4A PIs and so the anticipated clinical risk of developing drug-resistant mutants with VOX is anticipated to be lower than that associated with first and second generation NS3/4A PIs Accordingly, there was a lack of any viral breakthrough during therapy with VOX in the 3-day monotherapy study. Mutants generated in vitro to be resistant to VOX remain sensitive to SOF and GS-5816, supporting the clinical use of VOX in combination with other classes of HCV inhibitors. Lastly, this risk is balanced by the high efficacy shown in evaluations of SOF/VEL/VOX in Phase 2 studies and a very low rate of emergent resistance among subjects who relapsed.

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, NS5A, and NS3 inhibitors.

6.2 PROCEDURES

6.2.1 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 (450 ml over 6 weeks).

6.2.2 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.

6.2.3 Liver Biopsy

Liver biopsies performed within 36 months prior to Day 0, either the University of Maryland 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 as part of the screening process. 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.

7 BENEFITS/COMPENSATION/ALTERNATIVES

7.1 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 Institute of Human Virology, University of Maryland or Gilead Sciences

7.2 ALTERNATIVES

Subjects can receive hepatitis C treatment through their private physician or decide not to be treated at this time.

7.3 COMPENSATION

Subjects will receive remuneration for the immediate costs associated with their study-related expenses like travel expenses, lodging, etc. 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 for the inconvenience of the procedures necessary to obtain the samples. The compensation will be as follows:

- Liver Biopsy with research specimens: $250 cash per biopsy (maximum of 2)
- VK sub study: $200 cash after completion of all time points.
- Scheduled Study Visits: $25 cash or grocery gift card for lab visits and $50 cash or grocery gift card for study visits.

8 ADVERSE EVENTS AND TOXICITY MANAGEMENT

8.1 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.

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 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

Non-compliance: The failure to comply with applicable 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 UMD IRB
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

8.2 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.

Laboratory abnormalities that are gradable per the toxicity table will be recorded as AEs or SAEs. All other laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. Laboratory abnormalities that require medical or surgical intervention or lead to study drug interruption, modification or discontinuation must be recorded as an AE or SAE if applicable.

Laboratory assessments that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition.

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.

8.2.1 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

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)**

8.2.2 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.

8.3 SAFETY OVERSIGHT

Safety oversight will be conducted according to the Safety Monitoring Plan (see below) in a collaboration between the Principal Investigator (PI), lead Study Coordinator (SC) and the independent Medical Monitor.

8.3.1 Medical Monitor

An independent Medical Monitor (MM) has been appointed for oversight of safety in this clinical study. If at any point in the trial halting rules are met, the study team (PI and SC) will arrange a teleconference so that the event can be reviewed and the discussion documented. At the

end of each MM review meeting, the MM will be asked to provide a formal recommendation as to whether or not the protocol should be halted. A written summary of each MM review meeting will be provided to the MM and appropriate individuals. Participants on the MM teleconferences will include the MM, the PI and appropriate study team members.

8.4 SAFETY MONITORING PLAN

Ongoing Safety Monitoring by the Study Team: Cumulative safety data will be monitored by the study team (PI and SC). Upon recognition of any safety concerns, a teleconference may be held with the MM to discuss the concern. The PI will notify the MM and Gilead Clinical Safety Office (CSO) when enrollment begins and will provide verification of safety assessments to the MM and CSO. The ISM will review the viral kinetic, pharmacokinetic and resistance data to advise regarding continued study enrollment. The study team in collaboration with the study sponsor will then make a determination about whether the study enrollment needs to shut down.

Patient safety will be monitored by the PI and study team. Patient clinical data, safety data and virologic response will be monitored at weekly (or less frequently, as indicated by protocol activity) meetings by the study team and a summary report of these reviews will be retained as part of the study records. A complete evaluation of safety and efficacy data will be obtained when the first 20 patients complete 12 weeks of therapy. Thereafter, safety and data analysis will be performed every 12 weeks through completion of the study.
Additionally, the PI will be responsible for submitting the IRB Continuing Review package and will provide the necessary safety data for the FDA IND Annual Report.

8.5 SPECIFIC STUDY HALTING CRITERIA

8.5.1 Criteria to Pause Enrollment

- **Study will be paused** and the MM will be asked to review the data if 1: 3 participants experience virologic or therapeutic treatment failure while receiving treatment (see Dose Modification 3.4.1 and Treatment Failure Sections3.4.2)
- Dosing will be discontinued if 3 or more participants develop a similar related Grade 4 toxicity (excluding neutropenia, anemia, anorexia, weight loss and ALT and AST elevations). Further dosing will require review and approval after discussion with the MM. Grade 4 toxicities that result from patient non-compliance with medications for unrelated events will not be considered toward discontinuation.
- Enrollment will also be halted if the PI decides to stop or cancel the study or if the IRB or the FDA requests that the study be stopped.

8.6 INVESTIGATOR REPORTING RESPONSIBILITIES

8.6.1 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.

8.6.2 Serious Adverse Events

Any SAE will be reported to the IRB per institutional guidelines. SAEs (regardless of relationship) must be reported to Gilead Drug Safety & Public Health (DSPH) Office within 15 calendar days of first becoming aware of the event. Reporting any unexpected fatal or life-threatening suspected adverse reactions to the Division of Antiviral Agents at the FDA no later than 7 calendar days after initial receipt of the information. Safety reporting to the FDA will be done within the reporting requirement under 21 CFR 312.32

8.6.3 Gilead Safety Data Reporting

The Gilead DSPH will be notified via email (Safety_FC@gilead.com) of any potential safety issues or any protocol amendments or changes to the informed con sent form arising from a safety concern associated with any Gilead product within fifteen calendar days of first becoming aware of such event. Except for periodic safety reports, copies of all reports submitted to government agencies that are related to the study, as well as any correspondence with such authorities will be provided to Gilead.

Upon completion of the study, a listing of all safety information that has been sent to Gilead during the study will be sent to Gilead at standards.&collaborations@DSPH.com. At a minimum the listing must contain protocol number, patient ID number, case reference number, Gilead product and event term

8.7 DOCUMENTING AND RECORDING 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: case report forms (CRFs), 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 SOF, VEL and VOX will also be recorded.

8.8 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events that occur following initiation of investigational agent on day 0 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 and MM, as described above.

8.9 REPORTING PROCEDURES TO THE IRB

8.9.1 Expedited Reporting to the UMD IRB

Any serious and non-serious events, deaths, serious deviations, and serious or continuing non-compliance experienced by a subject or other individual which in the opinion of the primary investigator is unexpected and at least probably related to the Human Research procedures and suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized will be reported within 7 calendar days of investigator awareness. .

8.9.2 Waiver of Reporting Anticipated Protocol Deviations, Expected UPnonAEs and Deaths to the UMD 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. 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 will be reported at the time of continuing review.

8.9.3 Annual Reporting to the IRB

The following items will be reported to the 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

8.6.4 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 MM and CSO within 3 business days of the site's awareness on a protocol-specified form.

9 DATA HANDLING AND RECORD KEEPING

9.1 DATA HANDLING

All research data and results will be recorded using data collection forms. Source documents will support the data collected and will include, but not limited to; clinical findings and observations, laboratory and test data, hospital medical records, physician or office charts, physician or nursing notes, recorded data from automated instruments, x-rays, etc. Research data will be entered into a secure electronic database

9.2 STUDY RECORD 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 5 years. 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.

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