UTSouthwestern Harold C. Simmons Comprehensive Cancer Center | NCI CCC

Oral He**P**atitis C **T**reatment for **I**ndolent **L**ymphoma (OPTImaL) Study

Principal Investigator: Mamta K. Jain, MD, MPH
Infectious Diseases
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390-9113
214-648-6703
214-590-2689
Mamta.jain@utsouthwestern.edu

Sub-Site PI/ Investigators: Sonal Kumar, MD
GI/Liver Disease
Weil Cornell Medical Center
1305 York Ave
New York, New York 10021

Jia Ruan, MD
Hematology/Oncology
Weil Cornell Medical Center
1305 York Ave
New York, New York 10021

Maya Gambarin-Gewlan, MD
GI/Liver Disease
Memorial Sloan Kettering
1275 York Avenue
New York, New York 10065

Lia Palomba, MD
Hematology/Oncology
Memorial Sloan Kettering
1275 York Avenue
New York, New York 10065

Harris Nania, MD
Hematology/Oncology
Plaza Medical Center of Forth Worth
900 Eight Avenue
Fort Worth, TX 76104

Sub-Investigators (at UT) Robert Collins, MD
Hematology/Oncology
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390

Madhuri Vusirikala, MD
Hematology/oncology

UT Southwestern Medical Center
5323 Harry Hines
Dallas, Texas 75390

Prapti Patel, MD
Hematology Oncology
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390

Siayareh Rambally, MD
Hematology Oncology
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390

Jenny Li, MD
Hematology Oncology
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390

Biostatistician: Beverley Huet
UT Southwestern Medical Center
5323 Harry Hines Blvd
Dallas, Texas 75390
214-648-2788
Beverley.Huet@utsouthwestern.edu

Study Drug: Ribavirin, Sofobuvir, Sofosbuvir/Ledipasvir (Harvoni)
Sofosbuvir/Velpatasvir

Funding Source: Gilead Sciences, Inc. – IN-US-337-1811

Initial version: Version 4

Amended: **6/12/16**

UT Southwestern Medical Center (UTSW)
HIV/ID Research Unit
1936 Amelia Court
2nd floor Research Unit
Dallas, Texas 75235

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

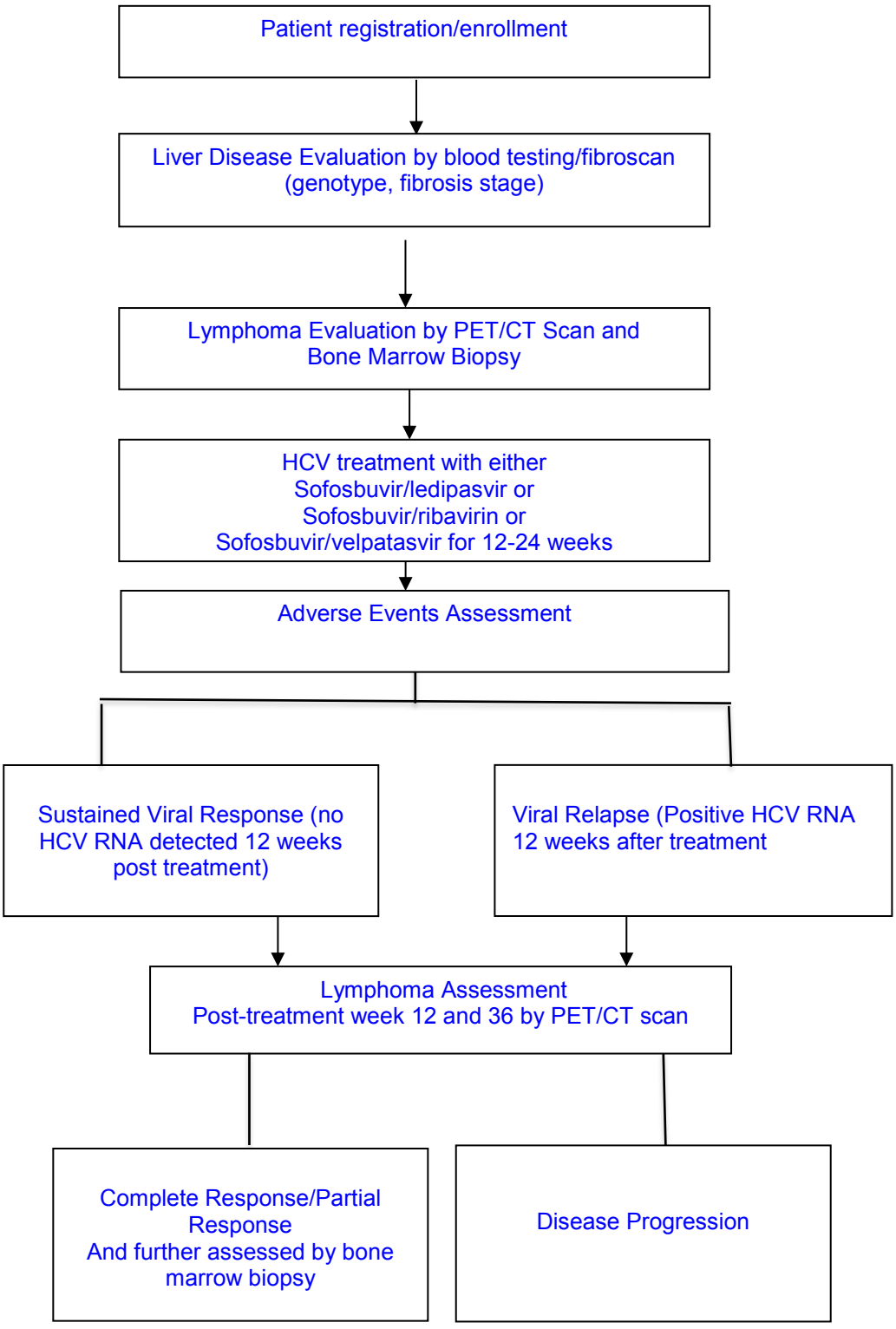
TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Disease
ACD	Anticoagulant
AE	Adverse Event
ALT	Alanine Aminotransferase
APRI	AST to Platelet Ratio Index
AST	Aspartate Aminotransferase
BCRP	Breast Cancer Resistance Protein
BID	Twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
BW	Body weight
CAP	College of American Pathologists
CBC	Complete Blood Count
CLIA	Clinical Laboratory Improvement Amendments
CMP	Comprehensive Metabolic Panel
CT	Computed Tomography
CV	Curriculum Vitae
DAIDS	Division of AIDS
dL	Deciliter
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FDC	Fixed-dose Combination
FDG	Fluorodeoxyglucose
FLIPI	Follicular Lymphoma International Prognostic Index
g	Gram
GCP	Good Clinical Practice
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C
Hg	Hemoglobin
HIV	Human immunodeficiency virus
IDSA	Infectious Disease Society of America
IFN	Interferon
IND	Investigational New Drug
IRB	Institutional Review Board
LD	Longest diameter
Kg	Kilogram
kPA	Kilopascal
LDH	Lactate Dehydrogenase
LDV	Ledipasvir
LFTS	Liver Function Tests

LLOQ	Lower limit of quantification
MC	Mixed cryoglobulinemia
Mcg	Microgram
NCI	National Cancer Institute
NHL	Non-Hodgkins Lymphoma
NS5A	Non-structural 5A
PCR	Polymerase chain reaction
PD	Progressive Disease
PE	Physical Exam
PEG	Pegylated interferon
PET	Positron Emission Tomography
PFS	Progression Free Survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PR	Partial Response
PT	Prothrombin time
PTT	Partial thromboplastin time
RBV	Ribavirin
REDCap	Research Electronic Data Capture
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
Scr	Serum creatinine
SD	Stable disease
sMZL	Splenic Marginal Zone Lymphoma
SPD	Sum of productions of the diameters
SOC	Standard of care
SOF	Sofosbuvir
SVR	Sustained Viral response
d. bili	Direct bilirubin
T. bili	Total bilirubin
UTSW	University of Texas Southwestern Medical Center
VL	Viral load

STUDY SCHEMA



STUDY SUMMARY

Title	**O**ral He**P**atitis C **T**reatment for **I**ndolent **L**ymphoma Study
Short Title	OPTImal
Protocol Number	STU 042015-086
Phase	IV
Methodology	This is a prospective, open-label, non-randomized interventional trial
Study Duration	2 years
Study Center(s)	Multi-center: UT Southwestern, Weil-Cornell Medical Center, Memorial Sloan Kettering
Objectives	This study will assess the safety, as measured by adverse events, in patients receiving Hepatitis C (HCV) treatment; lymphoma response; and sustained HCV viral response
Number of Subjects	21
Diagnosis and Main Inclusion Criteria	Patients must have hepatitis C and have low grade lymphoma that is stable and does not require chemotherapy.
Study Product(s), Dose, Route, Regimen	Ribavirin, Sofosbuvir (Sovaldi), Sofosbuvir/Ledipasvir (Harvoni), Sofosbuvir/velpatasvir
Duration of administration	12 weeks to 24 weeks depending on HCV genotype and stage of fibrosis and treatment regimen selected
Reference therapy	There is no reference therapy; this is an exploratory study
Statistical Methodology	The statistical analysis will be primarily descriptive. Descriptive statistics (e.g., mean, median, ranges, and frequencies) will be used to summarize AEs, SAEs, HCV treatment discontinuation and lymphoma treatment initiation. In addition these descriptive statistics will be used to for partial and complete response and SVR. 95% confidence intervals will be used to summarize the response for lymphoma and HCV. Any hypothesis testing will be considered exploratory and interpreted cautiously.

1.0 BACKGROUND AND RATIONALE

1.1 Background

Over 180 million people worldwide are chronically infected with the hepatitis C virus (HCV), a hepatotropic and potentially lymphotropic virus. HCV infection frequently leads to chronic hepatitis and is a major cause of liver cirrhosis and its sequelae such as hepatocellular carcinoma (HCC). While hepatocytes are the main reservoir and replication space for the virus, HCV is also potentially lymphotropic. A large body of clinical data supports the association of HCV infection and B-Non-Hodgkin's lymphoma (NHL). Epidemiologic studies, therapeutic approaches, and experimental data gathered in the last two decades established not only the mere association of viral infection and tumor development, but also suggests a causal relationship; e.g., sequencing of the Ig M heavy chain of patients with mixed cryoglobulinemia (MC) with and without B-NHL showed clonal B-cell expansion in 100% of HCV infected individuals in the peripheral blood. In a recent study of transgenic mice HCV genome was expressed in B cells which led to the development of NHL, thus further supporting the role of HCV in the pathogenesis of NHL. The most compelling argument for a causal relationship between HCV and B-NHL is made by interventional studies demonstrating that a sustained virologic response (SVR) to antiviral treatment containing alfa interferon and ribavirin treatment induced a regression of HCV-associated lymphomas and a viral relapse of HCV after initial virologic response led to lymphoma recurrence.

Hermine *et al*. evaluated the effect of HCV infection and antiviral therapy on the course of splenic marginal zone lymphoma (sMZL) with villous lymphocytes. Nine patients with HCV associated sMZL and 6 patients without HCV received recombinant interferon alfa-2b subcutaneously three times a week for six months. All nine patients had a negative HCV RT-PCR assay after antiviral therapy. Of the nine patients with HCV infection who received alfa interferon, seven had complete remission after the loss of detectable HCV RNA. The other two patients had a partial and complete remission after the addition of ribavirin and the loss of detectable HCV RNA. In contrast, none of the six HCV-negative patients had a response to interferon therapy.

A small multicenter prospective study conducted by Valliesa et al in which patients were treated with pegylated interferon alfa-2b 1.5 mcg/kg subcutaneously once a week and ribavirin 1,000 mg orally daily for 6 months, showed that of thirteen assessable patients with low grade lymphomas (one follicular lymphoma, four lymphoplasmacytic lymphomas, and eight marginal zone lymphomas), seven (58%) achieved complete response and two (16%) partial hematologic response at 14.1 -9.7 months (range, 2 to 24 months, median follow-up, 14 months), while two had stable disease with only one patient experiencing progression of disease. Hematologic responses (complete and partial, 75%) were highly significantly associated with clearance or decrease in serum HCV viral load following treatment (P= .005). Virologic response was more likely to be seen in HCV genotype 2 (P= 0.035), while hematologic response did not correlate with the viral genotype. Treatment-related toxicity did not cause discontinuation of therapy in all but two patients, one of whom, however, achieved complete response[1] . A recent epidemiological study from Italy showed 59% of HCV infection is due to genotype 2 and

remaining genotype 1. However, in the US, the predominant genotype is 1a/b followed by genotypes 2 and 3. These data suggest that treatment of HCV can treat low-grade B cell lymphoma. What remains unclear is if improvement of B-NHL is due, in part, to the indirect effect of interferon and cytokine modulation or if clearance of HCV itself leads to the response.

A recent retrospective analysis of 704 HIV-negative, HCV-positive, and patients with indolent NHL found the 5 year-survival was 78% and 5-year progression free survival was 48%. In a multivariate analysis, treatment for hepatitis C improved 5-year survival. Forty-four percent of those treated for HCV had a complete response and 33% had a partial response. The treatments occurred between 1993 and 2009 when interferon-based treatment was the only treatment option. Pegylated interferon and ribavirin combination therapy has efficacy of 40-50% in genotype 1 and 60-70% in genotype 2 and 3. However, new treatments for HCV is currently interferon free, all oral regimen(s), with high efficacy.

1.2 Treatment

1.2.1 Rationale for Sofosbuvir and Ledipasvir fixed dose combination

The combination of SOF 400 mg and LDV 90 mg has been administered in Phase 2 and Phase 3 studies to over 1600 subjects. After oral administration of SOF/LDV, SOF is rapidly absorbed and subject to extensive first-pass hepatic extraction. In clinical pharmacology studies, both Sofosbuvir and its inactive metabolite GS-331007 were monitored for purposes of pharmacokinetic analyses. Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of co-administered substrates for these transporters. Ledipasvir and Sofosbuvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. P-gp inducers (e.g., rifampin or St. John's wort) may decrease ledipasvir and Sofosbuvir plasma concentrations, leading to reduced therapeutic effect of SOF/LDV, and the use with P-gp inducers is not recommended with SOF/LDV.

The efficacy and safety of Sofosbuvir/ledipasvir were evaluated in four trials in genotype 1 HCV mono-infected subjects including one trial exclusively in treatment-experienced subjects with compensated cirrhosis (Child-Pugh A), one trial in genotype 1 or 4 HCV/HIV-1 co-infected subjects, and two trials in genotype 4, 5 or 6 HCV mono-infected subjects. Sofosbuvir/ledipasvir was administered once daily by mouth in these trials. For subjects who received ribavirin (RBV), the RBV dosage was 1000 mg per day for subjects weighing less than 75 kg or 1200 mg per day for subjects weighing at least 75 kg. RBV dose adjustments were performed according to the RBV labeling. Sustained virologic response (SVR12) was the primary endpoint and was defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment. Relapse was a secondary endpoint, which was defined as HCV RNA greater than or equal to LLOQ with 2 consecutive values or last available post-treatment measurement during the post-treatment period after achieving HCV RNA less than LLOQ at end of treatment.

ION-3 was a randomized, open-label trial in treatment-naïve non-cirrhotic subjects with genotype 1HCV. Subjects were randomized in a 1:1:1 ratio to one of the following three treatment groups and stratified by HCV genotype (1a vs 1b): Sofosbuvir/ledipasvir for 8 weeks, HARVONI for 12 weeks, or HARVONI + ribavirin for 8 weeks. Demographics and baseline characteristics of the 647 subjects were balanced across the treatment groups. SVR was 93% in 8

week arm and 96% in 12 week arm for genotype 1a. For genotype 1b it was 98% in 8 week and 12 week arm.

ION-1 was a randomized, open-label trial that evaluated 12 and 24 weeks of treatment with Sofosbuvir/ledipasvir with or without ribavirin in 865 treatment-naïve subjects with genotype 1 HCV including those with cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive Sofosbuvir/ledipasvir for 12 weeks, Sofosbuvir/ledipasvir + ribavirin for 12 weeks, Sofosbuvir/ledipasvir for 24 weeks, or Sofosbuvir/ledipasvir + ribavirin for 24 weeks. Randomization was stratified by the presence or absence of cirrhosis and HCV genotype (1a vs 1b). Demographics and baseline characteristics were balanced across the groups. Ribavirin + Sofosbuvir/ledipasvir was not found to impact SVR. SVR was 99% in treatment naïve patients without cirrhosis. Those with cirrhosis had SVR of 94%.

ION-2 was a randomized, open-label trial that evaluated 12 and 24 weeks of treatment with Sofosbuvir/ledipasvir with or without ribavirin in genotype 1 HCV-infected subjects with or without cirrhosis who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor. Subjects were randomized in a 1:1:1:1 ratio to receive Sofosbuvir/ledipasvir for 12 weeks, Sofosbuvir/ledipasvir + ribavirin for 12 weeks, Sofosbuvir/ledipasvir for 24 weeks, or Sofosbuvir/ledipasvir + ribavirin for 24 weeks. Randomization was stratified by the presence or absence of cirrhosis, HCV genotype (1a vs 1b) and response to prior HCV therapy (relapse/breakthrough vs nonresponse). Demographics and baseline characteristics were balanced across the treatment groups. SVR was 94% in 12 week and 99% in 24 week group. Those with cirrhosis had SVR in 12 week group of 86% and 100% in 24 week group.

In two open-label studies (Study 1119 and ION-4), Sofosbuvir/ledipasvir was administered for 12 weeks to treatment-naïve and previously-treated subjects with genotype 4 HCV infection. Study 1119 enrolled 44 treatment-naïve or previously-treated subjects with genotype 4 HCV, with or without cirrhosis. ION-4 enrolled 4 treatment-naïve and 4 previously-treated subjects with genotype 4 HCV infection who were coinfected with HIV-1, none of whom had cirrhosis. In Study 1119, the overall SVR12 rate was 93% (41/44). SVR12 was similar based upon prior HCV treatment history and cirrhosis status. In ION-4, all 8 subjects achieved SVR12.

Clinical studies have demonstrate >90% sustained viral response with Sofosbuvir/ledipasvir in genotype 1 and 4 patients. The combination of SOF 400 mg and LDV 90 mg as a fixed dose combination was approved by the FDA in October 2014 and will be the key treatment for HCV for this study.

Although limited, there is data for the use of Sofosbuvir/ledipasvir with ribavirin in patients with HCV genotype 3. In a phase 2 study, Sofosbuvir/ledipasvir plus ribavirin cured 73% (16/22) HCV genotype 3 patients with cirrhosis and 89% (25/28) non-cirrhotic treatment experienced patients.

1.2.2 Sofosbuvir and Ledipasvir (SOF/LDV) Common Adverse Events

Sofosbuvir with LDV have been given as two separate tablets and as one FDC tablet to over 2000 subjects. In the first part of one study, 200 patients who were being treated with the FDC

were evaluated 12 weeks after starting therapy. In this group, the most common adverse events that occurred in more than 15% of subjects were headache (29%), fatigue (22%), and nausea (19%).

Rare, but serious:

- One healthy volunteer developed significantly elevated liver tests (ALT) consistent with liver damage while taking SOF/LDV with abacavir/lamivudine (medications used to treat HIV). The patient's liver tests were normal after taking 10 days of SOF/LDV and then were elevated after taking another 5 days of SOF/LDV with abacavir/lamivudine. All study drugs were stopped and his liver tests improved a little but stayed elevated. Two weeks later, the patient had abdominal (belly) pain. An ultrasound showed he had gallstones and mild inflammation of the gallbladder. His gallbladder was removed. His liver tests completely returned to normal only after his gallbladder was removed. We do not know why he had elevated liver tests. The investigator thought that the elevated liver tests were related to SOF/LDV and abacavir/lamivudine. However, the volunteer's gallbladder disease may have played a role.

- One HCV-infected person developed superior mesenteric vein thrombosis (a clot in the blood vessel that drains blood from the small intestine) during treatment with SOF and LDV. The patient was a 52 year-old man with cirrhosis of the liver. About two weeks after starting treatment, he developed abdominal pain and then nausea and vomiting. The CT scan at the hospital showed a clot partially blocking a vessel draining blood from the small intestine. He was treated with pain medication and blood thinners. The event was considered to be related to the study drugs.

- A serious slowing of the heart rate (symptomatic bradycardia) can occur when this drug is used with antiarrhythmic drug **amiodarone**. This was a warning issued by the Federal Drug Administration as a *Warnings and Precautions, Drug Interactions, and Postmarketing Experience*.

1.2.3 Rationale for Sofosbuvir and ribavirin

Sofosbuvir 400 mg is pangenotypic inhibitor of NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form uridine analog triphosphate that leads to chain termination. Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. Following a single 400 mg oral dose of [14C]-Sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the Sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as Sofosbuvir. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of Sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively. Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not. Drugs that are P-gp inducers in the intestine (e.g., rifampin or St. John's wort) may decrease Sofosbuvir plasma concentration, leading to reduced therapeutic effect of Sofosbuvir, and thus concomitant use with Sofosbuvir is not recommended. Coadministration of Sofosbuvir with drugs that inhibit P-gp and/or BCRP may increase Sofosbuvir plasma

concentration without increasing GS-331007 plasma concentration; accordingly, sofosbuvir may be coadministered with P-gp and/or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and thus are not expected to increase exposures of drugs that are substrates of these transporters.

RBV is a guanosine analogue that inhibits the *in vitro* replication of a wide range of RNA and DNA viruses. RBV monotherapy has little or no effect on the replication of HCV *in vivo* but can result in normalization of serum ALT activity and improvement in liver histology. When combined with IFN or PEG-IFN therapy, RBV decreases substantially the relapse rate seen after cessation of IFN therapy.
Ribavirin is a known teratogen [Food and Drug Administration (FDA) category X]. Furthermore, RBV is known to accumulate intracellularly where it is cleared slowly, and is also excreted in semen. Therefore, extreme care must be taken to avoid pregnancy during RBV therapy and for up to 6 months following completion of treatment (7 months for males).

The safety and efficacy of Sofosbuvir was evaluated in five Phase 3 trials in a total of 1724 HCV mono-infected subjects with genotypes 1 to 6 chronic hepatitis C virus and one Phase 3 trial in 223 HCV/HIV-1 co-infected subjects with genotype 1, 2 or 3 HCV.

FISSION was a randomized, open-label, active-controlled trial that evaluated 12 weeks of treatment with Sofosbuvir and ribavirin compared to 24 weeks of treatment with peg interferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 2 and 3 HCV. The ribavirin dosage used in the Sofosbuvir + ribavirin and peg interferon alfa 2a + ribavirin arms were weight-based 1000-1200 mg per day and 800 mg per day regardless of weight, respectively. Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence), HCV genotype (2 vs. 3) and baseline HCV RNA level (less than 6 log10 IU/mL vs. at least 6 log10 IU/mL). Subjects with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio. SVR in genotype 2 without cirrhosis was 97% and 83% in those with cirrhosis compared to 81% without cirrhosis and 62% with cirrhosis in those receiving pegylated interferon and ribavirin for 24 weeks.

POSITRON was a randomized, double-blinded, placebo-controlled trial that evaluated 12 weeks of treatment with Sofosbuvir and ribavirin (N=207) compared to placebo (N=71) in subjects who are interferon intolerant, ineligible or unwilling. Subjects were randomized in 3:1 ratio and stratified by cirrhosis (presence vs. absence). SVR was 93%; with 92% in those without cirrhosis and 94% in those with cirrhosis.

FUSION was a randomized, double-blinded trial that evaluated 12 or 16 weeks of treatment with Sofosbuvir and ribavirin in subjects who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence) and HCV genotype (2 vs. 3). SVR was 82%; 90% in those without cirrhosis and 60% in those with cirrhosis.

The VALENCE trial evaluated Sofosbuvir in combination with weight-based ribavirin for the treatment of genotype 2 or 3 HCV infection in treatment-naïve subjects or subjects who did not

achieve SVR with prior interferon-based treatment, including subjects with compensated cirrhosis. The original trial design was a 4 to 1 randomization to Sofosbuvir + ribavirin for 12 weeks or placebo. Based on emerging data, this trial was unblinded and all genotype 2 HCV-infected subjects continued the original planned treatment and received Sofosbuvir + ribavirin for 12 weeks, and duration of treatment with Sofosbuvir + ribavirin in genotype 3 HCV-infected subjects was extended to 24 weeks. Eleven genotype 3 subjects had already completed Sofosbuvir + ribavirin for 12 weeks at the time of the amendment. SVR was 93% for genotype 2 and 84 % in genotype 3. Genotype 2, treatment naïve with or without cirrhosis had SVR of 97% but those who were treatment experienced had SVR of 91 without cirrhosis and 88% in those with cirrhosis. Genotype 3, treatment naïve patients without cirrhosis had SVR of 93% and with cirrhosis 92% (24 week treatment); however, treatment experienced patients without cirrhosis had SVR of 85% and those with cirrhosis was 60%.

Studies for HCV genotype 2 and 3 patients show that SOF 400mg in combination with weight-based RBV is effective with sustained viral response of >90% in genotype 2 and >80% in genotype 3. The combination of SOF and RBV weight-based, i.e. 1200 mg if≥75 kg or 1000 mg if <75 kg has been recommended by the AASLD/IDSA guidance as acceptable oral treatment for patients with genotype 2 and 3. Genotype 3, treatment experienced patients with cirrhosis would receive better response rates if treated with pegylated interferon, weight based RBV, and SOF. Thus, this group of patients will be excluded from the current protocol. SOF is and FDA approved agent.

1.2.4 Sofosbuvir Common Adverse Events

The safety profile of SOF in patients is based on the combined safety data from 4 studies where it was given for 12-16 weeks. In these studies, SOF was given at 400 mg once a day in combination with ribavirin (RBV) to 664 patients and in combination with RBV and pegylated interferon alfa 2a (PEG) to 327 patients. In patients taking SOF with RBV for 12-16 weeks, the most commonly reported side effects of these drugs were (≥10%) were fatigue (41%), trouble sleeping (18%), and irritability (10%).In patients taking SOF with RBV and PEG for 12 weeks, the most commonly reported adverse drug reactions (≥10%) were:

- fatigue (59%)
- headache (36%)
- nausea (34%)
- trouble sleeping (25%)
- low red blood cell count (21%)
- decreased appetite (18%)
- fever (18%)
- rash (18%)
- chills (17%)
- decreases in the blood cells that fight infection (17%)
- itchiness (17%)
- flu-like illness (16%)
- joint pain (14%)
- muscle pain (14%)
- dizziness (13%)
- irritability (13%)
- diarrhea (12%)
- shortness of breath (12%)
- vomiting (12%)
- cough (10%)
- pain (10%)

Most of these side effects were considered to be mild. These side effects overall were similar to those seen in subjects who took PEG and RBV without SOF. About one in forty subjects taking

SOF, RBV, and PEG had to stop their study medications early because of side effects. About one in sixty-five subjects taking SOF and RBV had to stop their study medications early because of side effects. Most of these side effects were believed to have been caused by PEG or RBV.

1.2.5 Ribavirin Common Adverse Events

RBV is usually taken with pegylated interferon (a once per week shot). The most common side effects when taking RBV combined with pegylated interferon are flu-like symptoms consisting of:

- body aches and pains
- fever
- chills
- headache
- overall feeling of sickness
- rash

Other common side effects are: anxiety, mood changes, depression, and irritability.
The most serious side effect seen with RBV is anemia (a decrease in the number of red blood cells in your body that carry oxygen). This may cause tiredness and lack of energy. RBV can cause severe damage and even death of an unborn child or fetus. **Extreme care should be taken to prevent pregnancy while you are taking ribavirin and afterwards.**
It is not expected that there will be all of these side effects. Other side effects may occur which are not listed here or were not seen before. Study subjects should speak to their study doctor for more information. Side effects are usually temporary and can often be treated. However, it is very important that you report all side effects as it is possible that these side effects could be serious or fatal.

1.2.6 Rationale for Sofosbuvir/Velpatasvir

Sofosbuvir/velpatasvir is a new combination of nucleotide polymerase inhibitor sofosbuvir with NS5A inhibitor velpatasvir.

Astral-2/ Astral-3

In a randomized phase 3 trial, open-label, study of previously treated genotype 2 or 3 and treatment naïve patients ,including patients with compensated cirrhosis. In genotype 2, subjects were randomized to sofosbuvir 400 mg/weight-based ribavirin (n=132) versus sofosbuvir/velpatasvir (n=134) for 12 weeks. Subjects on sofosbuvir 400 mg/velpatasvir 100mg achieved SVR 12 of 99% (95% CI, 96-100) vs. 94% (95% CI, 88-97) in the sofosbuvir/ribavirin arm, p=0.02) In genotype 3, subjects were assigned to sofosbuvir/velpatasvir (n=277) for 12 weeks versus sofosbuvir/weight-based ribavirin (n=275) for 24 weeks. SVR 12 was achieved in 95% (95% CI, 92-98) in the sofosbvuvir/velpatasvir compared to 80% (95% CI, 75-85) in the sofosbuvir/weight-based ribavirin group, p<0.001). Because of the superior efficacy of

sofosbuvir/velpatasvir, this fixed-dose combination will be considered the preferred threatment for genotype 2 and 3 [2].

Astral-1

In this study subjects with genotype 1, 2, 4, 5, 6 were enrolled. Subjects included those with compensated cirrhosis and prior treatment failure to interferon. Subjects were randomized 5:1 fashion to sofosbuvir/velpatasvir (400mg/100mg) versus placebo for 12 weeks. The overall SVR 12 was 99% (95% CI, 98 to >99) which was superior to prespecified performance goal of 85% (P,0.001). By genotype SVR 12 was 98% (95% CI, 95 to>99) for genotype 1a, 99% (95% CI, 95-100) with genotype 1b, 100% (95% CI, 97-100) with genotype 2, 100% (95% CI, 97 to100) with genotype 4, 97% (95% CI, 85to >99) with genotype 5, and 100% (95% CI, 91to 100) with genotype 6 [3]. Because of the high efficacy, subjects with genotype 1 or 4 will also be allowed to take sofosbuvir/velpatasvir if deemed appropriate by the study investigator.

1.2.7 Sofosbuvir/velpatasvir common adverse events

Of the 624 patients on fixed-dose combination of sofosbuvir/velpatasvir, 1 discontinued treatment prematurely because of an adverse event. There were 15 subjects (2%) had 19 serious adverse events. There was one death in the sofosbuvir/velpatasvir group. There were no significant differences in adverse events between sofosbvuir/velpatasvir compared to placebo (78% vs . 77%, respectively). Most common adverse events were headache, fatigue, nasopharyngitis, and nausea. Hematologic abnormalities were infrequent in sofosbuvir/velpatasvir group (1%). No patients in either study group had grade 3 or 4 elevation of creatinine or total bilirubin.
The most frequent AEs were headache (29%), fatigue (20%), nasopharyngitis (13%), nausea (12%), insomnia (8%), diarrhea (8%), asthenia (7%), arthralgia (6%), cough (6%), back pain (5%), myalgia (4%). Hematolgic events hemoglobin <10 g/dl (<1%), lymphocyte count 350<500 per mm^3 (<1%), Neutrophil count 500 to <750 per mm^3 (1%), platelet count 25,000 to <50,000 (<1%)[3].

1.3 Other Agents

No investigational agents will be used in this study.

1.4 Rationale

There still remains the question if HCV eradication with all oral therapy will lead to a regression or cure of the low grade lymphoma. Thus, our hypothesis is that oral HCV therapy will lead to a high rate of HCV eradication which will correlate with a reduction of the size and extent of low-grade lymphoma. We hypothesize that patients with HCV, regardless of genotype and who have low grade lymphoma when treated for HCV without pegylated interferon will have a regression of low grade NHL. In this pilot study we will evaluate the effect of Sofosbuvir/ledipasvir or Sofosbuvir/ribavirin based antiviral therapy on the course of a subset of HCV-related low grade B-NHL.

1.5 Correlative Studies

Blood will be stored for future genetic testing /mutational analysis if funding is available. Blood will be collected at three time points during the study and stored. In the future if funding is available, mutational analysis from the blood will be compare to mutational analysis from bone marrow biopsy. We hypothesize that clonal changes will be detected in the blood that will correlate with changes found in bone marrow. In addition, these changes will be detected at an earlier time point than the bone marrow biopsy. This study will be exploratory and hypothesis generating. Blood will be collected at baseline, post-treatment week 12 and post-treatment week 36. The blood will stored at each local site and shipped together (batched) at the end of the study.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

This study will assess the safety, as measured by adverse events, in patients receiving HCV treatment.

2.2 Secondary Objectives

The secondary objective(s) of this study is to assess the (1) rate of overall response of B-NHL defined as either as partial response or complete response according to revised international working group criteria for non-Hodgkin lymphoma and (2) rate of sustained viral response to hepatitis C treatment.

2.3 Endpoints

Primary Endpoints

Safety and tolerability of Sofosbuvir/ledipasvir or Sofosbuvir/ribavirin in patients with B-NHL will be assessed by number of AEs and SAEs. In addition, we will assess the number of patients who had to stop treatment due to AEs or SAEs. And we will also examine the number of patients in which treatment for lymphoma had to be given due to clinical progression.

Secondary Endpoints

The secondary endpoint(s) of this study is to (1) Assess the rate of overall response of B-NHL defined as either as partial response or complete response according to revised international working group criteria for non-Hodgkin lymphoma. (2) Determine the rate of SVR in patients with low-grade lymphoma.

3.0 Subject ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Willing and able to provide written informed consent.

3.1.2 Male or female >18 years of age

3.1.3 Serum HCV RNA levels of >1,000 IU per milliliter or higher

3.1.4 HCV treatment experienced or naïve.

i. HCV treatment naïve: No prior exposure to any IFN, RBV, or other approved or experimental HCV-specific DAA.

ii. HCV Treatment-Experienced: Virologic failure after treatment with PEG- IFN + RBV, NS3 protease inhibitor plus PEG-IFN + RBV, or regimen of SOF±RBV±PEG-IFN regimen.

3.1.5 Chronic Hepatitis C based on the judgment of the investigator

3.1.6 HCV genotype 1, 2, 3, 4

3.1.7 If the patient is determined to be cirrhotic (based on criteria outlined earlier), the patient must have an ultrasound done within 6 months prior to enrollment with no evidence of hepatocellular carcinoma.

3.1.8 Indolent Non-Hodgkin's lymphoma , which may include the following :

a. Nodal Marginal zone lymphoma
b. Extranodal marginal zone lymphoma MALT
c. Splenic marginal zone lymphoma
d. Follicular lymphoma Grade 1-3a with low tumor burden*, FLIPI 2 risk category of either low (i.e. no risk factors) or intermediate (1-2 risk factors), and with no B symptoms. B symptoms are defined as:
   i. Fever (i.e., temperature >38°C [>100.4°F]) for 3 consecutive days
   ii. Weight loss exceeding 10% of body weight in 6 months
   iii. Drenching night sweats
e. Lymphoplasmacytic lymphoma

3.1.9 No prior chemotherapy

*Low tumor burden is defined as normal lactate dehydrogenase, largest nodal or extranodal mass less than 7 cm, up to three nodal sites containing nodes with a diameter greater than 3 cm, no clinically significant serous effusions detectable by physical examination or PET/CT scan, and spleen enlargement up to 16 cm by CT without any evidence of portal hypertension.

3.1.10 Karnofsky performance status > 70%

3.1.11 Creatinine clearance ≥60 mL/min, as calculated by Cockcroft-Gault equation

3.1.12 If patient will need ribavirin in their regimen then the following inclusion:

a. Hg >12 g/dL for male
b. Hg >11 g/dL for female

3.1.13 All women of child-bearing potential who take ribavirin will need to have a negative pregnancy test

3.2 Exclusion Criteria

3.2.1 Life expectancy < 6 months based on judgement of investigator

3.2.2 Any subject who currently needs HCV treatment which uses pegylated interferon

3.2.3 Co-infection with hepatitis B

3.2.4 Prior chemotherapy for lymphoma

3.2.5 Lymphomas of other histologies other than the ones listed in section 3.1.8 above

3.2.6 Follicular lymphoma with large cell transformation

3.2.7 Decompensated liver disease in which pegylated interferon is contraindicated.

3.2.8 Female who is pregnant or breast feeding and HCV treatment requires use of ribavirin.

3.2.9 Solid organ transplant

3.2.10 Any IFN- containing agent within 8 weeks prior to screening or any prior exposure to HCV-specific antivirals agent(s), other than NS3/4A protease inhibitor and Sofosbuvir

3.2.11 Known hypersensitivity to ledipasvir, Sofosbuvir, or formulation excipients.

3.2.12 On a prohibited medication which cannot be stopped during the duration of HCV treatment.

3.2.13 Female subject who is pregnant or breastfeeding

3.2.14 HIV-infection

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

All treatment for this study will be administered orally and in the outpatient setting.

4.1.1 Genotype 1:

Treatment Naïve, with or without cirrhosis: Sofosbuvir/ledipasvir one pill once a day for 12 weeks.
Or

Sofosbuvir/velpatasvir one pill once a day for 12 weeks.

Treatment experienced, with or without cirrhosis:
Sofosbuvir/velpatasvir one pill once a day for 12 weeks
Or
Alternative: Sofosbuvir/ledipasvir one pill once a day with weight-based ribavirin for 12 weeks. Weight-based ribavirin refers to use 1200 mg of ribavirin in divided doses for those ≥75 kg and 1000 mg in divided dose for those <75kg.
Or

Alternative: Treatment experienced with cirrhosis unable to take ribavirin: Sofosbuvir/ledipasvir one pill once a day for 24 weeks.

4.1.2 Genotype 2:

Treatment naïve or experienced with or without cirrhosis: Sofosbuvir/velpatasvir one pill once a day for 12 weeks.

Alternative: Sofosbuvir 400mg once daily and ribavirin 1000/1200 mg weight-based dosing in divided dose BID for 12 weeks.

Alternative: Treatment naïve or experienced with cirrhosis: Sofosbuvir 400mg and weight-based ribavirin for 16 weeks.

4.1.3 Genotype 3:

Treatment naïve, non-cirrhotic or with cirrhosis:
Sofosbuvir/velpatasvir one pill once a day for 12 weeks.

or
Alternative: Sofosbuvir/ledipasvir fixed dose combination combined with weight-based ribavirin for 12 weeks
or

Alternative: Treatment naïve with cirrhosis: Sofosbuvir 400 mg daily with weight-based ribavirin for 24 weeks
or
Alternative:Treatment experienced, non-cirrhotic: Sofosbuvir 400mg daily with weight-based ribavirin for 24 weeks.

4.1.4 Genotype 4:

Treatment naïve or experienced with or without cirrhosis:
Sofosbuvir/velpatasvir one pill once a day for 12 weeks.
Or

Alternative: Sofosbuvir/ledipasvir fixed dose combination for 12 weeks.

or

Alternative: Treatment experienced with cirrhosis: Sofosbuvir/ledipasvir for 24 weeks.

**** Please note all regimens given must be orally administered and not include interferon. Thus, if FDA label and/or AASLD/IDSA guidance gives multiple options for treatment, the choice selected should be oral and include Sofosbuvir.**

4.2 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity during each study visit as outlined in the schedule of events Table 5.1. Toxicity will be assessed according to the Division of AIDS (DAIDS) Toxicity Management guidelines: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf .

4.2.1 Dose reduction or discontinuation of RBV

Dose reduction or discontinuation of ribavirin due to hemoglobin toxicity or related symptoms is allowed at the discretion of the Investigator.

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

4.3 Concomitant Medications

Concomitant medications taken within 30 days prior to Screening, up to and including post-treatment visit 48 weeks or Early Termination.

The following medications are prohibited during the screening period and for a minimum of 28 days prior to the Baseline/Day 1 Visit through the end of study:

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 PK interactions resulting in increases or decreases in exposure of study drug(s) are prohibited from 21 days prior to Baseline/Day 1 Visit through the end of study. P-gp inducers such as St. John's wort and rifampin should not be used.

Examples of representative medications which are listed below:

Disallowed and Concomitant Medications to be used with Caution

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing	Proton Pump Inhibitors > 20 mg of omeprazole or equivalent	H2 blockers Antacids separated by 4 hours
Antiarrhythmics	Amiodarone	Quinidine
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials	Rifabutin, Rifapentine, Rifampin	
Cardiac Medications		Valsartan, Olmesartan, Telmisartan, Ranolazine, Bosentan, Digoxin
Herbal/Natural Supplements	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb	

	sho-saikoto (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors	Rosuvastatin	Atorvastatin (<10 mg per day), Simvastatin, Pitavastatin, Fluvastatin, Lovastatin

4.4 Other Modalities or Procedures

There are no other treatment modalities that will be used in this protocol.

4.5 Duration of Treatment

The duration of HCV treatment will be determined by the principal investigator based on genotype, treatment experience, and presence of cirrhosis. Duration of treatment may vary. Please refer to section 4.0

4.6 Duration of Follow Up

Participations will be followed for 36 weeks post-treatment. Subject will have HCV RNA checked post-treatment week 12 to determine SVR. Subjects will have CT/PET scan post-treatment week 12 and 36 to measure any changes in lymphoma size.

4.7 Removal patients from Protocol Therapy

A subject may be discontinued from treatment for the following reasons:

1. Unacceptable toxicity, or toxicity that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
2. Pregnancy of female subject
3. HCV efficacy failure defined as HCV RNA >LLOQ on two separate measurements at least 1 week apart. Patient may remain in follow-up on study but off drug.

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

4.8 Subject Replacement

There will be no subject replacement.

5.0 STUDY PROCEDURES

Patients will have HCV RNA quantification done at baseline, week4, end of treatment, 4-weeks post-treatment and then 12-weeks post-treatment (SVR 12) and 24-weeks post-treatment (SVR 24). If patients are on extended treatment, HCV RNA will be collected at each visit during treatment except for week 8. We do not anticipate late relapses after 24 weeks post therapy. Patients will undergo a detailed clinical examination to assess the size of lymph nodes, liver and spleen. Patients will get a complete blood count, complete metabolic panel, β2 microglobulin, and LDH at baseline, 4 week, 8 week, and 12 weeks, then every 3 months to assess hematological response. LDH will also be collected at extended treatment visits. At screening a bone marrow biopsy will be done with flow cytometry. In those patients with bone marrow involvement who have evidence of complete remission by PET/CT scan, a repeat bone marrow biopsy with flow cytometry will be conducted to determine if patient achieved a complete remission. In addition to the clinical examination, patients will have a full body CT –PET scan at the time of enrollment, at 12 weeks post-HCV treatment and at 36 weeks post-HCV treatment.

5.1 Screening and Baseline

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 45 days prior to enrollment unless otherwise stated. The screening procedures include:

5.1.1 Pre-screen >1 month before enrollment.

Hepatitis C:
Patient will have evidence of hepatitis C based or standard of care serology. HCV RNA and HCV genotype will also be obtained as part of standard of care. The patient will be considered to have cirrhosis by one of the following methods:

- Liver biopsy showing cirrhosis
- FibroScan® showing cirrhosis or results >12.5 kPa
- A FibroTest® (or FibroSure®) score of >0.75 and an aspartate aminotransferase (AST):platelet ratio index (APRI) of >2 during Screening

If the patient has cirrhosis by the above criteria, then an ultrasound must be obtained to rule out hepatocellular carcinoma within 6 months of enrollment. This will be obtained as part of standard of care.

Lymphoma:

Patients must have a bone marrow biopsy with flow cytometry to assess for presence of low grade lymphoma performed at screening if there is no prior bone marrow biopsy or if prior biopsy showed no bone marrow involvement. A prior biopsy which shows bone marrow involvement may be used if obtained <3 months prior to screening.

5.1.2 Screen

Screen may take place 45 days to 1 day prior to enrollment.
Patients will have the following obtained during the screening period;

5.1.2.1 Informed Consent

The subject will read the informed consent. Study coordinator or site investigator will review key aspects of the study with the study participant. Subjects will be encouraged to ask questions. The subject will sign and date the consent after study treatment and procedures are explained and all questions answered.

Subjects will also sign a release of information (if needed) to obtain data outlined in the pre-screen section.

5.1.2.2 Medical History

Medical history including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing or stopped (date of resolution), and medication history will be collected on all subjects during screening. HCV treatment history will be used to categorize the subject as either a treatment intolerant, non-responder or relapse/breakthrough defined as:

- Treatment Intolerant: Subject discontinued prior HCV treatment regimen due to development or significant worsening of a treatment related AE.
- Non-Responder: Subject did not achieve undetectable HCV RNA levels (HCV RNA ≥ LLOQ) while on treatment. Subject must not have discontinued prior therapy due to an AE.
- ~For PEG-IFN/RBV non-responders, subjects should be further defined as Null or Partial Responders:
  - Null Responders: HCV RNA < 2 Log10 reduction during the first 12 weeks of treatment.
  - Partial Responders: HCV RNA ≥ 2 Log10 reduction during the first 12 weeks of treatment.
  - Relapse/Breakthrough: Subject achieved undetectable HCV RNA levels (HCV RNA < LLOQ) during treatment but did not achieve a SVR. Subject must not have discontinued prior therapy due to an AE

5.1.2.3 Review Subject inclusion /exclusion criteria

From the medical history and medical records, the coordinator will assess to determine if subject meets entry requirements. All inclusion/exclusion criteria must be verified by the site investigator.

5.1.2.4 Concomitant Medications

All medications which a subject is currently taking will be recorded. Start dates will be recorded and the reason for taking the medication. Medications will be check against prohibited and cautionary medications to make sure subject qualifies for study. If subject stops medications previously recorded, then a stop date will be recorded and reason for stopping the medication. Study medications will not be included in concomitant medications.

5.1.2.5 Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and temperature, weight, height. The vital signs performed at Study Day 1 will serve as the baseline for clinical assessments. Height will only be measured at Screening; the subject will not wear shoes.

Blood pressure will be measured using the following standardized process:

1. Subject should sit for > 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
2. Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
3. Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

5.1.2.6 Labs

The following labs will be obtained during the screening visit.
CBC with diff
Liver function tests (ALT, AST, T. Bili, D. Bili, alkaline phosphatase, total protein and albumin)
PT/PTT
Electrolytes (Sodium, potassium, carbon dioxide, chloride, glucose, calcium)
BUN
Creatinine
LDH
B2 microglobulin
Hepatitis B surface antigen
HIV antibody 1& 2

5.1.2.7 Pregnancy Testing

All females of childbearing potential will have a urine pregnancy dipstick test at screen. All women of child bearing potential who will be on ribavirin as part of their HCV regimen will have a urine pregnancy dipstick test at baseline and then every 4 weeks during the dosing period (until week 12) and then at week 12, 16, 24, and 36 of study . Positive urine pregnancy result, subjects will be instructed to stop study drugs immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

5.1.2.8 Blood and Tissue for storage for future studies and back-up

Patient will be required to sign a separate consent for acquisition of extra blood samples for research purposes. Blood will be collected and stored for future genetic analysis and compared to B cell mutations found from bone marrow biopsy. 10 ml of whole blood will be collected in

ACD or EDTA vacutainer tubes and must be completely filled. The samples collected will be batched and sent to UT Southwestern for storage. The de-identified samples will be sent for analysis once funding is available for the project. Blood will be stored locally as a back-up if a mishap occurs in the lab and if stored sample could be used for a replacement.

5.1.2.9 Karnofsky Score

The Karnofsky score will be determined based on the appendix (14.0)

5.1.2.10 Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation using actual body weight (BW).

$$\text{Male: CLcr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{BW (kg)}}{72 \times \text{Scr}}$$

$$\text{Female: CLcr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{BW (kg)} \times 0.85}{72 \times \text{Scr}}$$

Scr = serum creatinine (mg/dL)

5.1.2.11 Body Mass Index (BMI)

Height and weight will be measured without shoes. Height will be measured at Screening only; BMI will be calculated at Screening for inclusion criteria using the following formula:

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

5.1.2.1 Whole Body PET/CT SCAN

A whole body PET or CT scan will be obtained. The decision of PET vs. CT will be made by the treating oncologist or oncology investigator and will be based on the type of lymphoma the subject has.

5.1.1 Baseline

5.1.1.1 Complete Physical Examination

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

5.1.1.2 Drug dispensation

Drug will be dispensed as prescribed by the study investigator in accordance to the protocol. The number of bottles with number of pills will be recorded.

- Concomitant medications (as described above)
- Vital signs including BMI
- Karnofsky Score
- Labs:
  - HCV RNA
  - CBC with diff
  - LFTS
  - BUN
  - Creatinine
  - Electrolytes
  - LDH
  - B2 microglobulin
  - Urine pregnancy test by dipstick in women of child bearing potential
- Blood for storage
- Blood for genetic analysis

5.2 Procedures During Treatment

5.2.1 Week 2 visit (+/- 2 days)

5.2.1.1 Adverse Event Log

A record of symptoms experienced by the subject will be recorded. Start and stop dates will be recorded. Symptoms will be rated by NCI grading toxicity as defined in 7.2.1. Any action taken due to the adverse event will be recorded. Any laboratory abnormalities will be recorded and graded by grade 1-5.

5.2.1.2 Targeted PE

The subject will have target physical exam if there are any symptoms. If no symptoms, the exam will consist of examination of heart, lung, abdomen, skin and lymph nodes.

- Concomitant medication
- Vital signs
- Labs:
  - CBC with diff
  - Blood for storage

5.2.2 Week 4 visit (+/- 2 days)

- Concomitant medication and Adverse Event Log
- Vital signs
- Drug Dispensation
- Targeted PE
- Labs:
  - CBC with diff

Electrolytes
BUN
Creatinine
HCV RNA
LFTS
LDH
B2 microglobulin
Blood for storage

5.2.3 Week 8 (+/- 2 days)

- Concomitant medication and Adverse Event Log
- Vital signs
- Drug Dispensation
- Labs:
  - CBC with diff
  - Electrolytes
  - BUN
  - Creatinine
  - LFTs
  - LDH
  - B2 microglobulin
  - Blood for storage

5.2.4 Week 12, 16, 20 (+/- 2 days) for patients on extended therapy

- Concomitant medication and Adverse Event Log
- Vital signs
- Drug Dispensation
- Labs:
  - CBC with diff
  - Electrolytes
  - BUN
  - Creatinine
  - LFTs
  - LDH
  - HCV RNA
  - B2 microglobulin
  - Blood for storage

5.2.5 End of Treatment (+/- 2 days)

- Concomitant medication and adverse event log
- Vital signs
- Complete Physical Exam
- Labs:
  - CBC with diff
  - Electrolytes

BUN
Creatinine
LFTs
LDH
B2 microglobulin
HCV RNA
Blood for storage

5.3 Procedures Post-Treatment

5.3.1 Post Treatment Week 4 (+/-5 days)

- Concomitant medication and Adverse Event Log
- Vital signs
- Physical Exam
- Labs:
  - CBC with diff
  - Electrolytes
  - BUN
  - Creatinine
  - LFTs
  - HCV RNA
  - LDH
  - B2 microglobulin
  - Blood for storage

5.3.2 Post Treatment Week 12 (+/-7 days)

- Concomitant medication and Adverse Event Log
- Vital signs
- Physical Exam
- Whole body PET/CT Scan
- Labs:
  - CBC with diff
  - Electrolytes
  - BUN
  - Creatinine
  - LFTs
  - LDH
  - B2 microglobulin
  - HCV RNA
  - Labs for genetic analysis (batched)
  - Blood for storage

5.3.3 Post Treatment Week 24 (+/-7 days)

- Concomitant medication and Adverse Event Log

- Vital signs
- Physical Exam
- Labs:
  - CBC with diff
  - Electrolytes
  - BUN
  - Creatinine
  - LFTs
  - LDH
  - B2 microglobulin
  - HCV RNA
  - Blood for storage

5.3.4 Post Treatment Week 36 (+/-7 days)

5.3.4.1 Bone Marrow biopsy

A bone marrow biopsy with flow cytometry in those who have evidence of complete remission on PET/CT Scan

- Concomitant medication and Adverse Event Log
- Vital signs
- Physical Exam
- Whole Body PET/CT Scan
- Labs:
  - CBC with diff
  - Electrolytes
  - BUN
  - Creatinine
  - LFTs
  - LDH
  - Beta 2 microglobulin
  - HCV RNA
  - Labs for genetic analysis (batched)
  - Blood for storage

5.3.5 Early Termination Visit

- Concomitant Medications and Adverse Events Log
- Complete Physical Exam
- Vital Signs
- Labs:
  - CBC with diff
  - Complete Metabolic Panel
  - HCV RNA
  - Electrolytes
  - BUN

Creatinine
LDH
B2 microglobulin
Blood for storage

5.3.6 Unscheduled visit

A subject should attend an unscheduled visit if requested by the Sponsor or the Investigator. The assessments are at the Investigator's discretion, and will at a minimum collect adverse events (AE's) and concomitant medication information. At all unscheduled visits initiated for the purpose of confirming HCV failure a sample for viral RNA sequencing/phenotyping or genotyping/phenotyping, respectively, may be collected. Blood may be stored for HCV genotyping.

5.4 Time and Events Table

	Screen	Screening period	Baseline	Week 2	Week 4	Week 8	Week 12, 16, 20 [a]	EOT	PT Week 4	PT Week 12	PT Week 24	PT Week 36	Early Termination Visit
Informed Consent	X												
Review Inclusion/Exclusion	X												
Medical History	X												
Physical Exam (initial)	X												
Vital Signs, Weight, Height	X			X	X	X	X	X	X				X
Medication review /Accountability	X		X	X	X	X	X	X	X	X	X	X	X
Brief visit /Vitals			X					X		X	X	X	
Karnofsky Score[b]	X		X										
PET scan		X (SOC)								X		X	
HIV Antibody 1& 2	X												
Hepatitis B surface antigen	X												
HCV RNA			X	-	X		X	X	X	X	X		X
HCV genotype	X (SOC)												
CBC	X		X	X	X	X	X	X	X	X	X	X	X
B2 microglobulin	X		X		X	X	X	X	X	X	X	X	X
CMP[g]/LDH	X		X		X	X	X	X	X	X	X	X	X
PT/PTT		X[c]										X	
Urine pregnancy test[c] or urine dipstick[d]	X[d]		X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X		
Lymphoma, type stage	X												
Bone marrow biopsy and flow		X (SOC)										X[f]	
Fibrosis staging		X											
Blood draw	X		X	X	X	X		X	X	X	X	X	X
Ribavirin insurance/pap		X											
Drug dispensation			X		X	X							
Drug accountability					X	X	X	X					
Adverse Events				X	X	X	X	X	X	X	X	X	X
Special mutation analysis[h]			X							X		X	
Blood for storage	X		X	X	X	X	X	X	X	X	X	X	X

a. For those on extended therapy of 16 or 24 weeks
b. Karnofsky Score: See Appendix 1.
c. If needed for liver biopsy or bone marrow biopsy
d. Urine Pregnancy Test: To be done at screening for WOCBP
e. Urine Dipstick: To be done at all visits from baseline forward for WOCBP.
f. If needed for those who have complete response by Pet Scan
g. CMP includes electrolytes (Na, K, Chloride, Bicarb), BUN, Cr, LFT (ALT, AST, Alk phos, T. Bili, D. Bili, albumin, total protein), Calcium, glucose
h. Optional: Separate consent would need to be signed.

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject demonstrates disease progression

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the subject's best interest

5.5.7 Subject becomes pregnant

Pregnancy to be reported along same timelines as a serious adverse event

5.5.8 Development of second malignancy

Except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

6.0 MEASUREMENT EFFECT

6.1 HCV Treatment Response:

SVR: A patient will be considered to have achieved sustained viral response (SVR) if HCV RNA is undetectable 12 weeks after completion of HCV treatment.
Relapse: A patient will be considered to be a relapse if HCV RNA became undetectable during HCV treatment but became detectable post week 4 or 12.
Breakthrough: A patient will be considered to have breakthrough if HCV RNA becomes undetectable and then subsequently is confirmed detectable during HCV treatment.
Treatment Failure: The following on-treatment HCV virologic response-based treatment stopping criteria will be utilized:

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

Confirmation should be performed as soon as possible and must occur no later than 2 weeks after an initial observation indicating virologic failure. All subjects who terminate treatment early will complete the Early Termination (ET) Visit, Week 4, Week 12, and Week 24 Post-Treatment Visits.

6.2 Lymphoma Treatment Response

The 2014 Lugano classification criteria will be used for initial staging and treatment response assessment.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one dose of HCV treatment, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below.

Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior		

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
		sites of disease and no new sites on CT or PET		
		(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
		Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy		

- Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered

non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.3 Safety and Tolerability

At each study visits, adverse side effects to study treatment will be assessed in order to determine safety and tolerability of this treatment in this population.

7.0 ADVERSE EVENTS AND SERIOUS EVENTS

7.1 Experimental Therapy

There is no experimental therapy given.

7.2 Adverse Events Monitoring

Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- Death.

7.2.1 Definition

Adverse Events will be reported as indicated by the appropriate following table (see below).

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

Severity

Adverse events will be graded by a numerical score according to the defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf

- The Investigator or qualified Sub-Investigator is responsible for assessing the relationship to study drug treatment using clinical judgment and the following considerations:
- **No**: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting. The relationship to study procedures (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:
- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (e.g., venipuncture)
- The severity grading of AEs will be assessed as Grade 1, 2, 3, 4 per the Division of AIDS grading document (http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf)

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of

the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

7.2.2 Unanticipated Problems:

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- Unexpected (in terms of nature, severity or frequency) ***AND***
- Definitely, probably, or possibly related to participation in the research ***AND***
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.2.3 Reporting

The UTSW IRB requires reporting of all unanticipated problems according to the guidance below. For participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events. All SAEs occurring during the protocol-specified monitoring period should be submitted to the UTSW study team within 2 business days of the center learning of the event.

Unanticipated problems occurring on the study require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB by the UTSW study team and to the SCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the UTSW study team and will be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix IV of the SCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB in not required).*

All serious adverse events which occur on research subjects on protocols for which the SCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Optimal Study: Tianna Petersen 214-590-0611
Written reports to: Optimal Study/ Tianna Petersen 214-590-2689 1936 Amelia Court, 2nd floor Research Unit Dallas, Texas 75235 **UTSW SCC Data Safety Monitoring Committee Coordinator** Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 **UTSW Institutional Review Board (IRB)** Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. SAEs

Serious adverse events (SAEs) for studies where SCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

2. Unanticipated Problems

Unanticipated problems require reporting to the UTSW IRB within 2 working days of PI awareness of the event.

Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.
For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the DAIDS Adverse Event Table http://rsc.techres.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf)

Step 2: Grade the adverse event using the DAIDS Adverse Event Table

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
The reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.4 Unblinding Procedures

This study is not blinded. There are no unblinding procedures.

7.5 Stopping Rules

The Principal Investigator may terminate the study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to the Principal Investigator in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If the Principal Investigator terminates the study for safety reasons, the Principal Investigator will immediately notify the investigator(s) by phone and subsequently provide written instructions for study termination. The drugs used in this study are FDA approved and very well tolerated. It is not expected that drug toxicity would lead to a need to stop the study.

8.0 DRUG INFORMATION

8.1 Sofosbuvir

- Other names for the drug(s): Sovaldi

- Classification - type of agent: HCV nucleotide analog NS5B polymerase inhibitor

- Mode of action: Sofosbuvir is a direct-acting antiviral agent against the hepatitis C virus.

- Storage and stability: Store at room temperature 30° C (86° F). Dispense only in original container. Do not use if seal over bottle is opening is broken or missing.

- Protocol dose: 400 mg

- Preparation: Sovaldi tablets are yellow, capsule-shaped, film-coated tablets containing 400 mg of Sofosbuvir debossed with "GSI" on one side and "7977" on the other side. Each bottle contains 28 tablets, a silica gel desiccant and polyester coil with a child-resistant closure.

- Route of administration for this study: oral

- Incompatibilities: amiodarone

- Availability: medication will be provided by the study

- Side effects: Most common adverse events include: fatigue, headache, nausea, insomnia, pruritus. Please see Sofosbuvir package insert for comprehensive information on adverse events.

8.2 Sofosbuvir/ledipasvir

- Other names for the drug(s): Harvoni

- Classification - type of agent: HCV NS5A inhibitor (ledipasvir); HCV N5B5 polymerase inhibitor (Sofosbuvir)

- Mode of action: direct-acting antiviral agent against the hepatitis C virus.

- Storage and stability: Store at room temperature 30° C (86° F). Dispense only in original container. Do not use if seal over bottle is opening is broken or missing.

- Protocol dose: Ledipasvir 90 mg;/Sofosbuvir 400 mg (fixed dose combination): one pill

- Preparation: tablets are orange, diamond-shaped, film-coated, debossed with "GSI" on one side and "7985"on the other side.

- Route of administration for this study: oral

- Incompatibilities: amiodarone

- Availability: medication will be provided by the study

- Side effects: Most common adverse events include: fatigue, headache, nausea, diarrhea, and insomnia. Please see Sofosbuvir/ledipasvir package insert for comprehensive information on adverse events.

8.3 Ribavirin

- Other names for the drug(s): copegus
- Classification - type of agent: HCV NS5A inhibitor (ledipasvir); HCV N5B5 polymerase inhibitor (Sofosbuvir)
- Mode of action: direct-acting antiviral agent against the hepatitis C virus.
- Storage and stability: Store at room temperature 25° C (77° F). Excursions are permitted between 15°C and 30°C (59° F and 86° F)
- Protocol dose: 200mg tablets. Subjects will take 1000 mg in divided dose twice a day if ≤75kg and 1200 mg in divided dose twice a day if >75 kg.
- Preparation: tablets are light pink to pink colored, flat, oval-shaped, film-coated, and engraved with RIB 200 on one side and ROCHE on the other. They are packaged as bottle of 168.
- Route of administration for this study: oral
- Incompatibilities: women who are pregnant should not take this drug; men whose female partner is pregnant should not take this drug; Do not use with Didanosine.
- Availability: medication will be provided by the study
- Side effects: Most common adverse events include: anemia, rash, irritability, and insomnia. Please see ribavirin package insert for comprehensive information on adverse events

8.4 Sofosbuvir/velpatasvir

- Other name for the drug:
- Classification- type of drug: sofosbuvir is a nucleotide analogue inhibitor of the HCV NS5B polymerase. Velpatasvir is a pangenotypic HCV NS5A inhibitor with antiviral activity against HCV replicons in genotypes 1 through 6.
- Mode of action: direct-acting antiviral agent against the hepatitis C virus.

- Storage and stability: Store at room temperature 30° C (86° F). Dispense only in original container. Do not use if seal over bottle is opening is broken or missing.
- Protocol dose: sofosbuvir 400 mg and velpatasvir 100 mg fixed dose combination: one pill
- Preparation:
- Route of administration of study drug: oral
- Incompatibilities: amiodorone
- Availability: medication will be provided by the study
- Side effects: headache, fatigue, nasopharyngitis, nausea, insomnia, diarrhea, asthenia, arthralgia, cough, back pain, myalgia.

8.4.1 Return and Retention of Study Drug

Drug will be returned to study coordinator. Pharmacy will destroy all returned drug per UT Southwestern Institutional guidelines.

8.4.2 Compliance with study drug will be measured by the study coordinator through pill count.

9.0 CORRELATIVES/SPECIAL STUDIES

Patient will be required to sign a separate consent for acquisition of extra blood samples for research purposes. Blood will be collected and stored for future genetic analysis and compared to B cell mutations found from bone marrow biopsy. 10 ml of whole blood will be collected in ACD or EDTA vacutainer tubes and must be completely filled. The samples collected will be batched and sent to UT Southwestern for storage. The de-identified samples will be sent for analysis once funding is available for the project. Blood will be stored locally as a back-up if a mishap occurs in the lab and if stored sample could be used for a replacement. Samples will be collected at baseline, post-treatment week 12, and post-treatment week 36.

Subject samples collected for this study will be retained at UT Southwestern at the end of the study. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens.

Mamta K. Jain will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of UT Southwestern. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of UT Southwestern for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UT Southwestern, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a prospective, non-randomized, interventional, exploratory study. The statistical analysis will be primarily descriptive. Descriptive statistics (e.g., mean, median, ranges, and frequencies) will be used to summarize AEs, SAEs, HCV treatment discontinuation and lymphoma treatment initiation. Adverse events at each visit and for the entire study duration will be summarized as frequency counts and percentages. For the safety analysis, data will be collected at each visit on side effects that the patient may be experiencing while on medication. These symptoms will be graded and recorded in REDCaps. The grading will be from 1-4. The labs will be entered and abnormal labs will be graded by the DAIDS laboratory manual. This too will be recorded in REDCaps. REDCap provides data validation at time of entry with variable fields that have custom ranges and rules or coded drop down lists. In addition, monitoring visits will occur in which source documentation is compared to REDCaps data entry.

Symptoms will be categorized in binary fashion (yes/no) such as fatigue, headache, nausea/vomiting, etc. It will be graded 1-4 based on DAIDS AE grading scale (see link). Lab values will be reported in categorical fashion depending on grade of abnormality. Grade of abnormality will be determined by Division of AIDS AE grading table (http://rsc.techres.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf)

For the secondary endpoint, we will examine change in the size of the lymph node after HCV treatment. Patients will be classified as partial responders or complete responders or non-responders by post-treatment week 36 according to the international lymphoma grading scale.

The site investigator in oncology at each site will be responsible for making this assessment based on the PET/CT scans. The oncologist will have to write their assessment in a document. The assessment will be recorded in RedCaps by the study coordinator. The study team composed of the liver and hematology experts will review cases collectively if there are questions about classification of response to adjudicate discrepancies and to maintain consistency.

SVR data will be determine by HCV RNA results and will be based on having a negative HCV RNA >12 weeks post-treatment. The hepatology investigator for each site will be responsible for making this assessment and will document in source note. This data will be entered into REDCaps. It can also be verified by the monitor based on laboratory data and date of laboratory compared to treatment completion date.

In addition these descriptive statistics will be used to for partial and complete response and SVR. 95% confidence intervals will be used to summarize the response for lymphoma and HCV. Any hypothesis testing will be considered exploratory and interpreted cautiously

10.2 Sample Size and Accrual

The number of patients selected for this study was based on the feasibility of being able to recruit patients with the inclusion/exclusion criteria outlined within 6-12 months at each center.

10.3 Data Analyses Plans

The primary and secondary objectives will be analyzed in a descriptive fashion as this study is an exploratory study.

11.0 Other Risks Related to Study Participation

11.1 Viral Resistance

Treatment with drugs that directly inhibit the Hepatitis C virus has been shown to lead to development of Hepatitis C virus that is resistant to that drug and other drugs with the same type of action. These resistance mutations have been observed in the body as late as 4 to 5 years after treatment has ended. It is unknown whether having these resistance mutations might reduce the chance of treatment success with future drugs with the same type of action or with different types of action (such as protease inhibitors).

11.2 Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep the subject's information confidential; however, this cannot be guaranteed.

11.3 Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Because the effects of SOF and LDV on an unborn baby (fetus) or a nursing infant are not known, any female who is pregnant or breast feeding an infant will not be enrolled in this study.

For subjects taking SOF/LDV FDC, extreme care must be taken to avoid pregnancy in female subjects or in female partners of male subjects during this study and following completion of study treatment (30 days after completion for women, 90 days after completion for men).

Because of the evidence of risks of RBV on an unborn baby (fetus) or a nursing infant, extreme care should be taken to prevent pregnancy (in female subjects, female partners of male subjects, and must not donate sperm) during this study and for 6 months after completion of RBV.

Ribavirin is a category X drug. Women of child-bearing potential will need to use two forms of birth control during the course of treatment and for 6 months after completion of treatment.

11.3.1 Women Only

Women who can get pregnant should not take study drug(s) unless they and their partner do not have intercourse ever or are using 2 methods of birth control for the duration of the study (starting 3 weeks prior to the Baseline/Day 1 visit) and for a minimum of 30 days after last dose of study drug or longer as directed by the Study Doctor. If on ribavirin, the subject should not get pregnant for a minimum of 6 months after last dose of study drug or longer as directed by the Study Doctor.

At least one method of birth control must be a condom used correctly by your male partner. The Study Doctor will discuss with you other methods of birth control that can be used in combination with a condom.

Women who can get pregnant must have a negative pregnancy test at screening and at the Baseline/Day 1 visit, prior to taking the first dose of study medication. Pregnancy tests will be repeated every 4 weeks during the study treatment through the Post-Treatment week 4 follow up visit or longer depending on the use of ribavirin.

In the event of a positive urine pregnancy result, the subject will be instructed to stop study drugs immediately and return to the study clinic as soon as possible for a serum (blood) pregnancy test. The pregnancy will be followed to its completion and the outcome, including any premature termination, must be reported to the Sponsor.

11.3.2 Men Only

If the female partner becomes pregnant, the subject and his partner must use <u>two</u> forms of birth control for the entire study and for a minimum of 90 days after the last dose of study drug or longer if on ribavirin as directed by the Study Doctor. The subject must use a condom while his female partner uses 1 other method of birth control.

If the female sex partner becomes pregnant while the subject is in the study or within 90 days after the last dose of study drug (or within 6 months after last dose of ribavirin), the study drug may harm an unborn baby. If the subject has a female partner who becomes pregnant or suspects

that she has become pregnant while the subject is in the study or within 90 days after your last dose of study drug (or within 6 months of last dose of ribavirin), the subject will be required to notify the Study Doctor immediately. As the risk to the female partner and unborn baby are not known, it is recommended for the female partner to receive appropriate prenatal care. If the subject agrees, the female partner will be asked to sign a consent form to allow disclosure of medical information related to the pregnancy. The Study Doctor may need to disclose to his female partner details the study. The Study Sponsor and the Study Doctor will not be responsible for the costs related to the pregnancy, delivery, or care of your child.

Male subjects must also agree not to donate sperm from the time you take your first dose of study medication until 90 days after the last dose of study drug. If ribavirin was used than they must agree not donate sperm for 6 months after last dose was taken.

Please note: Hormonal birth control may be more effective when taken for at least 3 months. Even if the subject and his female partner use a medically proven birth control method, could still cause his partner to become pregnant.

11.4 Risks of Radiation – Diagnostic Test

This research study includes exposure to radiation from diagnostic tests in addition to that which you would receive from standard care. The risk of harm to the body from this radiation can be compared to risks from everyday activities. For example, the risk of developing fatal cancer during your lifetime from this radiation is comparative to the risk of suffering a fatal car crash while driving 6,050 miles in an automobile. The average household in the United States drives 23,000 miles per year (2001 data).

11.5 Risks of Blood Drawing

Risks associated with drawing blood is minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible, although unlikely. Approximately 43 tablespoons of blood collected through Week 48.

12.0 STUDY MANAGEMENT

12.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

12.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

12.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the HIV/AIDS Research Unit.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if [4] holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

12.3.1 Registration/Randomization Procedures

This study is not randomized. Subjects will obtain a screening number generated by REDCaps. Once eligibility is verified and reviewed by Project Director, the subject will be enrolled in REDCaps by site coordinator and an enrollment number will be generated. This will be the id for the subject during the study.

All subjects must be registered with the Lead site (UT Southwestern) before enrollment to study. The coordinator at each site will contact Project Director, Tianna Petersen at 214-590-0611 to notify of enrollment.

Prior to enrollment, eligibility criteria must be confirmed with the Study Coordinator.

A lead-in identifier for each site will be created. Each site will be assigned a number. The first patient consented and enrolled at the first site will be subject 01-001-01. The second subject enrolled at the second site might be 02-003-02.

New subjects will receive a number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 001 will become 001-01 upon enrollment. If subject 002 screen fails, and subject 003 is the next subject enrolled, subject 003 will become 003-02 and so-on.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

12.3.2 Data Management and Monitoring/Auditing

REDCap is the UTSW institutional choice for the electronic data capture of case report forms for this and all Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with requirements.

Other institutions participating in this trial as sub-sites will be expected to enter data into REDCap and upload de-identified source materials when instructed by the study team to facilitate remote source to case report form verification.

Regulatory: Regulatory data will be monitored for each site including documentation of Federal Wide Assurance by having each site provide copies for the central site to maintain. Copies of approved consent forms, including all amendments and protocol version changes, will be obtained throughout the study. A copy of the IRB approval letter will need to be provided by the site for activation and contract execution. In addition, yearly approval of informed consent needs to be provided by the sites. The central site will review changes made to the Informed Consent by each site by respective IRBs. If changes are required by an IRB that impacts the Informed Consent content, then changes to the Informed Consent may be required. Any changes to the protocol will require an amendment to the protocol.

Monitoring: Monitoring visits will be conducted at each site to review informed consent documents to ensure appropriate consent has been obtained, including signature, date, and documentation of consenting process in source document. The monitor will also review

inclusion and exclusion criteria on every patient enrolled to insure that patients are enrolled that are appropriate. Any enrollments that do not follow inclusion/exclusion criteria will be considered protocol violations. Protocol deviations will include missed lab tests or visits. The monitor will also review charts to verify all adverse events documented in the source have been reported on the adverse event log.
A monthly call will be done by the central site to discuss recruitment goals, problems in recruitment, challenges in procedures, or other aspects of study implementation at each site.
Safety: Adverse events will be reported by each site as described in the protocol. Serious Adverse Events will be reported by the site. Any serious adverse event(s) or adverse event(s) which changes the risk for the patient will be documented by a letter to the IRB.

12.3.3 Method and Frequency of Analysis:

Mamta Jain, MD will be responsible for the overall monitoring of data and safety for the study. The data collected at each site will be monitored by the Project Manager, Tianna Petersen. Dr. William Lee will be the Safety Officer for the study and will review adverse events and serious adverse events to determine if causality to study drug exists. The Project Manager will be responsible for creating reports of unanticipated problems, adverse events, protocol deviations and violations to the IRB. This study is not an IND study and no reporting of Adverse Events is required for the FDA.
The study accrual, protocol deviations and violations, unanticipated problems, and overall safety of participants will be submitted to the IRB yearly.
An interim analysis of data will be planned after 21 patients are enrolled or 1 year after the first patient is enrolled.

12.3.4 Reporting Unanticipated Problems, Adverse Events, Protocol Deviations and Protocol Violations:

The UTSW Simmons Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and unanticipated problems in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

The Project Manager will be responsible for monitoring at each site. She will develop a report of protocol deviations or violations. Problems observed at the site will be documented and the site staff will develop a corrective action plan if needed. The Project Manager will verify that the plan is being implemented at the next site visit. The site visits are anticipated to occur quarterly but may vary depending on enrollments at each site.
The Project Manager will also have to verify specific milestones have been met in order for sites to obtain payment.
Each Site Investigator will be responsible for reviewing the adverse events and serious adverse events at their site and determining the severity and relationship to study drug. The Project Manager will compile all safety data and report to the DSMC quarterly or as required.
If a modification of the informed consent will need to occur due to safety concerns, each site will be sent a modification of the informed consent for approval by their IRBs. In addition, a letter describing the change in risk or safety will be given to each site for submission to their IRB. All other adverse events or serious adverse events which do not change the risk or safety for the patient will be reported to the IRB yearly.

Procedures and Time Frames for Communicating Outcomes: The project manager will have 30 days to complete a report of the findings from each site. This report will be given to each respective site and will be the basis of the yearly reporting for the IRB.

Precautions for Maintaining Data Integrity: The Project Manager will monitor each site to determine if the site is adhering to the conduct of the study. This will include review of informed consent process, verification of adherence to inclusion and exclusion criteria, verification of study visits being conducted during the time-frame outlined in the protocol, verification that all laboratory and imaging that is required by the study is conducted as dictated by the protocol. Any findings of non-compliance to informed consent, inclusion/exclusion criteria, or collection of data at key time points such as SVR, PET scan, and failure to report adverse events or serious adverse events that are deemed by the site investigator to be causally related to study drug will be considered as a Protocol Violation. All other non-adherence to protocol will be protocol deviations. All data reported on case report forms will be verified by monitor against the source document. This will assure the validity and integrity of the data.

12.3.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within two (2) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

12.3.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

12.3.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.3.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

13.0 REFERENCES

1. Forghieri F, Luppi M, Barozzi P, et al. Pathogenetic mechanisms of hepatitis C virus-induced B-cell lymphomagenesis. Clinical & developmental immunology 2012;2012:807351.
2. Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. Journal of hepatology 2013;59:169-77.
3. Arcaini L, Merli M, Volpetti S, Rattotti S, Gotti M, Zaja F. Indolent B-cell lymphomas associated with HCV infection: clinical and virological features and role of antiviral therapy. Clinical & developmental immunology 2012;2012:638185.
4. Kasama Y, Mizukami T, Kusunoki H, et al. B-cell-intrinsic hepatitis C virus expression leads to B-cell-lymphomagenesis and induction of NF-kappaB signalling. PloS one 2014;9:e91373.
5. Hermine O, Lefrere F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. The New England journal of medicine 2002;347:89-94.
6. Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23:468-73.

7. Arcaini L, Vallisa D, Rattotti S, et al. Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2014;25:1404-10.
8. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. The New England journal of medicine 2014;370:1889-98.
9. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. The New England journal of medicine 2013;368:34-44.
10. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. The New England journal of medicine 2014;370:1879-88.
11. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014;383:515-23.
12. Zeuzem S, Dusheiko G, Salupere R, et al. Sofosbuvir +ribavirin for 12 or 24 weeks for patients with HCV gentoype 2 or 3: the VALENCE trial. 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 Nov 1-5, 2013; Washington, D.C.
13. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. The New England journal of medicine 2014;370:1993-2001.

14.0 APPENDICES

14.1 Appendix 1: Karnofsky Performance Status Scale

100 Normal, no complaints, no evidence of disease

90 Able to carry on normal activity, minor signs or symptoms of disease

80 Normal activity with effort, some signs or symptoms of disease

70 Cares for self. Unable to carry on normal activity or to do active work

60 Requires occasional assistance, but is able to care for most of his needs

50 Requires considerable assistance and frequent medical care

40 Disabled, requires special care and assistance

30 Severely disabled, hospitalization is indicated although death not imminent

20 Hospitalization necessary, very sick, active supportive treatment necessary

10 Moribund, fatal processes progressing rapidly.

0 Dead

14.2 Appendix 2. Follicular Lymphoma International Prognostic Index 2 (FLIPI2) Calculator

Prognostic score for untreated follicular lymphoma

Applies at the time of first treatment.

1. Sum the number of risk factors to calculate FLIPI-2 score

Age:

- ○ < 60 years
- ○ 60 years or older

Serum beta 2 microglobulin:

- Normal
- Raised

Hemoglobin:

- 12 g/dL or greater
- < 12 g/dL

Bone marrow involvement:

- Absent
- Present

Longest diameter of largest involved node:

- Less than 6 cm
- 6 cm or more

FLIPI-2 score:

2. Determine risk category and prognosis

FLIPI-2 score	FLIPI-2 risk category	5 year PFS (%)[1]	5 year PFS (%)[2]
0	Low risk	80	76
1 - 2	Intermediate risk	51	49
3 - 5	High risk	19	37

1. Vallisa D, Bernuzzi P, Arcaini L, et al. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(3):468-473.
2. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *The New England journal of medicine.* 2015;373(27):2608-2617.
3. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *The New England journal of medicine.* 2015;373(27):2599-2607.
4. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Annals of internal medicine.* 2006;144(10):705-714.