LIVE-C-FREE (LIVEr transplant for hepatitis C: recurrence FREE)
Early and late treatment of Hepatitis C with Sofosbuvir/Ledipasvir in Liver Transplant Recipients

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(Any modification to the protocol should be annotated on the coversheet or in an appendix. The annotation should note the exact words that are changed, the location in the protocol, the date the modification was approved by the Executive Committee, and the date it became effective.)

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1. STUDY OBJECTIVES

1.1 Primary Objective

LDV/SOF for 12 weeks will have an equivalent SVR12 compared to LDV/SOF+ribavirin for 12 weeks, both initiated after liver transplant.

1.2 Secondary Objectives

Secondary objectives include the emergence and effect of NS5A and NS5B viral substitutions at baseline and in the event of relapse.

2. BACKGROUND

2.1 Rationale

Therapeutic response rates for the treatment of recurrent hepatitis C virus (HCV) after liver transplant have historically lagged behind non-transplant patients (1). While the latest studies in HCV therapy with new direct-acting antivirals (DAA) have drastically improved sustained virologic response rates (SVR) in non-transplant patients, HCV is still the most common cause of end stage liver disease (ESLD) leading to liver transplant (2,3,4,5). Although the DAAs have shown efficacy in recurrent HCV post-transplant, this is with late treatment, since preemptive therapy has not shown benefit with previous agents (6,7). An attempt at preventing recurrence by clearing the virus with SOF and RBV prior to transplant has shown encouraging preliminary results in patients who had HCV RNA undetectability for $\geq$ 30 days, however this was in well-compensated cirrhotics (CTP $\leq$ 7) with concomitant HCC (8). Due to the poor tolerability of RBV in patients with more advanced cirrhosis, it is unknown if this regimen would have external validity to the overall HCV population awaiting liver transplant. Also complicating the reproducibility of this data is the unpredictable timing of liver transplant surgery.

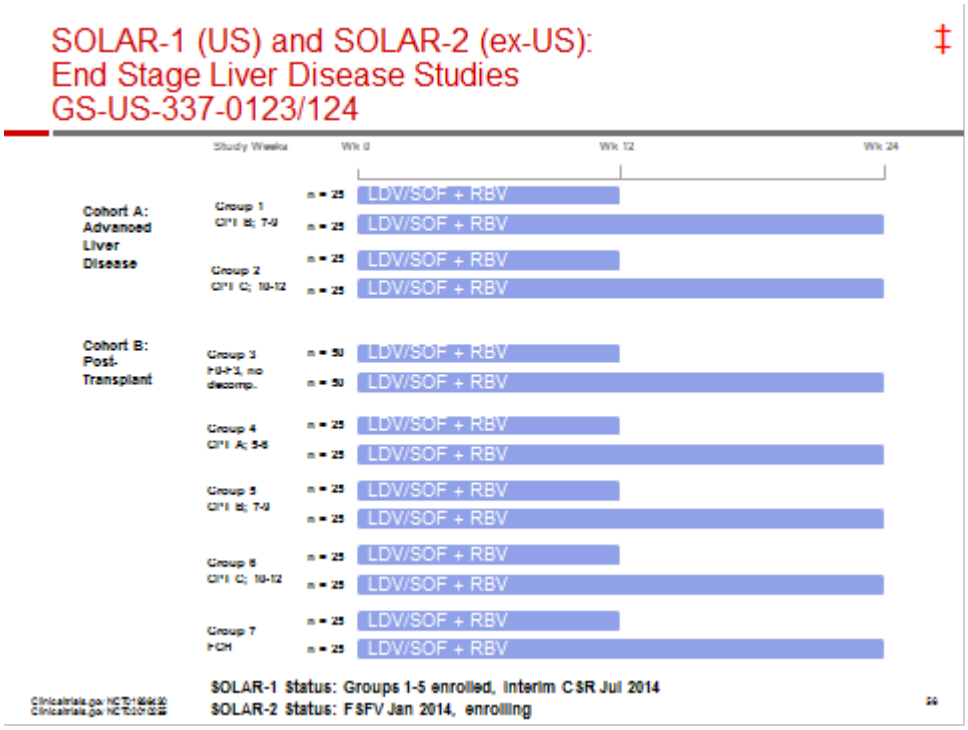
Preliminary results of the ongoing SOLAR-1 study have shown excellent sustained virologic response (SVR) rates with 12 weeks of therapy both pre and post-transplant, when utilizing a regimen of LDV/SOF and RBV (9). However, this is with a regimen that includes an antiviral with poor tolerability post-transplant, ribavirin.

The predominant remaining questions for post-transplant treatment of HCV in the DAA era are whether a ribavirin-free regimen is possible and whether pre-emptive treatment is now a potential option to prevent long-term damage to the allograft.

These questions require formal testing in a clinical trial conducted in transplant centers.

2.2 Supporting Data

SOLAR-1 – Phase III randomized, open-label study including post-transplant (Cohort B) (ongoing)



a. Results

Post-transplant F0-F3, CPT A/B/C (cohort B)

i. N=223, 12 vs 24 wks of LDV/SOF+riba (weight-based in F0-F3 and CPT A, 600mg titrated up in CPT B and C)
ii. Median time since transplant 2.9-8.1 yrs depending on arm
iii. SVR rate
    1. F0-F3 96-98% (N=111)
    2. CPT A 96-96% (N=51)
    3. CPT B 85-83% (N=44)
    4. CPT C (N=8) (only 9 pts in this arm, 1 has not reached SVR endpoint timeframe) 60-67%

Risks of therapy

	HARVONI 8 weeks	HARVONI 12 weeks	HARVONI 24 weeks
	N=215	N=539	N=326
Fatigue	16%	13%	18%
Headache	11%	14%	17%
Nausea	6%	7%	9%
Diarrhea	4%	3%	7%
Insomnia	3%	5%	6%
Bilirubin elevations 1.5x ULN	3%	<1%	2%
Lipase elevations 3x ULN	<1%	2%	3%

3. STUDY DESIGN

Multi-center, prospective, randomized, open-label, pilot study

ARM 1: LDV/SOF x 12 weeks
ARM 2: LDV/SOF + RBV x 12 weeks

Number subjects:
Multi-center
50 subjects, with 25 subjects in each arm

4. SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

a. At least 18 years of age

b. Signed informed consent

c. History of HCV genotype 1 or 4

d. No clinically significant abnormalities or changes on EKG

e. Randomization post orthotopic liver transplant

f. Detectable HCV RNA at baseline

g. Creatinine Clearance of at least 40ml/min using the Cockcroft Gault equation

h. Negative pregnancy test for female subjects of child bearing potential within 48 hours of randomization

   Subjects of reproductive potential agree to use (or have their partner use) two effective contraception methods through 6 weeks following completion of intervention. Subjects who are not of reproductive potential, not sexually active, whose current partner(s) is not of reproductive potential, or whose sexual activity is exclusively homosexual are eligible without requiring the use of contraception.

4.2 Exclusion Criteria

a. Pregnant or nursing female, or male with a pregnant female partner

b. A condition or disorder that, in the opinion of the investigator, may adversely affect the outcome of the study or the safety of the subject

c. Stomach disorder that could interfere with the absorption of study drug

d. Co-infected with HBV or HIV

e. Allergic to sofosbuvir or ledipasvir

f. History of completed treatment with a Nonstructural Protein 5A (NS5a) inhibitor

g. Participation in a clinical study with an investigational drug or biologic within 30 days of randomization

h. Fibrosing cholestatic hepatitis

i. Amiodarone use within 6 months of randomization

j. Unwilling/unable to stop taking any of the prohibited medications (Section 5.2)

k. Total bilirubin >10mg/dL

l. Alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase (ALP) ≥ 10x ULN

m. Serum sodium < 125mmol/L

n. Platelet count of ≤ 30 k/mm^3

o. Hemoglobin < 10g/dL

p. Allergic to or intolerant of ribavirin

q. Within 1 year of transplant AND history of Hepatocellular Carcinoma (HCC) with tumor burden outside of the Milan Criteria (See Appendix II) prior to transplant

r. History of significant or unstable cardiac disease

s. Recipients of an allograft from a donor that was infected with HCV with an unknown genotype or non-genotype 1 or 4 unless the recipient is demonstrated to have only genotype 1 or 4 HCV replication post-transplant

t. Childs Turcotte Pugh (CTP) B or C

4.3 Study Enrollment Procedures

4.3.1 Subject Identification/Recruitment: Members of the research team will identify potentially eligible patients who are undergoing liver transplantation or have previously undergone liver transplantation that are infected with Hepatitis C. An initial evaluation of existing patient information may be performed to determine potential eligibility. This initial review may be performed prior to consent; however no protocol driven tests or procedures may be performed until signed informed consent has been obtained.

4.3.2 Informed Consent: Authorized personnel will approach patients to explain the study and offer the opportunity to participate in the study. The personnel who will obtain

consent will have completed Human Subjects Protection Training. This research study will be explained in lay terms to each potential research participant. In compliance with the informed consent process outlined in CFR Title 21 Part 50, the authorized personnel will conduct a face-to-face meeting with the study candidate to review all of the required elements of informed consent. The potential study participant will sign an informed consent form before undergoing any screening study procedures. The original consent form will be kept with the subject's file in the office. A copy of the consent will be given to the patient and another copy will be put in his/her chart. At the time of consent, patients will be assured that their care will not be affected in any way if they choose not to participate in the study. Patients will also be reminded that it is their right to withdraw their participation in the study at any time.

4.3.3 Enrollment: Patients who give informed consent to study participation will go on to complete baseline procedures necessary to determine eligibility for randomization. Once deemed eligible for the study according to the inclusion/exclusion criteria, the patient will be enrolled as study subject in the WebDCU^{TM} clinical trial management system (CTMS). Information to be entered upon enrollment includes demographic information and date of transplant surgery. Enrolled subjects will be randomized to one of the treatment arms. The study team will receive the randomization assignment from WebDCU^{TM}.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

i. **SOF/LDV administration**

At the time of randomization, all subjects will be initiated on SOF/LDV 400mg/90mg enterally daily either with food or on an empty stomach. This medication will be administered predominantly outpatient, although it may be started or continued on both general hospital floors as well as the ICU. The medication will be continued for 12 weeks in both arms.

ii. **Ribavirin administration**

At the time of randomization, subjects in Arm 2 will be initiated on the appropriate weight-based dose to be taken with food. Subjects < 75kg will be initiated on RBV 400mg enterally in the morning (QAM) and 600mg enterally at night (QPM). Subjects ≥ 75kg will be initiated on RBV 600mg enterally in the morning and night (BID).

This medication will be administered predominantly outpatient, although it may be started or continued on both general hospital floors as well as the ICU.

Ribavirin dosing may be adjusted as medically required for toxicity (see section iii).

iii. **Dosage adjustment of ribavirin**

Laboratory Abnormality	Reduction in current ribavirin dose
Hgb 8.5 to <10 g/dL and/or decrease by > 2 g/dL within 4 weeks	1. Decrease dose to 600mg daily (200mg QAM, 400mg QPM) 2. If Hgb < 12 g/dL despite 4 weeks of dose reduction in subjects with a history of stable cardiac disease, discontinue ribavirin
Hgb <8.5 g/dL	Discontinue ribavirin
WBC <1000 mm^3 and/or ANC <500 mm^3	Discontinue ribavirin
Platelets < 25 k/mm^3	Discontinue ribavirin
eGFR 30-50 ml/min	Alternating doses, 200mg and 400mg every other day

5.2 Prohibited Interventions

Medications listed below will be prohibited during treatment period.

Concomitant Drug Class: Drug Name	**Effect on Concentration**	**Clinical Comment**
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;
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	Decreases ledipasvir Decreases sofosbuvir Decreases GS-331007	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 Rifapentine	Decreases sofosbuvir Decreases GS-331007	Coadministration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended Coadministration of HARVONI with rifampin, an intestinal P-gp inducer, is not recommended
Herbal supplements: St. John's wort (*Hypericum perforatum*)	Decreases sofosbuvir Decreases GS-331007	Coadministration of HARVONI with ST. Joh's wort, an intestinal P-gp inducer, is not recommended
HMG-CoA Reductase Inhibitors: Rosuvastatin	Increases 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 rosuvastat in not recommended

5.3 Adherence Assessment

Adherence to study intervention will be assessed at all study visits noted on the Schedule of Evaluations (Section 6.1).

Subjects will have adherence assessed based on medication counts. This will be utilized in a subanalysis to determine if measured adherence rates of < 80% impact clinical outcomes in each Arm.

6. CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

	Baseline / Randomi-zation	Days			Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36	End of Study
Day Post-Randomization	0	1	2	4	7	14	28 (+/-5 days)	56 (+/-5 days)	84 (+/-5 days)	112 (+/-5 days)		168 (+/-5 days)		252 (+/-5 days)	
Informed Consent Obtained	X														
Randomization	X														
Review of Inclusion and Exclu-sion Criteria	X														
Medical History	X														
Liver Transplant Recipient	X														
Liver Transplant Donor	X														
Vital Signs	X						O	O	O	O		O		O	
Laboratory Assessments	X						X	X	X	O		O		O	
Hepatitis C Viral Load Test (HCV PCR RNA)	X						X	X	X	X		X		X	
EKG	X													X	
Review of Immunosuppressants	X						X	X	X	X		X		X	
Viral Substitutions	X						O	O	O	O		O		O	
Pregnancy Test (within 48 hrs of randomization)	X														
Review of Prohibited Medications	X						X	X	X						
Study Drug Compliance							X	X	X						
Virologic Failure															X
Liver Allograft Biopsy							O	O	O	O		O		O	
Fibro Scan	O						O	O	O						
Adverse Events	X						X	X	X	X		X		X	
End of Study															X

X=required; O=optional

6.2 Timing of Evaluations

6.2.1 Pre-Randomization Evaluations

These evaluations occur prior to the subject receiving any study interventions.

Baseline

The evaluations listed under the Baseline visit may be performed up to 14 days prior to randomization, with the exception of the pregnancy test, which must be performed within 48 hours of randomization. Additionally, HCV PCRs may be performed up to 30 days prior to randomization, provided that it was performed after the liver transplant.

Once the subject has been successfully screened and accepted for randomization, randomization must be complete within 48 hours. All subjects randomized will be included in the intent-to-treat analysis.

6.2.2 Intervention and Evaluations

Once the subject has been successfully randomized, the intervention should be initiated upon that day, but must be initiated within 5 days in case of extenuating circumstances.

Study evaluations must take place within the time window indicated on the Schedule of Evaluations (Section 6.1).

6.2.3 Intervention Discontinuation Evaluations

At the scheduled time of intervention discontinuation (EOT, last date of study medication), the following evaluations must be completed: HCV PCR and HCV viral substitutions (in the event of virologic failure)

If a subject prematurely terminates study intervention, a visit will be scheduled with the Principal-Investigator (PI) or designee within 72 hours to evaluate the reason for early termination. The PI or designee will attempt to resolve any issues leading to early termination and encourage the subject to resume study intervention as soon as possible. It will be clarified whether they are terminating from all components of the trial or only from the primary intervention component of the trial. If possible, the subjects will be encouraged to continue to be followed and evaluated according to the Schedule of Evaluations (Section 6.1) even if they no longer wish to receive study treatment.

Subjects that discontinue intervention due to virologic failure will be withdrawn from the study and deemed a treatment failure. These subjects may receive alternative treatment at

the investigator's discretion. SOF/LDV will be supplied upon request and RBV will be reimbursed by Gilead Sciences, Inc for up to 24 weeks if requested.

7. MANAGEMENT OF COMMON OR EXPECTED ADVERSE EXPERIENCES

The severity of adverse events will be determined using the grading system outlined in the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE), as it best fits the diagnostic terminology used in naming the event at the site clinical level.

SOFOSBUVIR/LEDIPASVIR OR RIBAVIRIN (ADVERSE EVENTS IN COMMON)

CTCAE SOC	Adverse Event	Grade Description	Criteria for Modification of Intervention	Procedure for Modification
General disorders and administration site conditions	Fatigue	1 – Relieved by rest	Grade 3 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 – Not relieved by rest; limiting instrumental ADL		
		3 – Not relieved by rest; limiting self-care ADL		
Nervous system disorders	Headache	1 – Mild pain	Grade 3 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 – Moderate pain; limiting instrumental ADL		
		3 – Severe pain; limiting self-care ADL		
Gastrointestinal disorders	Nausea	1 – Loss of appetite without alteration in eating habits	Grade 3 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 – Oral intake decreased without significant weight loss, dehydration or malnutrition		
		3 – Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated		
Gastrointestinal disorders	**Vomiting**	1 – 1-2 episodes (separated by 5 minutes) in 24 hours	Grade 3 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 – 3-5 episodes (separated by 5 min) in 24 hours		

		3 - ≥ 6 episodes (separated by 5 min); tube feeding, TPN or hospitalization indicated		
Gastrointestinal disorders	Diarrhea	1 – Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Grade 3 if requested by study participant, treatment-resistant or recurrent; Grade 4 or 5	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		2 – Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline		
		3 – Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL		
		4 – Life-threatening consequences; urgent intervention indicated		
		5 - Death		
Psychiatric disorders	Insomnia	1 – Mild difficulty falling asleep, staying asleep or waking up early	If requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 – Moderate difficulty falling asleep, staying asleep or waking up early		
		3 – Severe difficulty in falling asleep, staying asleep or waking up early		
Musculoskeletal and connective tissue disorders	Arthralgia	1 – Mild pain	Grade 3 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 – Moderate pain; limiting instrumental ADL		
		3 – Severe pain; limiting self care ADL		

Renal and urinary disorders	Chronic kidney disease	1 – CrCl < LLN-60ml/min/1.73m2; proteinuria 2+ present; urine protein/creatinine > 0.5	Grade 2	Sofosbuvir/Ledipasvir to be held if CrCl <40ml/min/1.73m2. Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Ribavirin dose should be reduced to alternating doses of 200mg and 400mg every other day if CrCl 30-50ml/min/1.73m2 Interventions can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		2 – CrCl 59-30m/min/1.73m2		
		3 – CrCl 29-15ml/min/1.73m2		
		4 - < 15ml/min/1.73m2; dialysis indicated		
		5 - Death	Grade 3-5	
Investigations	Blood bilirubin increased	1 - >ULN – 1.5x ULN	Grade 3-4	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 - >1.5-3x ULN		
		3 - >3-10x ULN		
		4 - >10x ULN		
Investigations	Lipase increased	1 - > ULN-1.5x ULN	Grade 3-4	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 - >1.5-2x ULN		
		3 - >2-5x ULN		
		4 - >5x ULN		

Ribavirin

CTCAE SOC	**Adverse Event**	**Grade Description**	**Criteria for Modification of Intervention**	**Procedure for Modification**
Blood and lymphatic system disorders	Anemia	1 – Hgb <LLN-10g/dL	Grade 2, modifications to dosage Grade 3-5: permanently discontinue ribavirin	Grade 2: see dosage adjustment procedure in section 5.1.iii Grade 3-5: ribavirin will be permanently discontinued. Subject experiencing Grade 3 or 4 will continue the study intervention and follow study
		2 – Hgb <10-8g/dL		
		3 - < 8g/dL		
		4 – Life-threatening consequences; urgent intervention indicated		

		5 – Death		evaluations as detailed in section 6.1
Blood and lymphatic system disorders	Hemolysis	1 – Laboratory evidence of hemolysis only (e.g. DAT, Coombs', schistocytes, decreased haptoglobin)	Grade 2: modifications to dosage Grade 3-5: permanently discontinue	Grade 2: see dosage adjustment procedure in section 5.1.iii Grade 3-5: intervention will be permanently discontinued.
		2 – Evidence of hemolysis and ≥ 2g/dL decrease in Hgb		
		3 – Transfusion or medical intervention indicated		
		4 – Life-threatening consequences; urgent intervention indicated		
		5 – Death		
Hepatobiliary disorders	Hepatic failure	3 – Asterixis; mild encephalopathy; limiting self care ADL	Grade 3-5	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		4 – Moderate to severe encephalopathy; coma; life-threatening consequences		
		5 – Death		
Immune system disorders	Allergic reaction	1 – Transient flushing or rash, drug fever < 38 degrees C; intervention not indicated	Grade 3-5 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		2 – Intervention indicated; responds promptly to symptomatic treatment; prophylactic medications indicated for ≤ 24 hours		
		3 – Prolonged (not rapidly responsive to symptomatic medication); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae		

		4 – Life-threatening consequences; urgent intervention indicated 5 - Death		
Immune system disorders	Anaphylaxis	3 – Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension 4 – Life-threatening consequences; urgent intervention indicated 5 – Death	Grade 3-5	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
Gastrointestinal disorders	Pancreatitis	2 – Enzyme elevation or radiologic findings only 3 – Severe pain; vomiting; medical intervention indicated (e.g. analgesia, nutritional support) 4 – Life-threatening consequences; urgent intervention indicated 5 – Death	Grade 3-5	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
General disorders and administration site conditions	Irritability	1 – Mild; easily consolable 2 – Moderate; limiting instrumental ADL; increased attention indicated 3 – Severe abnormal or excessive response; limiting self care ADL; inconsolable	Grade 3 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
Skin and subcutaneous tissue disorders	Pruritis	1 – Mild or localized; topical intervention indicated	Grade 3 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be

		2 – Intense or widespread; intermittent; skin changes from scratching (e.g. edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL		discussed with the medical monitor and the intervention may be discontinued.
		3 – Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated		
Respiratory, thoracic and mediastinal disorders	Dyspnea	1 – Shortness of breath with moderate exertion	Grade 3-5 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		2 – Shortness of breath with minimal exertion; limiting instrumental ADL		
		3 – Shortness of breath at rest; limiting self care ADL		
		4 – Life-threatening consequences; urgent intervention indicated		
		5 – Death		
Musculoskeletal and connective tissue disorders	Myalgia	1 – Mild pain	Grade 3 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 – Moderate pain; limiting instrumental ADL		
		3 – Severe pain; limiting self care ADL		
Investigations	Neutrophil count decreased	1 - <LLN-1500/mm3	Grade 3-4	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued.
		2 - <1500-1000/mm3		
		3 - <1000-500/mm3		
		4 - <500/mm3		
Psychiatric disorders	Depression	1 – Mild depressive symptoms	Grade 3-5 or if requested by study participant	Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention
		2 – Moderate depressive symptoms; limiting instrumental ADL		

		3 – Severe depressive symptoms; limiting self care ADL; hospitalization not indicated		may be discontinued. Grade 5: Intervention will be permanently discontinued
		4 – Life-threatening consequences; threats of harm to self or others; hospitalization indicated		
		5 – Death		

Transplant and Immunosuppression-related

CTCAE SOC	Adverse Event	Grade Description	Criteria for Modification of Intervention	Procedure for Modification
Infections and infestations	Abdominal infection	3 – IV antibiotic, antifungal, or antiviral intervention indicate; radiologic or operative intervention indicated	Grade 4-5	Grade 4: Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		4 – Life-threatening consequences; urgent intervention indicated		
		5 – Death		
Infections and infestations	Biliary tract infection	3 – IV antibiotic, antifungal, or antiviral intervention indicate; radiologic or operative intervention indicated	Grade 4-5	Grade 4: Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		4 – Life-threatening consequences; urgent intervention indicated		
		5 – Death		
Infections and infestations	Hepatic infection	3 – IV antibiotic, antifungal, or antiviral intervention indicate; radiologic or operative intervention indicated	Grade 4-5	Grade 4: Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		4 – Life-threatening consequences; urgent intervention indicated		
		5 – Death		

Infections and infestations	CMV	1 – Isolation of CMV from blood or sterile site or positive CMV PCR without clinical symptoms	Grade 4-5	Grade 4: Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		2 – Isolation of CMV from blood or sterile site or positive CMV PCR with clinical symptoms (fever, malaise, leukopenia, thrombocytopenia)		
		3 - Isolation of CMV from blood or sterile site or positive CMV PCR with clinical symptoms (fever, malaise, leukopenia, thrombocytopenia) and histological evidence of viral cytopathic effect or positive CMV culture from a deep tissue specimen		
		4 – Life-threatening consequences; urgent intervention indicated		
		5 – Death		
Infections and infestations	Wound infection	2 – localized; local intervention indicated (e.g. topical antibiotic, antifungal, antiviral)	Grade 4-5	Grade 4: Intervention can be withheld for up to 5 days. If there is no resolution, the case will be discussed with the medical monitor and the intervention may be discontinued. Grade 5: Intervention will be permanently discontinued
		3 – IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated		
		4 – Life-threatening consequences; urgent intervention indicated		
		6 – Death		

8. CRITERIA FOR INTERVENTION DISCONTINUATION

The intervention will be withheld/discontinued for specific grades of adverse effects as detailed in section 7. Additionally, the intervention will be discontinued if the subject meets criteria for the following reasons:

Virologic failure, defined as:

Breakthrough: HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ, while on treatment, confirmed with 2 consecutive values (note: second confirmation value can be posttreatment), or last available on-treatment measurement with no subsequent follow up values, OR

Rebound: > 1 log10IU/mL increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values (note: second confirmation value can be post-treatment), or last available on-treatment measurement with no subsequent follow up values, OR

Nonresponse: HCV RNA persistently ≥ LLOQ through 8 weeks of treatment, OR

Relapse: HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available posttreatment measurement

Pregnancy: If a woman becomes pregnant or a male's female partner becomes pregnant while on-study, the subject will be required to instruct investigators immediately. If he/she is in Arm 1, he/she may remain on therapy but will be ineligible for treatment with ribavirin in the event of virologic failure. If he/she is in Arm 2, therapy must be discontinued immediately and the subject will be counseled on the potential risks of exposure by the PI or designee. A discussion will occur with the medical monitor to decide whether the subject is eligible to be continued on sofosbuvir/ledipasvir alone.

Loss of graft: Defined as death or need for retransplant. Patients will be deemed a treatment failure and the intervention will be discontinued.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a multi-center, prospective, randomized, open-label, intent-to-treat pilot study.

The primary objective is to estimate the effect that LDV/SOF for 12 weeks will have on SVR12 compared to LDV/SOF plus ribavirin for 12 weeks.

9.2 Outcomes

9.2.1 Primary outcome - Treatment efficacy, defined as the proportion of subjects achieving sustained virologic response 12 (SVR12) weeks after completing the antiviral regimen

9.2.2 Secondary outcomes - Secondary endpoints include the proportion of subjects achieving clearance of viremia during therapy, at the end of therapy, week 4 and 24 SVR (week 4, week 8, EOT, SVR4, SVR24).

9.2.3 Safety outcomes - Overall safety and tolerability of each regimen will be estimated by measuring the incidence of adverse drug reactions and the development of medication intolerance requiring dose reduction, temporary withdrawal, or removal of the study drug(s), incidence of the need for supportive medications (erythropoietins, colony-stimulating factors), incidence of intolerance requiring dose reduction, temporary withdrawal, or removal of immunosuppressants, overall and opportunistic infections, biopsy-proven rejection rates, death, and graft loss. Other safety outcomes include virologic mutations based on NS5A and NS5B viral substitutions at baseline and in the event of virologic failure.

9.3 Sample Size Estimation for the Primary Outcome

For a definitive trial, if we assume an efficacy rate of 95% with an acceptable noninferiority margin of 10%, 75 subjects would be needed in each arm to provide an alpha level of 0.05 with 80% power to demonstrate noninferiority. Assuming a 10% dropout rate (indicating randomization, but failure to receive a dose of study medication), 85 subjects would need to be randomized in each arm. In this pilot study of 50 subjects, we will be able to obtain estimates of these rates for the two groups for use in the future definitive trial.

9.4 Statistical Evaluation of Primary Endpoint

9.4.1 Statistical Hypotheses:

The specific null and alternative hypotheses for comparing these two treatments in a non-inferiority design are: H_0: $\pi_{LDV/SOF+ribavirin} - \pi_{LDV/SOF} = \delta_o$ and H_A: $\pi_{LDV/SOF+ribavirin} - \pi_{LDV/SOF} < \delta_o$ (non-inferior) where δ_o =0.10. where $\pi_{LDV/SOF+ribavirin}$ (assumed to be 95%) represents the proportion with a successful outcome due to treatment with LDV/SOF plus ribavirin for 12 weeks and $\pi_{LDV/SOF}$ represents the proportion of a successful outcome due to treatment with LDV/SOF for 12 weeks.

9.4.2 Efficacy Analysis:

Although there is insufficient power to conduct any formal statistical analyses, preliminary estimates of effects for treatment comprisons will be intent-to-treat, where all randomized subjects will be included in the analysis and each subject will be included in the treatment to which they were randomized.

Baseline demographics and clinical outcomes will be presented by treatment. Estimates of the differences between these, along with 95% confidence intervals, will be generated. The primary outcome of proportion of subjects with success (defined as the proportion of subjects achieving sustained virologic response 12 (SVR12) weeks after completing the antiviral regimen) as well as estimates of all secondary outcomes for each treatment will be reported along with 95% confidence intervals.

9.7 Safety Analysis

9.7.1 Safety Outcomes

Safety outcomes include the proportion of subjects who experience any treatment-related serious adverse events (SAEs) during the treatment phase and up to 30 days following completion of the treatment.

Overall safety and tolerability of each regimen will be estimated by measuring the incidence of:

- Development of medication intolerance requiring dose reduction, temporary withdrawal, or removal of the study drug(s)
- Incidence of the need for supportive medications (erythropoietins, colony-stimulating factors)
- Incidence of intolerance requiring dose reduction, temporary withdrawal, or removal of immunosuppressants
- Overall and opportunistic infections
- Biopsy-proven rejection rates
- Mortality
- Graft loss

Other specific SAEs to be monitored may be added in consultation with the DSMB. The cumulative incidences of each outcome will be estimated along with 95% confidence intervals.

9.7.2 Interim Safety Monitoring

The Data Safety Monitoring Board (DSMB) will review study safety event rates, center performance, adverse events (AEs), and serious adverse events (SAEs) periodically. This review will identify any clinical, operational, or other data issues that might require changes or adjustments in the way in which the trial is conducted as well as any safety issues that may need to be addressed. In order to accommodate this, the Data Coordination Unit (DCU) will generate safety monitoring reports as well as a comprehensive statistical report periodically for the DSMB. These reports will contain compiled data on enrollment, demographic and baseline characteristics, eligibility and protocol violations, safety data, concomitant medications and procedures, and data quality (e.g., timeliness of data entry, and number of data clarification requests generated and resolved). All AEs and SAEs will be coded using MedDRA and summarized in terms of frequency of the event, number of subjects having the event, timing relative to randomization, and severity and relatedness to treatment. For each review, the DCU will generate two statistical reports – an open, blinded report to be distributed to the Executive Committee and the DSMB, and a closed report to be distributed only to the DSMB. For the closed report only, the statistics will also be provided by partially blinded treatment group (A vs B). If the DSMB wishes to be completely unblinded for closed reports, a sealed treatment identification envelope will be provided to the DSMB; this envelope can be opened at the discretion of the DSMB. The closed report will also contain data listings identifying subjects with specific safety outcomes such as mortality.

9.7.3 Stopping the Trial Based on Interim Safety Data

In case of concern for safety issue arises from DSMB, the trial may be stopped temporarily or permanently if the serious adverse event rate (SAEs related to the study treatment) exceeds a clinically acceptable rate of 10% in either arm. Data for events will not be evaluated until the first 30 subjects have completed 30 day post treatment follow-up for each arm.

10. DATA COLLECTION, SITE MONITORING, ADVERSE EVENT REPORTING

10.1 Data Processing

Data management will be handled by DCU. All study activities will be conducted in coordination with the study PI, and will use an electronic data acquisition method where all clinical data on enrolled subjects will be entered by the site personnel in real time. The latest version of each CRF will be available as a PDF file on the study website for

use as worksheets and source documents by study personnel. The study data will be managed (including data queries) by DCU using the WebDCU™ system. This user-friendly web-based database system, developed by DCU, will be used for regulatory document management, subject randomization, data entry, data validation, project progress monitoring, subject tracking, user customizable report generation and secure data transfer.

10.2 Data Security and Confidentiality

During the course of the trial, user access to the files with subject identifiers, treatment assignment and files with study outcomes will be restricted to core staff. In addition to use of passwords and other security measures, all documents containing identifying information on individuals or physicians are considered confidential materials and will be safeguarded to the greatest possible extent. No information, which identifies a specific person, hospital, or physician, will be released to, or discussed with anyone other than study team members.

Because the DCU uses a web-based system, source documents and CRFs will remain at the participating sites. The study database only identifies study subjects by unique study identification codes. All data will be stored in a manner that is HIPAA compliant, without the ability to track the information back to a specific subject except through a password protected system. All collected information about a subject will be stored by a unique identification code. All DCU personnel have current Human Subjects Protection Training Certification. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, OHRP, the sponsor, or the sponsor's designee.

10.3 Data Quality Assurance

The study data will be managed (including data queries) by DCU using the WebDCU™ system. This user-friendly web-based database system, developed and validated by the DCU, will be used for regulatory document management, subject randomization, data entry, data validation, project progress monitoring, subject tracking, user customizable report generation and secure data transfer. In addition to the study database, the DCU will provide the clinical site staff access (via password) to a standard set of web-enabled tools, including subject visit calendar, subject accrual status, case report form completion status, and outstanding data clarification request status pertaining to their respective clinical sites. Furthermore, all approved study materials, such as the protocol, informed consent template and manual of procedures, will be housed on the website to ensure that the clinical sites always have access to the most current trial documents.

Data should be independently entered by the designated personnel at each clinical site into WebDCU™ within the time intervals specified in the schedule of assessments. Enrollment data, however, must be entered into the WebDCU™ database before the subject can be randomized. Serious adverse events must be entered into the WebDCU™ within 24 hours of the site staff's first awareness of the event. It is critically important to the effective and efficient conduct of the study that data be entered in a timely manner. An electronic copy of the CRFs will be made available to the clinical sites prior to initiation of the study to be used as worksheets to capture the required data for the study. The DCU staff will perform range verification, consistency checks, and quality assurance on the data. The staff at the DCU will contact the sites regarding missing data or queries on CRF data. They will maintain direct contact with the staff at the participating sites to ensure the study is conducted according to the Good Clinical Practice Guidelines and all applicable regulations.

Experienced clinical research monitors will be contracted through the DCU to perform on site source data verification (SDV) of key outcome and safety data variables during the study. In addition to data verification, the monitor will evaluate drug accountability and site facilities. The CRFs and corresponding source documents should be made available to the study monitor at each site visit. It is also expected that the PI, or a designated member of the research staff, will be available during the monitoring visit to review the data and resolve any queries.

10.4 Adverse Experience Reporting

In order to ensure prompt reporting of adverse events, all adverse events (as well as all related study data) must be entered into the WebDCU™ within five days of collection date. All serious adverse events (SAEs) must be reported on the WebDCU™ within 24 hours of the study site staff first being made aware of its occurrence. The site investigators are required to provide relevant information, including description of the adverse event, date/time of onset and resolution, severity and seriousness, action taken, and suspected relationship to the study treatment.

Reporting of any serious adverse event will trigger notification of the event to the DCU Project Manager (PM) and the independent Medical Safety Monitor (MSM). The MSM will conduct an independent review of each of these events to determine if it is serious, unexpected, and study treatment related.

Periodically throughout the study, the MSM will review reports on the incidence rates of all reported adverse events, whether serious or not. Should such monitoring uncover issues that may threaten subject safety (e.g. unexpectedly high rate of adverse events), the study statistician and principal investigator will prepare a report to be submitted to the DSMB for their review and further actions to be taken, if any.

11. HUMAN SUBJECTS

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the ICF, and any subsequent modifications must be reviewed and approved by the local IRB at each of the participating institutions. A signed and dated ICF must be obtained from the subject as defined in 21CFR50.3. The ICF must also be signed and dated by a member of the study staff qualified to be delegated the authority to obtain informed consent, and a witness (if required by the local IRB). A copy of the ICF must be given to the subject and the consent process must be documented in the subject's medical record. The PI or delegated sub-Investigator is responsible for ensuring that informed consent is obtained from each patient prior to conducting any study-related activities.

No deviations from or changes to the study protocol should be initiated except when necessary to eliminate immediate hazard to the subject. However, the IRB, DCU, and Study Sponsor must be informed of this as soon as possible thereafter. It is the study site PI's responsibility to report SAEs occurring during the study to their IRB, as required and as soon as possible.

11.2 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

12. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be reviewed and approved by all coinvestigators. Final results will be submitted to ClinicalTrials.gov. Any presentation, abstract, or manuscript will be made available for review by the sponsor prior to submission.

13. REFERENCES

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APPENDIX I

US Public Health Service (PHS)Guideline for Reducing Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Transmission Through Organ Transplantation, 2013 ed.

Donor at Increased Risk for recent HIV, HBV, and HCV infection

1. People who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 months
2. Men who have had sex with men (MSM) in the preceding 12 months
3. Women who have had sex with a man with a history of MSM behavior in the preceding 12 months
4. People who have had sex in exchange for money or drugs in the preceding 12 months
5. People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months
6. A child who is ≤ 18 months of age and born to a mother known to be infected with, or at increased risk for, HIV, HBV, or HCV infection
7. A child who has been breastfed within the preceding 12 months and the mother is known to be infected with, or at increased risk for, HIV infection
8. People who have injected drugs by intravenous, intramuscular, or subcutaneous route for non-medical reasons in the preceding 12 months
9. People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 12 months
10. People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhea, *Chlamydia*, or genital ulcers in the preceding 12 months
11. Donor who is at increased risk for recent HCV infection only:
    a. People who have been on hemodialysis in the preceding 12 months

APPENDIX II
Milan Criteria

1. A single HCC nodule with a maximum size of 5 cm
   OR
2. Up to 3 HCC nodules with the largest not exceeding 3 cm
   AND
   No macrovascular invasion