STUDY PROTOCOL

Study Title:	A multicenter, open-label study of Harvoni ® (sofosbuvir ledipasvir fixed dose combination) in subjects infected with chronic hepatitis C and advanced heart failure or lung disease
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PROTOCOL SYNOPSIS

Study Title: A multicenter, open-label study of sofosbuvir ledipasvir fixed dose combination in subjects infected with chronic hepatitis C and advanced heart failure or lung disease

Study sites: 5

Objectives: The primary objective is:

- To evaluate the safety and tolerability of sofosbuvir (SOF) + ledipasvir (LDV) fixed dose combination (FDC) for 12-24 weeks in subjects with chronic HCV and advanced heart failure or lung disease.

The secondary objective is:

- To determine the antiviral efficacy of SOF/LDV FDC for 12-24 weeks in subjects with chronic HCV and advanced heart failure or lung disease as measured by sustained virologic response 12 weeks after discontinuation of therapy (SVR12 defined as HCV RNA < lower limit of quantitation 12 weeks post-treatment).

Study Design: Approximately 25 subjects with chronic HCV and advanced heart failure and 25 subjects with chronic HCV and lung disease will be enrolled. Subjects must have genotype 1, 4, 5 or 6 HCV. All subjects will receive 12 weeks of the SOF/LDV FDC except for treatment experienced genotype 1 subjects with cirrhosis, who will receive 24 weeks of treatment.

Number of Subjects: Approximately 50 subjects

Eligibility Criteria: All subjects must meet all of the follow HCV criteria:

- Genotype 1, 4, 5, or 6
- HCV RNA $\geq 10^3$ IU/mL at screening
- Age $\geq$ 18 years
- Diagnosis of chronic HCV infection, defined as positive HCV antibody or HCV RNA more than 6 months prior to screening OR an assessment of fibrosis F2 or greater prior to screening.

Subjects in the advanced heart failure cohort must meet **ALL** HCV criteria, and all of the following criteria:

- New York Heart Association (NYHA) Class III or IV functional classification
    - NYHA Class III: Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary

physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
    - NYHA Class IV: Patient with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
- ejection fraction ≤ 30%
- hospitalized for heart failure in last 12 months

Subjects in the advanced lung disease cohort must have been diagnosed with chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD) must meet **ALL** HCV criteria, and meet the following criteria for COPD or ILD:

- ILD criteria: diagnosis of interstitial lung disease with chronic supplemental oxygen requirement at rest and/or with exertion.
- COPD criteria (one of the following):
    - Forced expiratory volume (FEV1)< 30% predicted
    - **OR** any FEV1 with chronic supplemental oxygen requirement at rest and/or with exertion
    - **OR** any FEV1 with chronic hypercapnea (baseline partial pressure of arterial carbon dioxide [PaCO2] > 45)

Subjects may not present with any of the criteria:

- Genotype 2 or 3 infection
- Treatment with any of the following agents
    - Amiodarone. Subjects previously treated with amiodarone must have stopped the amiodarone at least 60 days prior to day 1 of SOF/LDV FDC
    - Carbamazepine, phenytoin, phenobarbital, oxcarbazepine
    - Rifabutin, rifampin or rifapentine
    - HIV regimens containing tenofovir or tipranavir/ritonavir
    - St. John's wort
    - Rosuvastatin
- Have any serious or active medical or psychiatric illness which, in the opinion of the investigator, would interfere with subject treatment, assessment, or compliance
- History of hepatic encephalopathy or variceal hemorrhage
- Hepatitis B surface antigen positive
- Abnormal hematological and biochemical parameters, including:
    - Hemoglobin (Hb) < 8 g/dL

- Platelets ≤ 50,000/mm^3
- ALT (alanine aminotransferase), AST (aspartase aminotransferase), or alkaline phosphatase ≥ 10 times ULN
- Total bilirubin > 3 mg/dl
- Severe renal impairment creatinine clearance (CrCl), i.e. < 30 mL/min.

- History of major organ transplantation with an existing functional graft.
- History of clinically-significant drug allergy to nucleoside/nucleotide analogs.
- Pregnant women or women planning to become pregnant
- Women who are breastfeeding
- Active or recent history (≤ 1 year) of drug or alcohol abuse

Study Procedures/ Frequency:

Study visits will occur at screening, baseline/day 1, weeks 2, 4, 8, 12 for the 12-week treatment group and also weeks 16, 20 and 24 for the 24-week treatment group. Post-treatment follow-up visits will be performed at 4 and 12 weeks following the last dose of study drug for both groups.

Screening assessments include physical examination with height and weight measurements, vital signs, medical history review for eligibility determination, safety laboratory tests, HCV RNA and HCV genotyping, HIV and HBV testing, serum β-hCG (females of childbearing potential only), ECG, and Fibroscan (if needed)

On-treatment assessments include adverse events (AEs) assessments, concomitant medications, physical examination, vital signs, safety laboratory tests, HCV RNA, ECG

Post-treatment assessments include adverse events (AEs) assessments, concomitant medications, physical examination, vital signs, safety laboratory tests, HCV RNA, ECG

Test Product, Dose, and Mode of Administration:

All study subjects will receive the sofosbuvir 400 mg and ledipasvir 90 mg fixed dose combination. Subjects will take one tablet in the morning.

Evaluation criteria

Safety

AEs that lead to discontinuation, SAEs and safety laboratory tests will be collected until 4 weeks after the last dose of study drug. Safety endpoints will include

- Completion of full course of therapy
- Discontinuation for adverse events
- Serious adverse events

Efficacy

Efficacy will be evaluated using scheduled assessments of HCV RNA by PCR. All endpoints will be summarized with descriptive

statistics by cohort. Number and percent of subjects in each cohort will be presented for categorical variables. For continuous variables, N, mean, SD, Median, Q1, Q3, minimum and maximum will be presented.
The primary efficacy endpoint will be the SVR12 defined as HCV RNA < LLoQ for 12 weeks post-treatment.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BW	Body weight
CL_{cr}	creatinine clearance
COPD	Chronic obstructive pulmonary disease
CRF	case report form(s)
dL	deciliter
ECG	electrocardiogram
e.g.	For example
ET	Early termination
FDA	(United States) Food and Drug Administration
FDC	Fix Dosed Combination
FEV1	Forced expiratory volume
GCP	Good Clinical Practice (Guidelines)
Hb	hemoglobin
hCG	human chorionic gonadotropin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
i.e.	for explanation
ILD	Interstitial lung disease
INR	International normalized ratio
IRB	institutional review board
LDV	ledipasvir
LLoQ	lower limit of Quantification
MCV	Mean corpuscular volume
mg	milligram
mL	milliliter
Min	minutes
NYHA	New York Heart Association
PaCO2	Partial pressure of arterial carbon dioxide
PCR	Polymerase chain reaction
PI	Principal Investigator
PK	pharmacokinetic
PT	Prothrombin time
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	serious adverse event
S_{cr}	Serum creatinine
SD	Standard deviation
SOF	sofosbuvir
SVR	Sustained Virologic Response, generally at 4 and 12 weeks after last dose of medication
ULN	upper limit of the normal range
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Approximately 180 million people worldwide and more than 3 million Americans are infected with Hepatitis C virus (HCV).[1,2] Chronic HCV infection is a leading cause of cirrhosis and hepatocellular carcinoma and remains the most common indication for transplantation in the United States. For more than 20 years, HCV regimens included interferon-α, which led to a number of adverse events including constitutional symptoms, neuropsychiatric symptoms, and cytopenias. These adverse events meant that many patients were ineligible or could not tolerate treatment.[3] Due to the challenging side effect profile and moderate efficacy, a number of direct acting antiviral medications have been developed. Interferon-free regimens are now available and are well tolerated and offer sustained virologic response (SVR) rates over 90% for many patient groups.[4,5]

The development of these well tolerated, interferon-free regimens has led to the consideration of HCV treatment of patient groups felt to previously be ineligible. In the past with interferon regimens, patients with advanced heart and lung disease were not offered HCV treatment generally due to the risk of exacerbation of the underlying disease. At most transplant centers, the diagnosis of HCV infection is a contraindication to heart or lung transplantation. Case series among HCV-seropositive heart transplant recipients have demonstrated increased mortality related to cardiovascular disease and progressive liver disease.[6,7] Although a smaller number of patients, cases of progressive liver failure after lung transplantation have been reported in patients with HCV infection.[8,] Successful treatment of HCV infection for patients with advanced heart and lung disease would potentially bring back the possibility of transplantation for these patients.

1.2. Rationale for the current study

The fixed dose combination of sofosbuvir/ledipasvir is a Food and Drug Administration (FDA) approved regimen for the treatment of chronic HCV infection. Sofosbuvir/ledipasvir is recommended by the American Association for the Study of Liver Diseases and the Infectious Disease Society of America as a first line option for the treatment of genotype 1 and 4 patients. SVR rates over 90% were initially reported in the registration trials of sofosbuvir/ledipasvir for genotype 1 treatment naïve and experienced patients.[4,9] Sofosbuvir/ledipasvir has subsequently been evaluated in other genotypes, and recent studies have demonstrated SVR rates greater than 90% for sofosbuvir/ledipasvir in genotypes 2, 3, 4 and 6.[10,11] For genotype 3 infection, these high SVR rates require the addition of ribavirin to sofosbuvir/ledipasvir. The main adverse event of ribavirin is hemolytic anemia, which may not be tolerated by patients with underlying heart and lung disease. The protocol has therefore been restricted to genotypes 1, 4, 5 and 6 given the ability to treat with the ribavirin-free regimen of the sofosbuvir/ledipasvir fixed dose combination.

2. OBJECTIVES

The primary objective is:

- To evaluate the safety and tolerability of sofosbuvir (SOF) + ledipasvir (LDV) fixed dose combination (FDC) for 12-24 weeks in subjects with chronic HCV and advanced heart failure or lung disease

The secondary objective is:

- To determine the antiviral efficacy of SOF/LDV FDC for 12-24 weeks in subjects with chronic HCV and advanced heart failure or lung disease as measured by sustained virologic response 12 weeks after discontinuation of therapy (SVR12 defined as HCV RNA < lower limit of quantitation 12 weeks post-treatment).

3. SUBJECT POPULATION

3.1. Treatment plan and regimen

Approximately 25 subjects with chronic HCV and advanced heart failure; and 25 subjects with chronic HCV and advanced lung disease will be enrolled. Subjects must have genotype 1, 4, 5 or 6 HCV. All subjects will receive SOF/LDV FDC. The duration of treatment will be 12 weeks for treatment naïve subjects with or without cirrhosis. All subjects will receive 12 weeks of the SOF/LDV FDC except for treatment experienced genotype 1 subjects with cirrhosis, who will receive 24 weeks of treatment. All subjects will continue in the study follow-up period for 12 weeks after treatment has been completed.

3.2. Visit schedule

All subjects will complete screening, on-treatment, and post-treatment follow up assessments. Screening assessments will be completed within 28 days of the baseline/day 1 visit. Study visits will occur at screening, baseline/day 1, weeks 2, 4, 8, 12 for the 12-week duration subjects and then also weeks 16, 20 and 24 for the 24-week duration group. Post-treatment follow-up visits will be performed at 4 and 12 weeks following the last dose.

3.3. Number of subjects and subject selection

A total of approximately 50 subjects will be enrolled. Approximately 25 subjects with advanced heart failure and 25 subjects with advanced lung disease will be enrolled.

3.4. Inclusion criteria

All subjects must meet all of the follow HCV criteria:

- Genotype 1, 4, 5, or 6
- HCV RNA $\geq$ 10^3 IU/mL at screening
- Age $\geq$ 18 years
- Diagnosis of chronic HCV infection, defined as positive HCV antibody or HCV RNA more than 6 months prior to screening OR an assessment of fibrosis F2 or greater prior to screening.

Subjects in the advanced heart failure cohort must meet **ALL** HCV criteria, and all of the following criteria:

- New York Heart Association (NYHA) Class III or IV functional classification
    - NYHA Class III: Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.

    - NYHA Class IV: Patient with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
- ejection fraction ≤ 30%
- hospitalized for heart failure in last 12 months

Subjects in the advanced lung disease cohort must have been diagnosed with chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD) must meet **ALL** HCV criteria, and meet the following criteria for COPD or ILD:

- ILD criteria: diagnosis of interstitial lung disease with chronic supplemental oxygen requirement at rest and/or with exertion.
- COPD criteria (one of the following):
    - Forced expiratory volume (FEV1)< 30% predicted
    - **OR** any FEV1 with chronic supplemental oxygen requirement at rest and/or with exertion
    - **OR** any FEV1 with chronic hypercapnea (baseline partial pressure of arterial carbon dioxide [PaCO2] > 45)

3.5. Exclusion Criteria

- Genotype 2 or 3 infection
- Treatment with any of the following agents
    - Amiodarone. Subjects previously treated with amiodarone must have stopped the amiodarone at least 60 days prior to day 1 of SOF/LDV FDC
    - Carbamazepine, phenytoin, phenobarbital, oxcarbazepine
    - Rifabutin, rifampin or rifapentine
    - HIV regimens containing tenofovir or tipranavir/ritonavir
    - St. John's wort
    - Rosuvastatin
- Have any serious or active medical or psychiatric illness which, in the opinion of the investigator, would interfere with subject treatment, assessment, or compliance
- History of hepatic encephalopathy or variceal hemorrhage
- Hepatitis B surface antigen positive
- Abnormal hematological and biochemical parameters, including:
    - Hemoglobin (Hb) < 8 g/dL
    - Platelets ≤ 50,000/mm^3
    - ALT (alanine aminotransferase), AST (aspartase aminotransferase), or alkaline phosphatase ≥ 10 times ULN
    - Total bilirubin > 3 mg/dl
    - Severe renal impairment creatinine clearance (CrCl), i.e. < 30 mL/min.
- History of major organ transplantation with an existing functional graft.
- History of clinically-significant drug allergy to nucleoside/nucleotide analogs.
- Pregnant women or women planning to become pregnant
- Women who are breastfeeding
- Active or recent history (≤ 1 year) of drug or alcohol abuse

4. PACKAGING AND LABELING

Sufficient quantities of SOF/LDV FDC tablets to complete the entire study will be shipped to the investigator or qualified designee from Almac. Almac will receive marketed product, and label it specifically for this study.

5. STUDY PROCEDURES

5.1. Subject Enrollment

All subjects will complete screening, on-treatment, and post-treatment follow up assessments. Screening assessments will be completed within 28 days of the Baseline/Day 1 Visit. All subjects will receive 12 weeks of the SOF/LDV FDC except for treatment experienced genotype 1 subjects with cirrhosis, who will receive 24 weeks of treatment. Study visits will occur at screening, baseline/day 1, weeks 2, 4, 8, 12 for subjects receiving 12 weeks of treatment and then weeks 16, 20 and 24 for subjects receiving 24 weeks of treatment. Post-treatment follow-up visits will be performed at 4 and 12 weeks following the last dose of study drug.

5.2. Study Visit Procedures

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

Subjects will be screened within 28 days before baseline/Day 1 visit to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent.
- Review of inclusion and exclusion criteria including:
  - Adequate documentation of the following for treatment-experienced subjects:
    - Documentation of chronic HCV infection
    - Start and stop dates for prior HCV treatment history
    - Prior viral response data, if prior treatment taken
  - Review of excluded medications/concomitant medications
- Obtain medical history
- Complete physical examination including, vital signs, body weight, and height
- ECG
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - PT-INR
  - HCV RNA and HCV genotype and subtype
  - Serology for HBV and HIV
  - Serum β-hCG (females of child bearing potential only)
- Adequate documentation of chronic HCV infection, defined as positive HCV antibody; or HCV RNA more than 6 months prior to screening; or an assessment of fibrosis F2 or greater
- Fibroscan (unless performed within 6 months of screening)

Subjects who consent to the study and meet all of the inclusion criteria and none of the exclusion criteria may return to the clinic within 28 days after screening for enrollment into the study and baseline assessments.

5.2.2. Baseline/Day 1 Assessments

The following baseline tests and procedures must be completed prior to dosing/dispensing and administration of study drug:

- Review of inclusion and exclusion criteria and expectations for subject participation and protocol adherence, including list of excluded medications
- Perform complete physical examination
- Obtain vital signs and body weight
- Assessment of AEs and concomitant medications
- Pregnancy prevention counseling
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
- Urine β-hCG pregnancy test (females of child bearing potential only). If positive, a serum β-hCG must be performed and confirmed to be negative prior to initiation of study drug.
- Dispense drug
- Instruct the subject on the packaging, storage and administration of drug

5.2.3. Weeks 2 and 8 for 12-week duration and weeks 16 and 20 for 24-week duration (± 5 days)

The following tests and procedures are to be completed:

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA levels
- Urine β-hCG pregnancy test (females of child bearing potential only). If positive, a serum β-hCG must be performed and confirmed to be negative prior to initiation of study drug.
- Review medication compliance

5.2.4. Week 4 (± 5 days) for all durations

The following tests and procedures are to be completed:

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
- Urine β-hCG pregnancy test (females of child bearing potential only). If positive, a serum β-hCG must be performed and confirmed to be negative prior to initiation of study drug.
- ECG
- Review medication compliance

5.2.5. Week 12 for 12-week duration and Week 24 for 24-week duration (± 5 days)

The following tests and procedures are to be completed:

- Obtain vital signs
- Obtain weight
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - PT-INR
  - HCV RNA
- Urine β-hCG pregnancy test (females of child bearing potential only). If positive, a serum β-hCG must be performed and confirmed to be negative prior to initiation of study drug.
- ECG
- Review medication compliance

5.2.6. Early Termination (ET) or Unscheduled Visit

Subjects should complete an Early Termination (ET) Visit as soon as possible after study drug is discontinued. The subject should follow the scheduled Post-Treatment follow-up visits (refer to Section 6.4) based on the date of their last dose of study drug.
The following tests and procedures are to be completed at the Early Termination visit:

- Perform complete Physical examination
- Obtain vital signs
- Obtain weight
- Assessment of AEs and concomitant medications
- Review medication compliance with subject
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - PT-INR
  - HCV RNA
- Urine β-hCG pregnancy test (females of child bearing potential only).
- ECG

5.2.7. Post-Treatment Weeks 4 and 12 (± 5 days)

- Obtain vital signs (includes resting blood pressure, pulse, respiratory rate and temperature)
- Assessment of AEs and concomitant medications
- Obtain blood samples for:
  - Hematology
  - Chemistry
  - HCV RNA
- Urine β-hCG pregnancy test (females of child bearing potential only).
- ECG

5.3. Visit Specifications

5.3.1. Clinical Laboratory Analytes

Laboratory evaluations will be performed at the sites' local laboratory. Laboratory data will be entered into the REDCap database by the site.

Hematology: Hematocrit, Hemoglobin (Hb), Platelet count, Red blood cell count (RBC), White blood cell count (WBC) with differential (absolute and percentage) including Lymphocytes, Monocytes, Neutrophils, Eosinophils, Basophils, Reticulocyte count and MCV.
Coagulation: INR, Prothrombin time (PT)
Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Serum Creatinine, Total Bilirubin (Direct Bilirubin as reflex if total is elevated), Glucose, Lipase, Potassium, and Sodium.
Virologic Tests: Serology studies for HBV and HIV. HCV RNA by Polymerase Chain Reaction (PCR), HCV genotype and subtype,
Pregnancy Tests: Serum β-hCG at screening, Urine β-hCG at other visits (if positive, requires immediate confirmation with Serum β-hCG)

5.3.2. Medical History

Medical history including previous treatment, details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, and medication history will be collected on all subjects during screening. In addition, previous HCV treatment and response to that treatment (null responder, partial responders or relapser) will be captured in the source documents and database.

5.3.3. Complete Physical Examination

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

5.3.4. Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation[12] using actual body weight (BW).

Male: $$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times BW(kg)}{72 \times S_{cr}}$$

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

S_{cr} = serum creatinine (mg/dL)
Creatinine clearance will be calculated by the site, and entered into the database.

5.3.5. Body Mass Index (BMI)

Height and weight will be measured without shoes. Height will be measured at screening only; weight should be obtained at each study visit. BMI will be calculated at Screening for inclusion criteria using the following formula:

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

BMI will be calculated by the site, and entered into the database.

5.3.6. Vital Signs

Subjects will have a resting blood pressure, pulse, respiratory rate and temperature recorded.

5.3.7. 12-Lead ECGs

Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording. The investigator (or qualified designee) should review the ECG traces recorded in real time for gross abnormalities.

5.3.8. HCV Genotyping

HCV genotype (subtype) will be performed during Screening by the local laboratory using whatever standard testing is approved at the laboratory. This data will be entered into the database.

6. STOPPING CRITERIA

6.1. Virologic Response-Based Stopping Criteria

HCV RNA ≥LLoQ through 8 weeks of treatment
Confirmation should be performed as soon as possible but within 2 weeks after determination of initial observation. The investigator is responsible for reviewing HCV RNA data to determine if confirmation or retesting is required,

6.2. Stopping Rules for Individual Subjects

Subjects who meet any of the following criteria should be discontinued from the study and complete an Early Termination Visit and return for Post-treatment Follow-up visits:

- Elevation of ALT and/or AST >5x baseline or 5x nadir (unrelated to any interventional procedure)
- Confirmed total bilirubin >3x baseline or 3x nadir with the total bilirubin > 5 mg/dL
  - If total bilirubin > 5mg/dL, bilirubin should be monitored on a weekly basis.
  - If direct bilirubin > 3mg/dL, study drugs should be discontinued.
- Any non-laboratory Grade 4 event assessed as related to treatment with SOF/LDV
- Worsening of disease state as evidenced by progressing hepatic decompensation

The investigator is responsible for reviewing local laboratory results to determine if a stopping rule has been met.

6.3. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or create a safety risk for the subject.
- Unacceptable toxicity, as defined in the toxicity management section 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
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy or partner pregnancy during the study
- Discontinuation of the study at the request of study sponsor, regulatory agency or an IRB

6.4. Discontinuations

If the subject meets the Virologic Response-Based Criteria (Section 6.6), the Stopping Rules for Individual Subjects (Section 6.7) or other criteria for discontinuation of study treatment (Section 6.8), the subject should complete an Early Termination Visit as soon as possible after all therapy is discontinued. The subject should continue to follow the applicable Post-Treatment visit schedule. Evaluation of stopping rules for each subject will be determined by the Principal Investigator (PI) at the site.

Subjects discontinuing treatment prior to completion of the assigned dosing period for reasons other than those described in Section 6 should complete the assessments for early termination as described in Section 5.2.6.

Subjects with HCV RNA < LLoQ who permanently discontinue all study drugs for any reason including safety and/or tolerability concerns prior to completion of the assigned dosing period should complete the early termination visit and will be followed according to the post-treatment study assessments to determine whether the subject achieves SVR.

6.5. Assessments for Premature Discontinuation from Study

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

7. ADVERSE EVENTS

7.1. Adverse Events

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

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure (e.g. such as venipuncture, biopsy) during or after screening (before the administration of study medicinal product).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study medicinal product phase of a human clinical trial, will also be considered an AE.
- Complications and termination of pregnancy

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an adverse event
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae
- 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 pre-existing and should be documented on the medical history CRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

Only adverse events that lead to drug discontinuation or withdrawal will be entered into the database.

7.2. Assessment of Adverse Events

All AEs will be assessed by the investigator or qualified designee and only AEs that lead to discontinuation will be recorded on the AE CRF page. The AE entry should indicate whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to medicinal product, the action taken with medicinal product due to the AE, and the severity of the AE..

7.3. Serious Adverse Events

A **serious adverse event** (SAE) is defined as follows:
Any adverse drug experience occurring at any dose that results in any of the following outcomes:

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

Examples of such events are as follows:

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

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself. In reports of death due to "Disease Progression," where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the medicinal product(s).
- The subject may not have been on medicinal product at the occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 4. An event is defined as "serious" when it meets one of the predefined outcomes described above in Section 7.3.

7.3.1. Serious Adverse Event Reporting Requirements

Investigators are to submit a MedWatch 3500 form to FDA on any event that, in the investigator's opinion, is related to the study drug and is unexpected. Send a copy of the MedWatch form to the DCRI.

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that lead to discontinuation must be recorded as an AE, as well as an SAE, if applicable.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the safety and tolerability of SOF/ FDC for 12-24 weeks in subjects with advanced heart failure or lung disease

The secondary objective of this study is:

- To determine the antiviral efficacy of SOF/LDV FDC for 12-24 weeks in subjects with chronic HCV and advanced heart failure or lung disease as measured by sustained virologic response 12 weeks after discontinuation of therapy (SVR12 defined as HCV RNA < lower limit of quantitation 12 weeks post-treatment).

8.1.2. Primary Endpoint

The primary safety endpoint is the proportion of subjects who complete a full course of therapy. The primary efficacy endpoint is SVR12 (HCV RNA < lower limit of Quantification [LLoQ] 12 weeks after last dose of study drug).

8.1.3. Secondary Endpoints

The main efficacy endpoint will be the measurement of SVR12, 12 weeks after discontinuation of therapy. Secondary efficacy endpoints include SVR4, 4 weeks after discontinuation of therapy.

8.1.4. Safety Endpoints

In addition to the primary endpoint of completion of full course of therapy, safety endpoints will include rates of discontinuation for adverse events and serious adverse events. Safety will also be assessed with adverse events and laboratory tests.

8.1.5. Analysis Conventions

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software version 9.2 or higher (SAS Institute, Cary, North Carolina, USA).In general, all endpoints will be summarized with descriptive statistics by treatment group and analysis time point. For categorical variables, number and percentage of subjects in each category will be presented. Continuous variables will be descriptively summarized with n, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum by treatment group. For SVR endpoints 95% confidence intervals will also be constructed.

8.2. Analysis Sets

8.2.1. Efficacy

The primary analysis set for efficacy analyses will include all subjects with HCV infection who received at least one dose of study drug.

8.2.2. Safety

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

8.3. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by treatment arm and overall. Demographic summaries will include sex, race/ethnicity, stratification group, age. Baseline data will include a summary of body weight, height, body mass index, HCV genotype, and HCV RNA level (log_{10} IU/mL).

8.4. Primary Analysis

The primary efficacy analysis will report the number and percent of subjects achieving SVR12 response will be calculated for each arm along with exact 95% confidence intervals.

8.5. Secondary Analyses

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

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements, at various time points during the study, and by the documentation of AEs. All safety data collected while “on treatment” (i.e., on or after the first dose of study drug administration up to 30 days after the last dose of study drug) will be summarized by treatment arm according to the study drug received.

8.6.1. Adverse Events

Clinical and laboratory adverse events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event that begins on or after the date of first dose of medicinal product up to the date of last dose of medicinal product plus 30 days.

8.6.2. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) and study visit along with corresponding change from Baseline/Day 1. These laboratory data to be analyzed are:
Hematology: Hemoglobin (Hb), Platelet count, White blood cell count (WBC)
Coagulation: INR, Prothrombin time (PT)
Chemistry: Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline phosphatase, Serum Creatinine, Total Bilirubin (Direct Bilirubin as reflex if total is elevated)
Virologic Tests: HCV RNA; HCV genotype and subtype; HIV

9. INVESTIGATOR & SPONSOR RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" as expressed in the International Conference on Harmonisation (ICH) guidelines (ICH E6), or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

9.1.2. Institutional Review Board (IRB)

This protocol will be submitted by the investigator to an IRB (for studies conducted in the United States. 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. A copy of the IRB-approved Informed Consent Form (ICF) should be included with the approval documents. Any modifications made to the protocol after receipt of IRB approval must also be submitted to the IRB, for approval before implementation.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- 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.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are not disclosed to unauthorized parties. Only an identification code (i.e. not names, initials, or date of birth) should be recorded on any form or biological sample submitted to the Sponsor, IRB, or laboratory. The investigator agrees that all information received from the sponsor, including but not limited to the protocol, CRFs, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Drug Accountability

The investigator is responsible for ensuring accountability of all used and unused study drug. 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 and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the medication. Documentation will be maintained by the site; no data will be entered into the database.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study.

The investigator's study file will contain the protocol/amendments, IRB approval, approved ICF, and drug records, at a minimum, source records to be documented in the medical record by the investigator are listed below:

- subject identification by study code;
- 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);
- 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 medication 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.

9.1.7. Case Report Forms

For each subject enrolled, REDCAP database screens must be completed by the investigator or designee within a reasonable time period after patient visit. This also applies to records for those subjects who fail to complete the study. Information on subjects who choose to not enroll or screen fail, will not be collected. If a subject withdraws from the study, the reason must be noted in the database. If a subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

9.1.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from DCRI or its representatives, to IRBs, and to regulatory authorities as needed.

9.1.9. Protocol Compliance

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

9.1.10. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice guidelines (ICH E6), the study monitor or other study personnel must have direct access to the investigator's source documentation in the event source data verification is required. The investigator agrees to cooperate with the monitor to ensure that any discrepancies detected in the course of data monitoring are resolved.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Drug:

All study subjects will receive the sofosbuvir 400 mg and ledipasvir 90 mg fixed dose combination. Subjects will take one tablet in the morning.

Study medication will be provided by Gilead. Gilead will ship drug to Almac, for distribution to the sites. Sites will be responsible for tracking drug, and reordering if needed. For questions related to study drug, contact the sponsor Project Leader who will work with Almac to resolve any questions.

9.3. Study Discontinuation

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

10. REFERENCES

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APPENDIX 1. STUDY PROCEDURES TABLE

Procedure	Screening: Day -28 to -1	Baseline Day 1[1]	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Term or Unscheduled	Post-treatment Week 4	Post-treatment Week 12
Informed Consent	X											
Eligibility review[2]	X	X										
AE and con meds assessment		X	X	X	X	X	X	X	X	X	X	X
Pregnancy prevention counseling		X										
Dispense and instruct on use of drug		X										
Medication Compliance			X	X	X	X	X	X	X	X		
Medical History	X											
Physical exam[3]	X	X								X		
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X
Weight[5]	X	X				X			X	X		

[1] All physical procedures and review procedures to be performed prior to dispensing or dosing with drug
[2] Includes adequate documentation of start/stop dates for prior HCV therapy; prior viral response data; and chronic HCV infection. Includes review of excluded concomitant medications.
[3] General appearance; body system review: head, neck, thyroid, eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory, cardiovascular; lymph nodes, abdomen; skin, hair nails; musculoskeletal; neurological
[4] Resting blood pressure, pulse, respiratory rate, and temperature
[5] Weight to be obtained at last treatment visit, either week 12 or week 24

Procedure	Screening: Day -28 to -1	Baseline Day 1[1]	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Term or Unscheduled	Post-treatment Week 4	Post-treatment Week 12
Height	X											
ECG[6]	X			X		X			X	X	X	X
Fibroscan[7]	X											
Laboratory Assessments												
Hematology[8]	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[9]	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation[10]	X					X			X	X		
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X
HCV Genotype	X											
HIV serology	X											
HBV serology	X											
Serum β-hCG	X											
Urine β-hCG[11]		X	X	X	X	X	X	X	X	X	X	X

[6] After resting in supine position for ≥ 5 minutes
[7] If not done within 6 months of screening
[8] Includes 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
[9] Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SCOT), albumin, alkaline phosphatase, serum creatinine, total bilirubin (direct bilirubin as reflex if total is elevated), glucose, lipase, potassium, and sodium
[10] Includes INR, and Prothrombin time (PT)
[11] If positive, requires immediate confirmation with serum β-hCG