Study Title: Efficacy of All-Oral Anti-Viral Therapy for Symptomatic Hepatitis C Virus Infection-Related Cryoglobulinemia
PI: Peter Gorevic, M.D.
NCT02825212
Protocol Version/Date: 10 March 2017

CLINICAL STUDY PROTOCOL

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Clinicaltrials.gov identifier: NCT02825212

Indication: Hepatitis C Infection and Cryoglobulinemia

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Protocol ID: IND-US-337-1716

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TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Study Title: Efficacy of All-Oral Anti-Viral Therapy for Symptomatic Hepatitis C Virus Infection-Related Cryoglobulinemia

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Study Centers: One site at the Icahn School of Medicine at Mount Sinai with anticipated referrals from other institutions within the system. The Mount Sinai Health Care System includes:

- Mount Sinai Hospital
- Mount Sinai Beth Israel
- Mount Sinai Saint Luke's Roosevelt

Patients will be identified at these additional sites but will be referred to the Icahn School of Medicine at Mount Sinai where the study will be conducted and the IRB will be based. All visits, as well as clinical and laboratory-based studies will be performed at Mount Sinai Health Care System.

Target Population:

Adults with chronic genotypes 1-6 hepatitis C virus (HCV) infection and cryoglobulinemia.

Objectives:

The **primary objectives** of this study are:

- To assess the efficacy of new direct acting oral antivirals: LDV/SOF FDC (Harvoni®) or SOF/VEL FDC (Epclusa®) in patients with chronic HCV infection and MC, measuring the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment.
- To assess efficacy of new direct acting oral antivirals: LDV/SOF FDC (Harvoni®) or SOF/VEL FDC (Epclusa®) in patients with mixed cryoglobulinemia (MC) secondary to chronic HCV infection:

- A complete response is defined as disappearance of arthropathy or kidney involvement, and/or purpura, and >50% reduction in IgM-RF and cryocrit.
- A partial response is a 10-50% reduction in cryocrit and one (but not all) clinical and laboratory signs of systemic vasculitis.

The **secondary objectives** of this study are:

- To assess immunological response of MC to new direct acting oral antivirals: LDV/SOF (Harvoni®) or SOF/VEL FDC (Epclusa®) treatment measuring:
  - FACS/CyTOF analysis of PBMC to determine the effect of DAA treatment on cell-surface markers or MC
  - analysis of isolated mixed cryoglobulins for localization of viral RNA, the presence of HCV core antigen, C1q protein, C1q binding activity and soluble gC1qR.
  - accumulate kinetic data to address the issues of (a) redistribution of viral RNA and core protein between cryoprecipitable and noncryoprecipitable immune complexes with treatment (27) (b) persistence of cryoglobulins and cryoglobulinemic vasculitis following apparent clearance of virus (13,14,28); and (c) persistence of virus in PBMC or cryoprecipitates following apparent systemic clearance (i.e. occult infection) (29).
- To assess safety and tolerability of new direct acting oral antivirals: LDV/SOF FDC (Harvoni®) or SOF/VEL FDC (Epclusa®) in patients with chronic HCV infection and MC.

Treatment Duration:

Subjects that have been enrolled and started treatment under protocol version 1 will continue and complete the planned treatment with LDV/SOF FDC (Harvoni®):

- Treatment-naïve subjects will be treated for 12 weeks
- Treatment-experienced non-cirrhotic subjects will be treated for 12 weeks
- Treatment-experienced compensated cirrhotic subjects will be treated for 24 weeks

Subjects enrolled under protocol version 2 will receive SOF/VEL FDC (Epclusa®):

- Treatment-naïve subjects will be treated for 12 weeks
- Treatment-experienced non-cirrhotic subjects will be treated for 12 weeks

- Treatment-experienced compensated cirrhotic subjects will be treated for 12 weeks

Study Design: 10 patients with chronic HCV infection and mixed cryoglobulinemia will be treated with new direct acting oral antivirals:

- Ledipasvir/Sofosbuvir 90mg/400 mg FDC once daily for 12 weeks (naïve subjects, non-cirrhotic treatment experienced subjects) or 24 weeks (treatment experienced subjects with compensated cirrhosis)for genotype 1 subjects already enrolled in protocol version 1.
- Sofosbuvir/Velpatasvir 400mg/100mg 400mg/100mg FDC once daily for 12 weeks (naïve subjects, non-cirrhotic treatment experienced or treatment experienced subjects with compensated cirrhosis) for genotype 1-6 subjects enrolled in protocol version 2.

We anticipate that approximately 20% of subjects may have cirrhosis.

Diagnosis and Main Eligibility Criteria:

Chronic genotypes 1-6 HCV infected, male and non-pregnant female subjects, ages 18 or older with cryoglobulinemia.

Refer to Sections 4.2 and 4.3 for detailed Inclusion and Exclusion Criteria.

Study Procedures/Frequency:

Screening assessments will be completed within 30 days of the Baseline/Day 1 visit. The screening window can be extended to 42 days for subjects requiring liver biopsy or additional HCV genotype testing.

All subjects will complete the following study visits: Screening, Baseline/Day 1, on-treatment visits at the end of Weeks 2, 4, 8 and 12 . Subjects who were already enrolled in the study and receiving 12 weeks treatment with Harvoni® will complete the same visits and schedule of events as subjects receiving Epclusa® (detailed in the current protocol version 2). Subjects that receiving 24 weeks treatment with Harvoni® will also complete treatment visits at week 20 and 24. All subjects will complete the post treatment Week 4, 12 and 24 visits.

Screening assessments will include physical examination, medical history, height, weight, vital signs, 12-lead ECG, adverse events related to screening procedures,

concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), HCV genotype and HCV RNA, serology (HIV, HCV, HBV), assessment of the presence or absence of cirrhosis, screening for hepatocellular carcinoma if cirrhosis is present, serum β-hCG (females of child bearing potential only), IL28B genotyping, urinalysis, analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement, HCV core ELISA and FACS (appendix 1).
On-treatment assessments include adverse events (AEs), concomitant medications, study medication pill count, physical examination, weight, vital signs, safety laboratory tests (hematology, chemistry, coagulation), HCV RNA (after Baseline/Day1), urine pregnancy tests (females of child bearing potential only), urinalysis, analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement, HCV core ELISA and clonality/lymphoproliferation / FACS (appendix 1).
Post treatment assessments include AEs, concomitant medications, vital signs, safety laboratory tests, HCV RNA, urine pregnancy tests (females of child bearing potential only) and analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement, HCV core ELISA and clonality/lymphoproliferation / FACS (appendix 1).

Test Product, Dose, and Mode of Administration:

- Ledipasvir/Sofosbuvir (HARVONI®) is manufactured as a 90mg/400 mg FDC tablet for oral administration. Subjects will take 1 tablet daily with or without food.
- SOF/VEL FDC (Epclusa®) is manufactured as a 400 mg / 100 mg FDC tablet for oral administration. Subjects will take 1 tablet daily with or without food.

Evaluation Criteria:

- Efficacy:
    - Efficacy of treatment on MC will be assessed as follows:
        - Complete response is defined as disappearance of arthropathy or kidney involvement, and/or purpura, and >50% reduction in IgM-RF and cryocrit.
        - Partial response is a 10-50% reduction in cryocrit and one (but not all) clinical and laboratory signs of systemic vasculitis.

  - Efficacy of treatment on HCV infection will be evaluated using scheduled assessments of HCV RNA performed using COBAS® TaqMan® HCV Test, v2.0 for use with Ampliprep.
- Safety: AEs and laboratory tests will be collected throughout the study.

Statistical Methods:

This is a pilot study in which 10 patients will be enrolled to explore the efficacy of all-oral anti-viral therapy for symptomatic hepatitis C virus infection-related cryoglobulinemia.
With 10 patients in the study we will be able to estimate the rate of patients who obtain an SVR with a margin of error of approximately 15%.
We will use frequency table and 95% confidence interval to describe the rate of SVR in the total sample and the two subgroups of interest.
Results will be compared to previous published studies (28), as well as unpublished experience, that have delineated the natural history of type 2 cryoglobulinemia, and the response to immunomodulatory therapies, including IFN/Peg-IFN, Ribavirin and Rituximab (27).

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP)

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ACR American College of Rheumatology

AE Adverse event

ALT Alanine aminotransferase

AST Aspartate aminotransferase

BW Body weight

CLcr Creatinine Clearance

CR complete response

CRF case report form(s)

DAAs Direct-acting antiviral agents

eCRF Electronic case report form(s)

EOT end of treatment

ET early termination

EU European Union

EudraCT European clinical trials database

FDA (United States) Food and Drug Administration

FLC Free Light Chain

GCP Good Clinical Practice (Guidelines)

HAQ Health Assessment Questionnaire

HBV Hepatitis B virus

HCC Hepatocellular carcinoma

HCV Hepatitis C virus

HDPE high density polyethylene

HIV human immunodeficiency virus

ICH International Conference on Harmonisation

IFN Interferon

IL28B Interleukin 28B gene

IND Investigational New Drug (Application)

IRB Institutional review board

IU International unit

LDV Ledipasvir

LLoQ Lower limit of quantification

MAb monoclonal antibody

MC Mixed cryoglobulinemia

mL Milliliter

MPGN membranoproliferative glomerulonephritis

N Number

NHL Non-Hodgkins Lymphoma

NSPs non-structural proteins

PBMC Peripheral blood mononuclear cell

PEG-IFN Pegylated interferon

PI Protease inhibitor or principal investigator

PT Prothrombin time

RBC Red blood cell count

RBV Ribavirin

RNA ribonucleic acid

Scr serum creatinine

SAE Serious adverse event

SOF Sofosbuvir

SOF/VEL Sofosbuvir/Velpatasvir

LDV/SOF Ledipasvir/Sofosbuvir

SUSAR Suspected Unexpected Serious Adverse Reaction

SVR Sustained virologic response

ULN upper limit of the normal range

VEL Velpatasvir

WBC White blood cell count

1. INTRODUCTION

1.1. Background

Hepatitis C Virus (HCV) is a major cause of both hepatic and extrahepatic disease. The former includes the spectrum of autoimmune hepatitis extending to cirrhosis, liver failure, and a long-term increased incidence of Hepatocellular Carcinoma. Cryoglobulinemia includes a group of overlapping syndromes (arthropathy, cutaneous vasculitis, nephropathy, sicca syndrome, and neuropathy) and a long-term increased incidence of Non-Hodgkin Lymphoma (NHL) (1). Extrahepatic disease is significantly associated with chronicity and the presence in blood of easily detectable cold-precipitable rheumatoid factors (i.e. mixed cryoglobulins) (2). In addition, rarer organ-specific disease manifestations that may be associated with HCV include cutaneous (lichen planus), neuromuscular (fibromyalgia), hematologic (autoimmune thrombocytopenia), and endocrine (diabetes mellitus) disorders (3). Although the disease burden of HCV has been estimated to be 3-4M for the United States and ~170-180M worldwide, the exact prevalence of extrahepatic HCV is less certain and has only been studied to a limited extent to include countries in which genotype distribution differs from that found in North America, or among populations in the United States (e.g. HIV co-infected persons, the homeless, the incarcerated) known to have an increased prevalence of clinical diseases that may mimic the overlapping syndromes of mixed cryoglobulinemia (MC) noted above. In one study of ~34,000 HCV-positive veterans versus controls, there was an 11-fold increased incidence of cryoglobulinemia, a 7-fold increase in membranoproliferative glomerulonephritis (MPGN), a 20-30% increase in NHL, and a 2-fold increase in lichen planus compared to HCV-negative controls (4). In addition, both the laboratory finding of mixed cryoglobulins and the clinical syndromes of cryoglobulinemic vasculitis may occur with only minimal or no liver pathology, and may be uncovered in the course of evaluations of MPGN, leukocytoclastic vasculitis, rheumatoid-like arthritis, Sjogren's syndrome, or autoimmune neuropathy (5).

We have a long-standing interest in the cryopathies, including early recognition of the prevalence of hepatic disease among patients affected by purpura, arthralgias and MPGN, progression to liver failure in some patients with long-term follow-up (15), characterization of the clonality of the IgMk component of type 2 cryoglobulins, phlogistic activity of mixed cryoglobulins with regard to complement and other mediators

(16), and methodology for the accurate isolation of characterization of cold-precipitable RFs (17). Our current data base includes 180 patients with the syndrome of MC with long-term follow-up of 40 patients spanning 1960-2010. The cohort of MC since the description of HCV in 1989 is 55% female, with an overall incidence of 68% cutaneous disease, 56% arthropathy, 35% nephropathy, 58% neuropathy, 60% type 2/40% type 3 mixed cryoglobulins, and 60% HCV. In addition, we recently completed a retrospective chart review of 51 HCV-positive patients with MC seen at our medical center between 2003-2013, 60% having genotype 1, 14% genotype 2 and 10% genotype 3, in which we specifically analyzed the efficacy of current antiviral therapy and Rituximab in this cohort with regard to progression of liver disease to transplantation and MPGN to end-stage renal disease requiring dialysis (16). This experience may be compared to a very recent report from Italywhich noted a ~30% incidence of genotype 2 among their MC patients receiving direct acting antivirals (DAA) treatment (19).

Mount Sinai Health Care System is a major referral center for HCV-infected patients, many of whom are being uncovered as a result of mandated screening, because of our free-standing Hepatology division, specialized HIV, hemophilia, and common variable immunodeficiency patient populations, and our active liver transplantation program. Ongoing clinical studies are testing the efficacy all-oral antiviral therapy in co-infected patients and in post-transplant patients susceptible to recurrence of disease. A review of the morphologic features of extrahepatic disease in this patient population has recently been published from our institution (5). The laboratory of Dr. Gorevic has extensive experience in the performance of the immunologic and rheumatologic procedures and techniques that are proposed. Dr. Gorevic also has extensive experience in performing the clinical assessments for clinical MC. Drs. Schiano and Branch have significant experience in the use of DAAs for HCV, including participation in the ASTRAL-4 study of Sofosbuvir and Velpatasvir for HCV in patients with decompensated cirrhosis (20), and the validation of efficacy of Sofosbuvir and Ledispasvir for recurrent Hepatitis C in liver transplant recipients (21). Lastly, Dr. Branch's laboratory has published studies of the basic virology of HCV, including hepatitis core antigen, HCV quasi-species, and cell surface markers in established and treated disease.

1.2. Rationale for the Current Study

The treatment of extrahepatic disease manifestations of HCV has largely paralleled that of hepatic disease. Interferon was reported to have efficacy for MC even before linkage of the syndrome to HCV in 1989, and successful combination therapy with ribavirin was found to eliminate virus and lead to the resolution of immunologic abnormalities associated with extrahepatic disease (1). In addition, ~75% of HCV-associated indolent asymptomatic lymphroproliferative diseases remit with successful antiviral therapy (6). However, in many instances, MC (notably cutaneous vasculitis) will relapse with recurrence of virus, and may occasionally persist even after clearance (7). In particular, side effects of Interferon alpha, including the uncovering of frank autoimmune disease, theoretically may mitigate response of extrahepatic disease to treatment (8). Peg-interferon increased the response rate of MC, and decreased the duration of treatment, but side effects remained problematic (1).

An alternative approach to the treatment of MC has been the use of immunomodulatory agents. In particular, B-cell expansion in peripheral blood and in lymphoid follicles in the liver prevalent amongst HCV-infected persons provided a rationale for the use of depletion as a therapeutic strategy. Rituximab (anti-CD20) monotherapy has been used mostly for treatment failures/intolerance or in the setting NHL, and has yielded response rates in the setting of involvement of skin (73%); MPGN (70%); joint (53%); and nerve (36%). However, this monoclonal antibody (MAb) has the potential to form immune-complexes with mixed cryoglobulin RF and cause clinical vasculitis in patients with high cryocrits, and may raise the HCV RNA level in rare patients, causing cytotoxicity. Following Rituximab with Peg-IFN plus ribavirin achieved greater than a 60% complete response (CR) in patients resistant to combination treatment alone (9). Other approaches include the use of Aldesleukin, an inducer of regulatory T-cell activity, MAbs targeted to specific B-cell subsets or costimulatory signal molecules (e.g. BAFF) or agents inhibiting the interaction of HCV core antigen with C1q in cryoprecipitates via the receptor for the globular domain of C1q (gC1qR) (1).

The development of low molecular weight inhibitors of the non-structural proteins (NSPs) elaborated by HCV, in particular 5A, 5B nucleoside and non-nucleoside polymerase inhibitors, and inhibitors of 3/4A serine proteases; to selectively inhibit HCV replication has raised the prospect of “all-oral” treatment for both hepatic and extrahepatic

manifestations of disease. However, the use of first generation direct-acting antiviral agents (Telaprevir® and Boceprevir® linear NS3/4A protease inhibitors) was limited by frequent escape mutants, efficacy restricted to genotype-1, need to retain protocols including PegIFN and ribavirin, potential for significant drug interactions, and serious side effects. In a trial of combination therapy including Telaprevir® for 13 patients with MC, all had significant AEs, including asthenia (92%), anemia (84%), neutropenia and bacterial infection (54%) (10). Approval of an uridine nucleoside analogue that selectively inhibits HCV NS5B RNA-dependent RNA polymerase (Sofosbuvir) by the FDA late 2013 has led to proof-of-concept trials in which combination all-oral therapy has proven effective for both genotype 1 and other genotypes, with a number of other regimens under development. In particular, the combination of Sobosbuvir (SOF) and Ledipasvir (LDV) has been reported to have almost universal efficacy in a 12 week regimen for genotype 1, and the combination of SOF and Ribavirin (RBV) for genotypes 2-6 in a 24 week regimen (11,12). Most recently, the combination of Sofosbuvir and Velpatasvir (SOF/VEL), Epclusa®, has been shown to have pan-genotypic efficacy in pivotal studies (23,24) and is rapidly becoming standard-of care for chronic HCV infection (25). Inclusion of genotypes 1-6 in our study will allow us to correlate possible confounding factors (e.g. specific extra-hepatic disease manifestations, immunoglobulin V-region gene usage; IL28B genotype; HCV Core gene mutations) compared to the published experience for Sofosbuvir and Velpasavir for other genotypes (23,24). It will also allow us to increase enrollment from a diminishing pool of patients who have yet to undergo treatment with 12 week course of Epclusa® (sofosbuvir/velpatasvir) in compensated patients (Child-Pugh A).In addition, persistence of cryoglobulainemia even after viral clearance with the newer regimens has also raised the question of whether longer treatment regimens may be appropriate in the setting of significant extrahepatic disease (13). To date, only limited published experience exists with regard to the “post-viral” phase of HCV MC, consisting of retrospective analyses involving various genotypes and differing regimens of DAAs (19,26). Thus, the timing is right for a prospective trial of all-oral treatment with Epclusa® (SOF/VEL) to rigorously evaluate the effect on extrahepatic disease manifestations in patients with MC of all genotypes, and to re-establish the efficacy of antiviral therapy in halting the direct and indirect role of HCV in driving autoimmune disease and lymphoproliferation. Using an interferon-sparing regimen to treat patients with HCV-related cryoglobulinemia will help answer the

question as to whether immunomodulating therapy plays a role at all in eradicating cryoglobulins long-term, and whether antiviral therapy alone is adequate. If the latter, appreciable morbidity and mortality may be saved in avoiding treating these potentially sick, often cirrhotic patients, with immunomodulatory therapies.

2. OBJECTIVES

The **primary objectives** of this study are:

- To assess the efficacy of new direct acting oral antivirals: LDV/SOF FDC (Harvoni®) or SOF/VEL FDC (Epclusa®) in patients with chronic HCV infection and MC, measuring the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment.
- To assess efficacy of new direct acting oral antivirals: LDV/SOF FDC (Harvoni®) or SOF/VEL FDC (Epclusa®) in patients with MC secondary to chronic HCV infection:
    - A complete response is defined as disappearance of arthropathy or kidney involvement, and/or purpura, and >50% reduction in IgM-RF and cryocrit.
    - A partial response is a 10-50% reduction in cryocrit and one (but not all) clinical and laboratory signs of systemic vasculitis (see below) (33)

Clinical Responses:

- For patients whose predominant clinical manifestation is a *rheumatoid-like arthritis*, the primary evaluation will be a joint count in order to conform to American College of Rheumatology (ACR) outcome criteria (34).
- For patients whose predominant clinical manifestation is *vasculitis*, cutaneous disease will be assessed as number and distribution (scored as 1=<10; 2=>10; 3=upper and lower extremity; 4=complicated by ulcerations, gangrene or both) of purpuric lesions. Systemic vasculitis will be evaluated by a modification of the Birmingham Vasculitis Activity Score (35).
- *Glomerulonephritis* is defined as the presence of hematuria, proteinuria and red blood cell casts (i.e. an active urinary sediment) by urinalysis, further quantitated as total mg proteinuria, >300mg (upper limits of normal) on a 24 hour collection, or as the protein/creatinine ratio of a spot sample of urine. Concomitant renal insufficiency is defined as a serum creatinine >2.0mg/dL. Most patients will have also had renal biopsies showing typical features of membranoproliferative glomerulonephritis associated with cryoglobulinemia (36)

- *Neuropathy* is evaluated as being symmetrical or asymmetrical, pure sensory or sensorimotor, and further defined as number of extremities involved. Neuropathy may be corroborated by electrophysiologic testing as indicated (37).
- *Functional outcome* is evaluated as the Health Assessment Questionnaire (HAQ) .

Virologic Responses:

- Measure of *HCV antigens* in un-dissociated cryocomplexes relative to serum by sandwich ELISA for *core antigen* (31). The presence of HCV RNA in mixed cryoglobulins will be correlated with the presence of core antigen as a measure of un-encapsulated virus and nucleocapsid antigens.

Immunologic Responses:

- Kinetics of response with regard to *compartmentalization of viral RNA and core antigen* between cryoprecipitible and non-cryoprecipitible immune complexes.
- Serial *quantitation of cryoprecipitates* and correlation with RF titers determined by nephelometry, and C4 levels measured in freshly collected serum.
- *C1q and C1q binding assays* are available through our clinical immunology laboratory, and will be compared to our previously published experience in MC with these assays. Quantitation of soluble forms of the *receptor for the globular domain of C1q (gC1qR)* is available through the laboratory of Dr. Berhane Ghebrehiwet (State University of New York, Stony Brook) (32).
- *Regression of clonality* assessed by immunofixation of isolated cryoprecipitates, and kappa/lambda Free Light Chain (FLC) measurements in blood.
- *Regression of clonality and lymphoproliferation* assessed by FACS analysis for specific B-cell subsets and MC cross-reactive idiotypes.
- Isolation *PMBCs for analyzing by FACS/ Cytometry* cell-surface markers during and after DAA treatment

Results will be compared to previous published studies, as well as unpublished experience, that have delineated the natural history of type 2 cryoglobulinemia, and the response to immunomodulatory therapies, including IFN, Ribavirin and Rituximab (27, 38).

The **secondary objectives** of this study are:

- To assess immunological response of MC to new direct acting oral antivirals: SOF/VEL FDC (Harvoni®) or SOF/VEL FDC (Epclusa®) treatment measuring:
    - FACS/CyTOF analysis of PBMC
    - analysis of isolated mixed cryoglobulins for localization of viral RNA, the presence HCV core antigen, C1q protein, C1q binding activity and soluble gC1qR.
    - accumulate kinetic data to address the issues of:
        - (a) redistribution of viral RNA and core protein between cryoprecipitable and noncryoprecipitable immune complexes with treatment (27);
        - (b) persistence of cryoglobulins and cryoglobulinemic vasculitis following apparent clearance of virus (13,28 ,29); and
        - (c) persistence of virus in PBMC or cryoprecipitates following apparent systemic clearance (i.e. occult infection) (29).
- To assess safety and tolerability of new direct acting oral antivirals: LDV/SOF FDC (Harvoni®) LDV/SOF FDC (Harvoni®) or SOF/VEL FDC (Epclusa®) in patients with chronic HCV infection and MC.

3. STUDY DESIGN

3.1. Treatment plan and regimen

This is a single-center, open-label study to evaluate the safety, tolerability and efficacy of new direct acting oral antivirals:

- Ledipasvir/Sofosbuvir 90mg/400 mg FDC (LDV/SOF;Harvoni®, for those subjects enrolled under protocol version 1 only) in patients with genotype 1 HCV infection and MC already enrolled in protocol version 1 or
- Sofosbuvir/Velpatasvir 400mg/100mg FDC (SOF/VEL; Epclusa®, for all subjects enrolled under protocol version 2) in patients with chronic genotypes 1-6 HCV infection and MC. All subjects enrolled in protocol version 2 will receive Epclusa®

who have failed or only partially responded to other MC therapies.

Treatment duration is as follows:

Subjects that have been already enrolled and started treatment under protocol version 1 will continue and complete the planned treatment with LDV/SOF FDC (Harvoni®):

- Treatment naïve subjects will be treated for 12 weeks.
- Treatment experienced non-cirrhotic subjects will be treated for 12 weeks.
- Treatment experienced compensated cirrhotic subjects will be treated for 24 weeks.

Subjects enrolled under protocol version 2 will receive SOF/VEL FDC (Epclusa®):

- Treatment-naïve subjects will be treated for 12 weeks
- Treatment-experienced non-cirrhotic subjects will be treated for 12 weeks
- Treatment-experienced compensated cirrhotic subjects will be treated for 12 weeks

Approximately 20% of subjects may have cirrhosis.

3.2. Visits schedule

All subjects will complete screening, on-treatment, and post treatment assessments.

Screening assessments will be completed within 30 days of the Baseline/Day 1 visit, 42 days if liver biopsy is required.

All subjects will complete the following study visits: Screening, Baseline/Day 1, on-treatment visits at Weeks 2, 4, 8 and 12 (for all patients) and weeks 20 and 24 (for those patients receiving 24 weeks of Harvoni® treatment).

Visits	Screening	Baseline / Day 1	Week 2	Week 4	Week 8	Week 12	Week 20	Week 24
12 weeks (Harvoni® or Epclusa®) treatment arm	X	X	X	X	X	X		
24 weeks (Harvoni®) treatment arm	X	X	X	X	X	X	X	X

All subjects will complete post treatment Week 4, 12 and 24 visits.
The assessments performed at each visit are described in Section 6 and shown in Appendix 1.

3.3. Virologic Response-Based Stopping Criteria

The following on-treatment virologic response-based treatment stopping criteria will be utilized:

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

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

All subjects who terminate treatment early will complete the early termination (ET) visit and post treatment 12 and 24 visits.

3.4. Cryoglobulinemia Response-Based Stopping Criteria

The following on-treatment response-based treatment stopping criteria will be utilized:

- Unacceptable side effect of the drug (i.e. hypersensitivity reaction, abnormal liver function tests; gastrointestinal side effects).
- Paradoxical effect on the disease manifestations (i.e. increased of systemic vasculitis, renal failure).

3.5. Treatment Discontinuation Criteria

Study drug(s) must be discontinued in the following instances:

- Unacceptable toxicity, as defined in Section 7 of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree.
- Pregnancy of female subject during the study
- Lack of efficacy (virologic failure) as defined in Section 3.3 and Section 3.4.
- Significant protocol violation.
- Subject request to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy or other reason.
- Discontinuation of the study at the request of Gilead Sciences, principal investigator, regulatory agency or an Institutional Review Board (IRB).

All subjects who terminate early will be asked to complete the (ET) visit and post treatment Week 12 visits and week 24.

3.6. Discontinuations

Subjects discontinuing treatment prior to completion of the assigned dosing period should complete an Early Termination (ET) visit (see Section 6.2.7). All subjects who terminate treatment early will complete the Early Termination (ET) visit and post treatment 12 and 24 visits.

4. SUBJECT POPULATION

4.1. Number of Subjects

Ten patients will be enrolled in this study.

4.2. Inclusion Criteria

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

1. Willing and able to provide written informed consent
2. Male or female, age ≥18 years
3. HCV RNA ≥ 15 IU/mL at Screening
4. All HCV genotypes (1 to 6)
5. Chronic HCV infection (≥ 6 months) documented by prior medical history or liver biopsy
6. Classification as treatment naïve or treatment experienced:
   a) *Treatment naïve* is defined as having never been exposed to approved or experimental HCV-specific direct-acting antiviral agents or prior treatment of HCV with interferon or ribavirin or DAAs (except for SOF-containing regimens).
   b) *Treatment experienced* is defined as prior treatment failure or relapse to a regimen containing interferon either with or without RBV or DAAs that was completed at least 8 weeks prior to Baseline/Day 1.

   The subject's medical records must include sufficient detail of prior virologic failure to allow for categorization of prior response (Reference Section 4.2), as either:
      a. Non-Responder: Subject did not achieve undetectable HCV RNA levels while on treatment, or
      b. Relapse/Breakthrough: Subject achieved undetectable HCV RNA levels during treatment or within 4 weeks of the end of treatment but did not achieve SVR.
7. Cirrhosis determination (approximately 20% of subjects may have cirrhosis)
   a. Cirrhosis is defined as any one of the following:
      i) Any previous liver biopsy showing cirrhosis (e.g., Metavir score = 4 or Ishak score ≥5)

ii) FibroMeter® score >0.442 or an AST:platelet ratio index (APRI) >2 during Screening

iii) Fibroscan with a result of >12.5 kPa at any time prior to or during screening.

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

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

ii) FibroMeter® score <0.442 or APRI ≤ 1 performed during Screening

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

Fibroscan results will supersede FibroMeter® /APRI; liver biopsy results will supersede FibroMeter® /APRI or Fibroscan results and be considered definitive.

8. Liver imaging (ultrasound, CT scan or MRI) within 6 months of screening is required in patients with cirrhosis to exclude hepatocellular carcinoma (HCC)
9. Presence of mixed cryoglobulinemia (please see criteria on the note below).
10. Null or partial response to previous therapies for MC, including corticosteroids, cytotoxic agents (cyclophosphamide, azathioprine), hydroxycloroquine, methotrexate, mono- or combination therapy with IFNα/PEG-IFN and ribavirin, and/or CD20 depletion with Rituximab.
    a. Patients can be on ongoing treatment with one of the drugs described above at inclusion unless there is significant DDI.
11. Subjects has the following laboratory parameters at screening:
    a) ALT <10 x the upper limit of normal (ULN)
    b) AST <10 x ULN
    c) Adequate bone marrow function as indicated hematologic parameters listed below and/or bone marrow cellularity >60-70% average for age.
        a. WBC >1500 /uL
        b. Platelets > 50,000/uL
    d) Direct bilirubin >2 x ULN
    e) INR >1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR
12. Females of childbearing potential (as defined in Appendix 3) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Baseline/Day 1 prior to treatment.

13. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.
14. Lactating females must agree to discontinue nursing before the study drug is administered.
15. Subject must be of generally good health, with the exception of chronic HCV infection, as determined by the Investigator.
16. Subject must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.

Note: Definition of Mixed Cryoglobulinemia (patients must meet one of the five overlapping syndromes listed below and the presence/documentation of cold-precipitable immune complexes in blood on two different occasions.

- Clinical evidence of cryoglobulinemia, overlapping syndromes:
    1. Cutaneous vasculitis (Raynaud's phenomenon, purpura, skin ulcers, livedo, acrocyanosis)
    2. Glomerulonephritis (hypertension, hematuria, nephrotic syndrome)
    3. Arthropathy (arthralgias, arthritis)
    4. Neuropathy (peripheral and/or central nervous system, distal sensorimotor, mononeuritis multiplex)
    5. Sicca syndrome (xerostomia, xerophthalmia)

Other factors that will be assessed / recorded in patients with MC will be:

1. Associated laboratory abnormalities including:
    - Positive HCV serology (recombinant immunoblot assay), viral nucleic acid quantitation diagnostic for HCV infection, and reflex genotyping.
    - Evidence of glomerulonephritis, including an active urinary sediment, hypoalbuminemia (albumin <3gm/dL) and/or significant proteinuria (>300mg/day).
    - Abnormal nerve conduction testing.

2. Pathologic evidence of cryoglobulinemia including:
   - Leukocytoclastic vasculitis.
   - Membranoproliferative glomerulonephritis.
   - Vasculopathy and/or mononuclear cell infiltrates on sural nerve biopsy.
   - Lip biopsy suggestive for Sjogren's syndrome.

3. Laboratory evidence of cryoglobulinemia including:
   - Characterization of cryoprecipitable material in serum by immunofixation, cryocrit, and/or quantitation of protein.
   - Associated immunological abnormalities, such as depressed levels of complement, elevated titers of rheumatoid factor, abnormal immunoglobulin quantitations, and serum immunofixation carried out on serum and/or isolated cryoglobulins.

4. Laboratory evidence of B-cell clonality, including:
   - IgMk determined by immunofixation of serum and/or cryoglobulin, and kappa excess >2.65:1 on Free Light Chain (FLC) assay

4.3. Exclusion criteria

1. Chronic liver disease of a non-HCV etiology (e.g., alcoholic liver disease, hepatotoxic drug exposure, autoimmune hepatitis hemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency, cholangitis).
2. Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV).
3. Patients with cirrhosis and Child-Pugh class B or C (Child-Pugh score will be calculated using laboratory parameters from screening visit).
4. Current or prior history of any of the following:
   4.1. Clinically-significant illness (other than HCV) or any other major medical disorder that in the opinion of the Investigator may interfere with subject treatment, assessment or compliance with the protocol; subjects currently under evaluation for a potentially clinically-significant illness (other than HCV) are also excluded.
5. Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy.

6. Clinical hepatic decompensation (i.e. ascites, encephalopathy or variceal hemorrhage).
7. Solid organ transplantation.
8. Clinically significant pulmonary disease, cardiac disease or psychiatric disease that in the opinion of the investigator renders the subject a poor risk for inclusion into the study.
9. Malignancy within the 5 years prior to screening, with the exception of specific cancers that have been cured by surgical resection (basal cell skin cancer, etc). Subjects under evaluation for possible malignancy are not eligible.
10. Significant drug allergy (such as anaphylaxis or hepatotoxicity).
11. Pregnant (serum pregnancy test to be performed for all women of childbearing potential at screening and urine pregnancy test at baseline); nursing female or unwillingness to practice birth control. Patients are expected to maintain adequate birth control to prevent pregnancy for 30 days post-completion of the drug (appendix 3).
12. Known hypersensitivity to SOF, VEL or formulation excipients.
13. Participation in an investigational trial of a drug or device (excluding observational studies) within 30 days prior to screening and through the duration of study participation.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Treatment Codes

Each patient will receive a treatment code after the screening visit. This treatment code will be a correlative number of 2 digits.

5.2. Description and Handling of Ledipasvir/ Sofosbuvir and Sofosbuvir/Velpatasvir

5.2.1. Formulation

The LDV/SOF (90mg/400 mg) tablets are orange colored, diamond shaped, film-coated tablet debossed with “GSI” on one side and “7985” on the other side of the tablet. In addition to the active ingredient, LDV/SOF tablets contain the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

The tablet film-coat contains: FD&C yellow #6/sunset yellow FCF aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

The SOF/VEL (400mg/100mg) tablets are orange colored, diamond shaped, film-coated tablet debossed with “GSI” on one side and “7916” on the other side of the tablet. In addition to the active ingredient, SOF/VEL tablets contain the following inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.2. Packaging and Labeling

LDV/SOF 90mg/400 mg tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

SOF/VEL 400mg/100mg tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 28 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

LDV/SOF 90mg/400 mg and SOF/VEL 400mg/100mg bottles shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA) and/or other local regulations as applicable.

Subjects will be provided with 2 bottles of medication (Harvoni or Epclusa) on Day 1 and another one on Week 4 visit. Thus, subjects will receive a total of 3 bottles of medication (28 tablets*3 bottles= 84 tables), enough to complete the 12 weeks of treatment (84 days).

Subjects that are receiving 24 weeks of treatment with Harvoni will be provided with 2 bottles of medication on Day, another one on Week 4 visit, another one on week 8 and 2 bottles on week 12. Thus, subjects will receive a total of 6 bottles of medication (28 tablets*6 bottles= 168 tables), enough to complete the 24 weeks of treatment (84 days).

	Day 1	Week 4	Week 8	Week 12	Week 20	Week 24
12 weeks treatment	2 bottles	1 bottle	-	Return all bottles		
24 weeks treatment	2 bottles	1 bottle	1 bottle	2 bottles	-	Return all bottles

5.2.3. Storage and Handling

LDV/SOF and SOF/VEL bottles should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as below 30°C (86°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

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

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

5.3. Study Drug Adherence and Drug Accountability

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

Study medications will be reconciled using medication pill count at all on treatment visits by the investigator or designee (i.e. study coordinator) in order to monitor the subject's adherence with the medication regimen.

5.4. Concomitant Medications

After oral administration of LDV/SOF, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. In clinical pharmacology studies, both sofosbuvir and the inactive metabolite GS-331007 were monitored for purposes of pharmacokinetic analyses.

Use of HARVONI® with amiodarone is not recommended. Coadministration with amiodarone may result in serious symptomatic bradycardia.

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered 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 LDV/SOF, and the use with P-gp inducers is not recommended with LDV/SOF.

Concomitant medications taken within 30 days prior to Screening, up to and including 30 days after the last dose of study drug need to be recorded in the source documents and eCRFs.

After oral administration of SOF/VEL, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. In clinical pharmacology studies, both sofosbuvir and the primary circulating metabolite GS-331007, were monitored for purposes of pharmacokinetic analyses.

Use of Epclusa® with amiodarone is not recommended. Coadministration with amiodarone may result in serious symptomatic bradycardia.

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e., P-gp) with study drug(s) may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug(s) or these medications. Velpatasvir is an inhibitor of P-gp, organic anion-transporting polypeptides (OATPs) and CYP 2B6, CYP 2C8, and CYP 3A4 and may increase intestinal absorption

of coadministered substrates for these transporters. P-gp inducers (e.g., rifampin or St. John's wort) may decrease sofosbuvir plasma concentrations, leading to reduced therapeutic effect, and the use with P-gp inducers is not recommended with Epclusa®. Concomitant medications taken within 30 days prior to Screening, up to and including 30 days after the last dose of study drug need to be recorded in the source documents and eCRFs.

Table 1 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either LDV/SOF or SOF/VEL, the components as individual agents, or are predicted drug interactions that may occur with LDV/SOF or SOF/VEL. The use of the following agents is prohibited from 15 days prior to Baseline/Day 1 through the end of treatment.

Table 1a. Potentially Significant Drug Interactions. Harvoni®

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Acid Reducing Agents:	↓ ledipasvir	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		It is recommended to separate antacid and HARVONI administration by 4 hours.
H_2-receptor antagonists[c] (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g., omeprazole)		Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.
Antiarrhythmics: amiodarone	Effect on amiodarone, ledipasvir, and sofosbuvir concentrations unknown	Coadministration of amiodarone with HARVONI may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended; if coadministration is required, cardiac monitoring is recommended *[see Warnings and Precautions (5.1), Adverse Reactions (6.2)]*.
digoxin	↑ digoxin	Coadministration of HARVONI with digoxin may increase the concentration of digoxin. Therapeutic concentration monitoring of digoxin is recommended when coadministered with HARVONI.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin[c] rifapentine	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. Coadministration of HARVONI with rifampin, a P-gp inducer, is not recommended *[see Warnings and Precautions (5.2)]*.

HIV Antiretrovirals:		
Regimens containing tenofovir DF without an HIV protease inhibitor/ritonavir or cobicistat	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving HARVONI concomitantly with a regimen containing tenofovir DF without an HIV protease inhibitor/ritonavir or cobicistat. Refer to VIREAD or TRUVADA prescribing information for recommendations on renal monitoring.
Regimens containing tenofovir DF and an HIV protease inhibitor/ritonavir or cobicistat • atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir DF[c] • darunavir/ritonavir or cobicistat + emtricitabine/tenofovir DF[c] • lopinavir/ritonavir + emtricitabine/tenofovir DF	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of HARVONI and an HIV protease inhibitor/ritonavir or cobicistat has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for recommendations on renal monitoring.
elvitegravir, cobicistat, emtricitabine, tenofovir DF	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of HARVONI and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF has not been established. Coadministration is not recommended.
tipranavir/ritonavir	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
HCV Products: simeprevir[c]	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased when simeprevir is coadministered with ledipasvir. Coadministration of HARVONI with simeprevir is not recommended.
Herbal Supplements: St. John's wort *(Hypericum perforatum)*	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with St. John's wort, a P-gp inducer, is not recommended *[see Warnings and Precautions (5.2)]*.
HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Coadministration of HARVONI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of HARVONI with rosuvastatin is not recommended.

tenofovir DF = tenofovir disoproxil fumarate
a. This table is not all inclusive.
b. ↓ = decrease, ↑ = increase
c. These interactions have been studied in healthy adults.

Table 1b. **Potentially Significant Drug Interactions. Epclusa®**

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
Acid Reducing Agents:	↓ velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		Separate antacid and EPCLUSA administration by 4 hours.
H_2-receptor antagonists[c] (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from EPCLUSA at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g., omeprazole)		Coadministration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to coadminister, EPCLUSA should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton-pump inhibitors has not been studied.

Antiarrhythmics: amiodarone	Effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown	Coadministration of amiodarone with EPCLUSA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with EPCLUSA is not recommended; if coadministration is required, cardiac monitoring is recommended *[see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*.
digoxin[c]	↑ digoxin	Therapeutic concentration monitoring of digoxin is recommended when coadministered with EPCLUSA. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancers: topotecan	↑ topotecan	Coadministration is not recommended.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin[c] rifapentine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HIV Antiretrovirals: efavirenz[c]	↓ velpatasvir	Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir DF	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving EPCLUSA concomitantly with a regimen containing tenofovir DF. Refer to the prescribing information of the tenofovir DF-containing product for recommendations on renal monitoring.
tipranavir/ritonavir	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Herbal Supplements: St. John's wort *(Hypericum perforatum)*	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: rosuvastatin[c]	↑ rosuvastatin	Coadministration of EPCLUSA with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with EPCLUSA at a dose that does not exceed 10 mg.
atorvastatin	↑ atorvastatin	Coadministration of EPCLUSA with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.

DF = disoproxil fumarate.
a. This table is not all inclusive.
b. ↓ = decrease, ↑ = increase.
c. These interactions have been studied in healthy adults.

6. STUDY PROCEDURES

Study visits will occur at Screening, Baseline/Day 1, and on-treatment at Weeks 2, 4, 8, and 12 (weeks 20 and 24 for 24 weeks treatment period subjects). Post treatment Visits will occur at Weeks 4, 12, and 24 following the last dose of study medications.
Information on the specific laboratory parameters to be measured and clinical assessments to be performed are described below and in **Appendix 1**.

6.1. Screening assessments

6.1.1. Screening Visits (Day -30/-42 to Day 0)

Screening assessments will be completed within 30 days of the Baseline/Day 1 visit. The screening window can be extended to 42 days for subjects requiring liver biopsy or additional HCV genotype testing.
The following procedures will be performed and documented:

- Obtain written informed consent
- Obtain a detailed medical history
- Determine inclusion eligibility including cirrhosis determination (Reference Section 4.2)
    - If the presence of cirrhosis is determined, then appropriate diagnostic imaging (CT or Ultrasound) should have been performed in the last 6 months prior to screening or should be performed during the screening period to exclude the presence of hepatocellular carcinoma (HCC)
- Obtain HCV and MC medical history
    - Regarding HCV, if treatment-experienced, record the duration of the prior treatment and the type of interferon and/or ribavirin and/or DAA administered.
        - Record whether the subject had a Non-response or Relapse/Breakthrough during prior treatment
            - *Non-Response:* Subject did not achieve undetectable HCV RNA while on treatment.
            - *Relapse/Breakthrough:* Subject achieved undetectable HCV RNA during treatment or within 4 weeks of the end of treatment, but did not achieve SVR.

  - Regarding MC, record date of diagnosis, clinical manifestations, investigations done and previous treatments.
- Obtain details of adverse events (AE) related to screening procedures
- Obtain details of concomitant medications taken within 30 days of screening visit
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse and temperature)
- Perform complete physical examination, including vasculitis and joint evaluation
- 12-lead ECG
- Complete neurological evaluation. Those subjects with neuropathy associated cryoglobulinemia must have acomplete physical examination and electrophysiological tests (Mount Sinai Hospital Neurology Department).
- Vasculitis activity score (Birmingham vasculitis score) for subjects with vasculitis.
- Sicca evaluation: evaluation by medical history and physical examination for subjects with Sicca syndrome.
  - Sicca evaluation: evaluation of xerostomia (saliva elicited from Stenson's duct after sucking on a lemondrop) and xerophtalmia (Schirmer test).
- Glomerulonephritis evaluation (urine sample and quantitation of serum creatinine) for subjects with glomerulonephritis
- ACR20-70 score (for subjects with Rheumatoid arthritis). This score includes a physical exam, a HAQ and a blood sample to evaluate ESR or CRP.
- Assessment of cirrhosis. Presence of absence of cirrhosis will be assessed by Fibroscan or APRI score or FibroMeter®.
- Obtain blood samples for tests:
  - Hematology profile
  - Chemistry profile
  - Coagulation profile
  - HIV 1/2 antibody and Hepatitis B surface antigen. If patient has a negative serology performed in the last 6 months, it does not need to be repeated.
  - HCV antibody and HCV RNA
  - Determination of genotype and subtype of HCV infection
  - IL28B genotype. All patients will have genotype determined and screened for IL28B genotype CC in order to corroborate previous studies of patients with

MC with regard to both, and with regard to response to treatment (20). If patient has an historical IL28B, it does not need to be repeated.
    - Analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement and HCV core ELISA.
    - Serum β -hCG pregnancy test for females of childbearing potential only
    - CRP and ESR
- Obtain urine sample for:
    - Urinalysis and urine creatinine
- Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the Baseline/Day 1 visit assessments.

6.2. Treatment Assessments

6.2.1. Baseline/Day 1 assessments

The following baseline tests and procedures must be completed prior to first dose of study drug(s):

- Confirm eligibility
- Perform a detailed medical history
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling and confirmation of contraception
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse and temperature)
- Perform complete physical examination, including vasculitis, joint, neuropathy examination and sicca syndrome (for subjects with Sicca syndrome)
- Vasculitis activity score (Birmingham vasculitis score) for subjects with vasculitis.
- Glomerulonephritis evaluation (urine sample and serum creatinine) for subjects with glomerulonephritis
- ACR20-70 score (for subjects with Rheumatoid arthritis). This score includes a physical exam, a HAQ and a blood sample to evaluate ESR or CRP.
- Obtain blood samples for:
    - Hematology profile
    - Chemistry profile
    - Coagulation profile

- ESR and CRP
- Analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement, HCV core ELISA and Clonality/Lymproliferation / FACS.

- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only
  - Urinalysis and urine creatinine
- Subject completes Health Assessment Questionnaire
- Drug Administration
  - Dispense study drugs
  - Instruct the subject on the packaging, storage, compliance and administration of all study drugs (Epclusa® patient information. Appendix 4).
  - Observe the subject taking the first dose of study drugs and record the time of first dose and whether it was taken with or without food.

6.2.2. Treatment assessments (week 2 +/-3 days)

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

- Perform a detailed medical history
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling and confirmation of contraception
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse and temperature)
- Perform complete physical examination, including vasculitis, joint, neuropathy examination and sicca syndrome (for subjects with Sicca syndrome)
- Vasculitis activity score (Birmingham vasculitis score) for subjects with vasculitis.
- Glomerulonephritis evaluation (urine sample and serum creatinine sample) for subjects with glomerulonephritis
- ACR20-70 score (for subjects with Rheumatoid arthritis). This score includes a physical exam, a HAQ and a blood sample to evaluate ESR or CRP.
- Obtain blood samples for:
  - Hematology profile
  - Chemistry profile

- Analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement and HCV core ELISA.

- Obtain urine sample for:
  - Urinalysis and urine creatinine
- Subject completes Health Assessment Questionnaire
- Review study drug compliance and drug administration instructions with subject

6.2.3. Treatment assessments (week 4+/-7 days)

- Perform a detailed medical history
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling and confirmation of contraception
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse and temperature)
- Vasculitis activity score (Birmingham vasculitis score) for subjects with vasculitis.
- Glomerulonephritis evaluation (urine sample and serum creatinine sample) for subjects with glomerulonephritis
- ACR20-70 score (for subjects with Rheumatoid arthritis). This score includes a physical exam, a HAQ and a blood sample to evaluate ESR or CRP.
- Perform complete physical examination, including vasculitis, joint, neuropathy examination and sicca syndrome (for subjects with Sicca syndrome)
- Obtain blood samples for:
  - Hematology profile
  - Chemistry profile
  - Coagulation profile
  - HCV RNA
  - ESR and CRP
  - Analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement, HCV core ELISA and FACS
- Obtain urine sample for:
  - Urine pregnancy test for females of childbearing potential only
  - Urinalysis and urine creatinine
- Subject completes Health Assessment Questionnaire

- Review study drug compliance and drug administration instructions with subject
- Drug Administration:
    - Dispense study drug
    - Review study drug compliance

6.2.4. Treatment assessments (week 8+/-7 days and week 20+/-7 for those subjects on Harvoni 24 weeks)

- Perform a detailed medical history
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling and confirmation of contraception
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse and temperature)
- Vasculitis activity score (Birmingham vasculitis score) for subjects with vasculitis.
- Glomerulonephritis evaluation (urine sample and serum creatinine sample) for subjects with glomerulonephritis
- ACR20-70 score (for subjects with Rheumatoid arthritis). This score includes a physical exam, a HAQ and a blood sample to evaluate ESR or CRP.
- Perform complete physical examination, including vasculitis, joint, neuropathy examination and sicca syndrome (for subjects with Sicca syndrome)
- Obtain blood samples for:
    - Hematology profile
    - Chemistry profile
    - Coagulation profile
    - ESR and CRP
    - HCV RNA
- Analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement and HCV core ELISA
- Obtain urine sample for:
    - Urine pregnancy test for females of childbearing potential only
    - Urinalysis and urine creatinine
- Subject completes Health Assessment Questionnaire
- Review study drug compliance and drug administration instructions with subject

- Review study drug compliance

6.2.5. End of treatment (week 12 or week 24 +/-7 days)

The following procedures/assessments are to be completed at the end of treatment(week 12 or week 24, depending on treatment arm):

- Perform a detailed medical history
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling and confirmation of contraception
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse and temperature)
- Vasculitis activity score (Birmingham vasculitis score) for subjects with vasculitis.
- Glomerulonephritis evaluation (urine sample and serum creatinine sample) for subjects with glomerulonephritis
- ACR20-70 score (for subjects with Rheumatoid arthritis). This score includes a physical exam, a HAQ and a blood sample to evaluate ESR or CRP.
- Perform complete physical examination, including vasculitis, joint, neuropathy examination and sicca syndrome (for subjects with Sicca syndrome)
- Subject completes Health Assessment Questionnaire
- Obtain blood samples for:
    - Hematology profile
    - Chemistry profile
    - Coagulation profile
    - HCV RNA
    - ESR and CRP
    - Analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement, HCV core ELISA and Clonality/Lymphoproliferation / FACS
- Obtain urine sample for:
    - Urine pregnancy test for females of childbearing potential only
    - Urinalysis and urine creatinine
- Complete medication pill count.

6.3. Post-treatment assessments

The post treatment Week 4, 12 and 24 visits should be timed from the date of last administration of study drugs.

6.3.1. Post Treatment Week 4 (+/- 7 days)

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

- Perform a detailed medical history
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse and temperature)
- Vasculitis activity score (Birmingham vasculitis score) for subjects with vasculitis.
- Glomerulonephritis evaluation (urine sample and serum creatinine sample) for subjects with glomerulonephritis
- ACR20-70 score (for subjects with Rheumatoid arthritis). This score includes a physical exam, a HAQ and a blood sample to evaluate ESR or CRP.
- Perform complete physical examination, including vasculitis, joint, neuropathy examination and sicca syndrome (for subjects with Sicca syndrome)
- Subject completes Health Assessment Questionnaire
- Obtain blood samples for:
    - Hematology profile
    - Chemistry profile
    - Coagulation profile
    - ESR and CRP
    - HCV RNA
    - Analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement, HCV core ELISA and FACS.
- Obtain urine sample for:
    - Urine pregnancy test
    - If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.
    - Urinalysis and urine creatinine

6.3.2. Post Treatment Week 12 and 24 (+/- 7 days)

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

- Perform a detailed medical history
- Assessment of SAEs and concomitant medications
- Obtain body height and weight
- Obtain vital signs (resting blood pressure, pulse and temperature)
- Vasculitis activity score (Birmingham vasculitis score) for subjects with vasculitis.
- Glomerulonephritis evaluation (urine sample and serum creatinine sample) for subjects with glomerulonephritis
- ACR20-70 score (for subjects with Rheumatoid arthritis). This score includes a physical exam, a HAQ and a blood sample to evaluate ESR or CRP.
- Perform complete physical examination, including vasculitis, joint and neuropathy examination.
- Sicca evaluation: evaluation by medical history and physical examination (for subjects with Sicca syndrome).
    - Sicca evaluation: evaluation of xerostomia (saliva from Stensen's duct) and xerophtalmia (Schirmer tests) will be performed at PT week 24.
- For those subjects with neuropathy associated to cryoglobulinemia: A complete neurological examination will be performed (Mount Sinai Hospital Department of Neurology) will be performed at Post treatment week 24.
- Obtain blood samples for:
    - Hematology profile
    - Chemistry profile
    - Coagulation profile
    - ESR and CRP
    - HCV RNA
    - Analysis of cryoglobulinemia measuring cryoglobulins, analyzing cross reactive idiotypes, analysis of complement, HCV core ELISA and clonality/lymphoproliferation / FACS.
- Obtain urine sample for:

- urinalysis and urine creatinine

- Subject completes Health Assessment Questionnaire

6.4. Procedures and Specifications

Fasting is not required for any of the procedures except for Fibroscan that requires 6 hour fasting.

6.4.1. Clinical Laboratory Analytes

- Hematology profile: Hematocrit, Hemoglobin (Hb), Platelet count, Red blood cell count (RBC), White blood cell count (WBC) with differential (absolute and percentage) including Lymphocytes, Monocytes, Neutrophils, Eosinophils, Basophils, Reticulocyte count and MCV. These studies will be performed at Core Laboratory at Mount Sinai Hospital.
- Coagulation profile: INR, Prothrombin time (PT), Activated partial thromboplastin time (APTT). These studies will be performed at Core Laboratory at Mount Sinai Hospital.
- Chemistry profile: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Creatine Kinase, Creatinine, Total Bilirubin (reflex to Direct Bilirubin), Glucose, Lipase, Potassium, Sodium; Fibrotest® /APRI calculation, and Direct Bilirubin at Screening only. These studies will be performed at Core Laboratory at Mount Sinai Hospital.
- Urinalysis: Appearance, Blood, Color, Glucose, Leukocyte esterase, pH, Protein, Urobilinogen. These studies will be performed at Core Laboratory at Mount Sinai Hospital.
- Urine creatinine level. This study will be performed at Core Laboratory at Mount Sinai Hospital.
- Virological Tests: Serologies for HCV, HBV and HIV. HCV RNA will be measured using the COBAS® TaqMan® HCV Test, v2.0 for use with Ampliprep. HCV genotype and subtype will be determined using the Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay. These studies will be performed at Core Laboratory at Mount Sinai Hospital.

- IL28B genotype will be determined by polymerase chain reaction (PCR) amplification of the SNP, rs12979860, with sequence specific forward and reverse primers and allele specific fluorescently labeled TaqMan® MGB probes. These studies will be performed at Core Laboratory at Mount Sinai Hospital.
- Pregnancy Tests: Serum β-hCG or Urine β-hCG.

6.4.2. Medical History

Medical history including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history, including prior HCV treatment history (only applicable for treatment experienced subjects), will be collected on all subjects during screening.

Obtain HCV treatment history as per Section 4.2.

Obtain MC treatment history as per Section 4.2.

6.4.3. Complete Physical Examination

A complete physical examination will include source documentation of general appearance, and the following body systems: Head: eyes, ears, nose, throat, mouth and tongue; Neck Range of motion (ROM, thyroid, cervical nodes Chest: (excluding breasts); respiratory; Cardiovascular: heart rate and rhythm, murmurs and gallops Lymph nodes: axillary, inguinal Abdomen: tenderness, organomegaly Skin: rashes, hair, nails Joints: tenderness, ROM, heat, swelling Musculoskeletal: muscle strength and tenderness Neurological. Physical examination will also include evaluation of the amount of saliva and tear production by visual inspection of the salivary and lacrimal glands.

6.4.4. Vital Signs

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and temperature.

Blood pressure will be measured using the following standardized process:

- Subject should sit for ≥5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;

- Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

6.4.5. Creatinine Clearance (CLcr)

Creatinine clearance is calculated by the Cockcroft-Gault equation {2202} using actual body weight (BW).

Male: CLcr (mL/min) = [140 - age (years)] x BW(kg) / 72 s Scr

Female: CLcr (mL/min) = [140 - age (years)] x BW(kg) x0.85 / 72 x Scr

Scr = serum creatinine (mg/dL)

6.4.6. 12-Lead ECGs

Subjects will be required to rest in a supine position for ≥5 minutes prior to making a recording.

The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities.

6.4.7. Viral RNA Sequencing / Phenotyping Sample

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

6.4.8. Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the dosing period and 30 days after last dose of study drug.

Definition of childbearing potential is described in Appendix 3.

If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test.

6.4.9. Other procedures

- Vasculitis activity score (Birmingham vasculitis score). This score includes the following items: (1) general, (2) cutaneous, (3) mucous membranes/eyes, (4) ENT, (5) chest, (6) cardiovascular, (7) Abdominal, (7) renal, (8) Nervous system, (9) other. This score is based on patient self-report, medical history, physical examination

serum creatinine, urine creatinine and urinalysis (proteinuria, hematuria). Appendix 6. Only for subjects with vasculitis.

- Sicca syndrome evaluation. This will be assessed by PI in all visits based on patient self-report and physical examination to assess amount of saliva and tears. On screening and post treatment week 24 visits Dr Gorevic will perform a Schirmer test to assess xerophtalmia and will measure saliva from Stensen's duct to assess xerostomia (39,40). Only for subjects with sicca syndrome.
- ACR20-70 score. This score includes the assessment following items: 1) at swollen joint counts, 2) tender joint counts, 3) patient-assessed global disease activity (i.e. by VAS), 4) evaluator-assessed global disease activity (i.e. by VAS), 5) patient pain assessment (i.e. by VAS), 6) functional disability (i.e. by HAQ), 7) acute phase response (ESR or PCR). A 20 and 70 percent response (ACR20-70) represents improvement of at least 20 or 70 percent (41). Only for subjects with Rheumatoid arthritis.
- Glomerulonephritis evaluation. This will be assessed by 1) the presence of hematuria, proteinuria and red cell casts by urinalysis, 2) quantification of proteinuria on a 24 hour collection or as the protein/creatinine ratio of a spot sample of urine and 3) concomitant renal insufficiency is defined as serum creatinine >2.0mg/dL. Only for subjects with glomerulonephritis.
- Neuropathy evaluation will be evaluated by complete and detailed physical examination performed by Dr Gorevic in every visit. For those subjects with neuropathy associated cryoglobulinemia, on screen and post-treatment week 24 visits this will be performed by Dr Jessica Robinson-Papp, and neuropathy will be corroborated by electrophysiologic testing.
- Complement studies:
    - MBL, Generation attack complex (C5-9), Rheumatoid factor, IgM, C3, C4 and C4a analysis will be performed through the Core Laboratory at Mount Sinai Health Care System.
    - C1q, C1q binding assays and gC1qR will be performed at our clinical immunology laboratory, and in the Laboratory of Dr Berhane Ghebrehiwet (State University of New York, Stony Brook).
- Cryoprecipitation characterization studies:

- Analysis of MC and of cross-reactive idiotypes (CRI) will be separated and frozen to be analyzed on a later date at the Flow Cytometry Laboratory at Mount Sinai Health Care System.

- Regression of clonality/lymphoproliferation and FACS analysis, this includes:
  - B-cell surface antigens, kappa/lambda light chain on B cells, CLL lymphoma panel and CD81, that will be performed at the Flow Cytometry Shared Resource Core Facility and at our Clinical Immunology Laboratory
  - Isolate PBMCs for CyTOF analysis to investigate the patients mononuclear cellular immunity profile during and after DAA treatment cell populations to be analyzed by CyTOF. Samples will be frozen and and analysis on a later date.

- HCV core ELISA: this includes:
  - Compartmentalization of viral RNA and core antigen between cryoprecipitible and non-cryoprecipitible immune complexes will be performed with support from our institutional Human Immune Monitoring Core Facility.
  - HRP conjugated HCV core Ag antibodies will be obtained commercially with assays to be performed with support from our Human Immune Monitoring Core Facility.
  - FITC-conjugated secondary antibodies will be obtained commercially and tested for optimal resolution in our institutional Flow Cytometry Shared Resource Core Facility.

7. TOXICITY MANAGEMENT

7.1. Dose Modification Due to Toxicity

There is no option for dose reduction or modification of LDV/SOF or SOF/VEL.

7.2. Toxicity Stopping Criteria

Administration of all study medication(s) may be discontinued in the event of a clinical or laboratory event. The PI must be consulted prior to dose discontinuation of LDV/SOF or SOF/VEL unless the investigator believes that immediate action is warranted to ensure the continued safety of the subject. Subjects who meet any of the following laboratory criteria must stop all study medication(s):

- Elevation of ALT and/or AST >5x Baseline/Day 1 or nadir, confirmed by immediate repeat testing
- Abnormal elevation of ALT >3x Baseline/Day 1 and total bilirubin >2 x ULN, confirmed by immediate repeat testing
- Elevation of ALT >15 x ULN, confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 adverse event or laboratory abnormality assessed (and confirmed by immediate repeat testing) as related to LDV/SOF or to SOF/VEL.
- Any unacceptable side effect of the drug (i.e. hypersensitivity reaction, abnormal Liver function tests; gastrointestinal side effects) 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.
- A paradoxic effect on the disease manifestations (i.e. increased or systemic vasculitis, renal failure)

8. ADVERSE EVENTS MANAGEMENT

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

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

An AE does not include the following:

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

8.1.1. Classification of Adverse Events

8.1.1.1. Serious Adverse Events

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

- Death

- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

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

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (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 as described. If the laboratory abnormality is part of a syndrome, we will record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

8.2. Assessment of Adverse Events and Serious Adverse Events

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

8.2.1.1. Assessment of Causality for Study Drugs and Procedures

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

- No: Evidence exists that the adverse event has an etiology other than the 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 (eg., venipuncture)

8.2.1.2. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 2). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

8.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, until 4 weeks after last administration of study drug must be collected and reported on the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, will be reported to the CRF/eCRF database and to the FDA. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment visit, regardless of causality, will also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, this will be promptly documented, and the event reported to the FDA.

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline and will be reported within 24 hours. SAEs will be reported accordingly to FDA guidelines. As soon as it is possible to do so, any SAE reported via paper will be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- For fatal or life-threatening events, copies of hospital reports, autopsy reports, and other documents will also be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE will be recorded onto the concomitant medication section of the subject's CRF/eCRF, and the event description section of the SAE form.
- The investigator will notify the IRB of SUSAR reports as soon as practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

8.4. Special Situations Reports

8.4.1.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

- Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.
- Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.
- Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.
- An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject is unable to account for the discrepancy, except in cases in which the investigator has reason to suspect that the subject has taken additional dose(s).
    - No specific antidote is available for overdose with Harvoni® or Epclusa®. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with HARVONI® or Epclusa® consists of general supportive measures including monitoring of vital signs as well as observation

of the clinical status of the patient. Hemodialysis is unlikely to result in significant removal of ledipasvir since ledipasvir is highly bound to plasma protein. Hemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Hemodialysis is unlikely to result in significant removal of velpatasvir since velpatasvir is highly bound to plasma protein.

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

8.4.1.2. Instructions for Reporting Special Situations

8.4.1.2.1. Instructions for Reporting Pregnancies

The investigator will report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period.

Pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reason.

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

A spontaneous abortion is always considered to be an SAE and will be reported as described above. Furthermore, any SAE occurring as an adverse pregnancy outcome post study will be reported to the FDA.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome will be reported to the FDA using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the FDA.

Pregnancies of female partners of male study subjects exposed to study drugs will also be reported, and relevant information submitted to the FDA using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject will continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the FDA,

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

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

8.5. Warnings and Precautions

Refer to HARVONI® (Ledipasvir/sofosbuvir) package insert for additional information (Appendix 5b).

Refer to Epclusa® (Sofosbuvir/Velpatasvir) package insert for additional information (Appendix 5b).

9. STATISTICAL CONSIDERATIONS

This is a pilot study in which 10 patients will be enrolled to explore the efficacy of all-oral anti-viral therapy for symptomatic hepatitis C virus infection-related cryoglobulinemia.
With 10 patients in the study we will be able to estimate the rate of patients who obtain an SVR with a margin of error of approximately 15%.
We will use frequency table and 95% confidence interval to describe the rate of SVR in the total sample and the two subgroups of interest.
Results will be compared to previous published studies (28), as well as unpublished experience, that have delineated the natural history of type 2 cryoglobulinemia, and the response to immunomodulatory therapies, including IFN/Peg-IFN, Ribavirin and Rituximab (27).

10. INVESTIGATOR RESPONSABILITIES

10.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the “Declaration of Helsinki” (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States IND, the investigator will ensure that the basic principles of “Good Clinical Practice,” as outlined in 21 CFR 312, subpart D, “Responsibilities of Sponsors and Investigators,” 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

10.2. Institutional Review Board (IRB) Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter to the

investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

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

10.3. Informed Consent

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

10.4. Confidentiality

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

10.5. Study Files and Retention of Records

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

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

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

- subject identification (name, date of birth, gender);
- documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- participation in trial (including trial number);
- trial discussed and date of informed consent;
- dates of all visits;
- documentation that protocol specific procedures were performed;
- results of efficacy parameters, as required by the protocol;
- start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- record of all adverse events and other safety parameters (start and end date, and preferably including causality and intensity);
- concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents will be retained by the investigator until study publication.

10.6. Electronic Case Report Forms (eCRF, RedCap)

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

REDCap platform will be used for our eCRF (http://www.project-redcap.org).

10.7. Drug accountability

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

Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. Destruction or return of unused investigational medicinal product supplies will be destroyed at on site Pharmacy.

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

10.8. Protocol compliance

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

10.9. Protocol Modifications

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

10.10. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies).

Principal Investigator will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media.

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 7 days and 30 days before submission of the abstract or publication, respectively.

10.11. Access to Information for Auditing or Inspections

Representatives of regulatory authorities may conduct inspections or audits of the clinical study. The investigator agrees to provide to representatives of a regulatory agency access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.12. Study Discontinuation

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

11. REFERENCES

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(3) Manifestations of chronic hepatitis C virus infection beyond the liver. Jacobson IM, Cacoub P, Dal Maso L, Harrison SA, Younossi ZM. Clin Gastroenterol Hepatol. 2010;8:1017-29.

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12. APPENDICES

- Appendix 1a. Study procedures and study visits table.
- Appendix 1b. Laboratory tests per visits table
- Appendix 2. Common Terminology Criteria for Adverse Events (CTCAE). GSI grading scale for severity of adverse events and laboratory abnormalities.
- Appendix 3. Pregnancy Precautions, definition for female of childbearing potential and contraceptive requirements.
- Appendix 4. Epclusa® patient information.
- Appendix 5a. Epclusa package insert.
- Appendix 5b. Harvoni® patient package insert.
- Appendix 6. Birmingham vasculitis score.
- Appendix 7. Health Assessment Questionnaire (HAQ-DI)
- Appendix 8. Visual Analog Scale (VAS)

PRINCIPAL INVESTIGATORS STATEMENT

This is an investigator initiated trial. The sponsor is Mount Sinai.

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

My signature below constitute my approval of this protocol and proved the necessary assurances that this study will be conducted according to the Declaration of Helsinki, GCP, ICH guidelines, local legal and regulatory regulations as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

Investigator's printed name and signature	Date
Co-Investigator's printed name and signature	Date

Protocol Number: IND-US-337-1716

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