Title: OPEN-LABELED TRIAL OF DIRECT-ACTING ANTIVIRAL TREATMENT OF HEPATITIS C NEGATIVE PATIENTS WHO RECEIVE LUNG TRANSPLANTS FROM HEPATITIS C POSITIVE DONORS (SHELTER)

Study Identifier: NCT03724149

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OPEN-LABELED TRIAL OF DIRECT-ACTING ANTIVIRAL TREATMENT OF HEPATITIS C NEGATIVE PATIENTS WHO RECEIVE LUNG TRANSPLANTS FROM HEPATITIS C POSITIVE DONORS (SHELTER)

Test drug:	**Zepatier or another antiviral regimen for hepatitis C virus infection**
Clinical study phase:	**II**
Sponsor:	**University of Pennsylvania**
Funder:	**Merck**
IND#	**Exempt**
IRB#	**829397**
NCT#	**03724149**
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The study will be conducted in adherence with the protocol, ICH-GCP and any applicable regulatory requirements.

1 SYNOPSIS

Title	Open-Labeled Trial Of Direct-Acting Antiviral Treatment Of Hepatitis C-Negative Patients Who Receive Lung Transplants From Hepatitis C-Positive Donors
Clinical study phase	II
Study objectives	This study is being conducted to determine safety and efficacy of transplanting lungs from HCV virus (HCV)-infected donors into HCV-negative patients on the lung transplant waitlist, who will then be treated with Zepatier, Epclusa, or another appropriate antiviral treatment status post lung transplantation. **Primary aim:** 1. Primary efficacy objective: to determine sustained virologic response (SVR) rates of open-label Zepatier, Epclusa, or another appropriate antiviral treatment in HCV-negative patients who receive a lung transplant from an HCV-infected donor, leading to post-transplantation de-novo HCV infection. 2. Primary safety objective: to determine the safety of administration of open-label Zepatier, Epclusa, or another appropriate antiviral treatment among HCV-negative patients who receive a lung transplant from an HCV-infected donor and develop post-transplant HCV infection. **Secondary aims:** 3. To determine 1-year graft survival rates of HCV-negative lung transplant patients who receive a lung transplant from an HCV-infected donor, including those who spontaneously clear HCV (and those who receive open-label Zepatier, Epclusa, or another appropriate antiviral treatment upon development of de-novo HCV. 4. To evaluate rates of spontaneous clearance of HCV among HCV-negative patients who receive a lung transplant from an HCV-infected donor.
Indication	Chronic HCV post-lung transplantation
Diagnosis and main criteria for inclusion	*Inclusion criteria* • *18-67 years of age* • *Obtained agreement for participation from the lung transplant team* • *No evident contraindication to lung transplantation other than the underlying lung disorder* • *Able to travel to the University of Pennsylvania for routine post-transplant visits and study visits for a minimum of 12 months after transplantation* • *No active illicit substance abuse* • *Women must agree to use birth control in accordance with Mycophenolate Risk Evaluation and Mitigation Strategy (REMS) following transplant due to the increased risk of birth defects and/or miscarriage*

	• *Both men and women must agree to use at least one barrier method of birth control or remain abstinent following transplant due to risk of HCV transmission* • *Inclusion criteria for treatment (not for entry as study patient) will include any detectable HCV RNA by week 4 post-lung transplantation* • *Able to provide informed consent* *<u>Exclusion criteria</u>* • *Hepatocellular carcinoma* • *HIV positive* • *HCV RNA positive* • *Hepatitis B surface antigen and/or DNA positive* • *Any chronic liver disease (excluding non-alcoholic fatty liver disease (NAFLD)) that is occurring in the setting of persistently elevated liver enzymes (patients with Alpha-1-antitrypsin lung disease without hepatic involvement are eligible)* • *Significant fibrosis (≥F2 on the Fibroscan)—for patients with cystic fibrosis, the cutoff will be 11kPa (cutoff for F2 for patients with chronic cholestatic liver disease), whereas for all other patients the cutoff will be 8kPa (the cutoff for fatty liver disease used in the THINKER study).* • *Pregnant or nursing (lactating) women* • *Known allergy or intolerance to tacrolimus that would require post-transplant administration of cyclosporine, rather than tacrolimus given the drug-drug interaction between cyclosporine and Zepatier and Epclusa* • *Pre-transplant treatment with amiodarone given the drug-drug interaction between amiodarone and Epclusa* • *Waitlisted for a multi-organ transplant* • *Patients with underlying liver disease with or without liver cirrhosis* • *Patients with cystic fibrosis who have underlying liver disease* • *Re-transplant candidate* • *Use of ECMO or mechanical ventilation as a bridge to lung transplantation* • *Inability to provide study consent* • *Chronic kidney disease with GFR<50 ml/min/1.73 m2* *<u>Relative contraindications for study subjects that will be reviewed on a case-by-case basis by the Lung Transplant Selection Committee and the Principal Investigators</u>* • *Evidence of end organ damage due to diabetes (e.g. retinopathy, nephropathy, ulcerations) and /or brittle diabetes mellitus (e.g. history of diabetic ketoacidosis) and/or uncontrolled diabetes as evidence by a HgbA1C of 7.5-8.5.* • *Hematologic: Significant coagulation abnormalities, and/or bleeding diatheses.* • *Active or recent solid or liquid malignancy in the past 5 years (apart from select skin malignancies).* • *Patient refusal to receive blood products or transfusions during lung transplant surgery.*

	• *Psychosocial: Profound neurocognitive impairment with absence of social support.* • *Active mental illness or psychosocial instability* • *Inadequate insurance and/or financial support for post-transplant care.* • *Evidence of drug, tobacco or alcohol abuse within the past six months and failure to satisfy recommended therapy/services/parameters as indicated by social work staff and/or consult team.* • *History of chronic non-adherence to medical recommendations and/or medications* • *PRA >10%.* • *Severe malnutrition, BMI <18 kg/m2* • *Major chronic disabling comorbidity (e.g. lupus, severe arthritis, neurologic diseases, previous stroke with profound residual).* • *Symptomatic or severe vascular disease (History of CABG, Aorta-femoral surgery)*
Study design	*Open-labelled pilot clinical trial of Zepatier (MK-5172 and MK-8742/Grazoprevir + Elbasvir) or Epclusa or another appropriate antiviral treatment in up to 11 HCV-negative subjects with lung failure receiving a lung transplant from a HCV-positive donor. Eligible subjects will receive a lung transplant from a deceased-donor with detectable HCV nucleic acid, and then will receive 12 weeks of Zepatier, Epclusa, or another appropriate antiviral treatment after lung transplantation when infection with HCV is confirmed in these lung transplant recipients. For Zepatier, treatment will be complete after 12 weeks.** * Patients with Genotype 1a and Genotype 1 with an unknown subtype will have baseline NS5A drug resistance assay testing checked at the start of treatment, and if patients have polymorphisms at positions M28, Q30, L31, and/or Y93, treatment with Zepatier will be extended to 16 weeks, rather than 12 weeks, and renally-adjusted Ribavirin at the clinician's discretion will be initiated, and continued for the remainder of therapy (until the 16 week mark). Such a strategy will provide optimal treatment, without delaying therapy prior to receipt of results of NS5A drug resistant testing.*
Study observations	• *Laboratory tests including hepatic function panel at screening and at multiple time points during follow-up.* • *Fibroscan at screening, post-transplant (prior to treating HCV), and post-treatment.* • *HCV RNA prior to treatment, on treatment, and 4 and 12 weeks after completing Zepatier*, Epclusa, or another appropriate antiviral treatment.
Type of control	*None*
Number of subjects	*Estimated 11 HCV-negative subjects transplanted with a lung from an HCV-infected donor*
Plan for statistical analysis	*Primary endpoint:*

	• *Post-treatment sustained virologic response (SVR)* *Secondary endpoints:* • *Determine if there are major adverse events attributable to HCV therapy in post-lung transplant patients.* • *Evaluate 1-year lung graft survival in HCV-negative patients who receive a lung transplant from an HCV-positive donor* • *Determine the rates of spontaneous HCV clearance among HCV-negative patients with lung failure receiving a lung from an HCV-positive donor* *Data analysis:* *The primary analysis will be based on a calculation of SVR rates (number of subjects with SVR-12; negative HCV RNA 12 weeks after completing Zepatier, Epclusa, or another appropriate antiviral treatment / (number of subjects treated with Zepatier*, Epclusa, or another appropriate antiviral treatment *post-lung transplantation)*

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3 ABSTRACT

There has only been a modest increase in the number of lung transplants each year, increasing from a yearly average of 2,400 between 2009 and 2011, to 2,800 in 2016. Despite this, more than 300 patients died or became too sick to transplant on the lung transplant waiting list in 2016. These numbers don't even account for the large population of patients in need of a lung transplant who are never waitlisted because of the scarcity of donor organs relative to the number in need. Thus, there is a critical need to expand the pool of lung donors in order to save more lives from end-stage lung disease.

We will perform a pilot trial to prove feasibility of knowingly using HCV-positive organs for HCV-negative recipients, by transplanting up to 11 HCV-negative subjects with lungs from HCV-positive donors, and then treating these subjects' with Zepatier, Epclusa, or another appropriate antiviral treatment in the early post-transplant phase in order to cure their HCV. If any subjects clear HCV spontaneously within the first four weeks post-transplantation, and do not require treatment, subjects will be added until there have been 11 HCV-negative subjects who receive a lung transplant from an HCV-positive donor, develop HCV, and are then treated for their HCV with Zepatier, Epclusa, or another appropriate antiviral treatment.

4 CHAPTER 1: BACKGROUND AND SIGNIFICANCE

4.1. Background

There has only been a modest increase in the number of lung transplants each year, increasing from a yearly average of 2,400 between 2009 and 2011, to 2,800 in 2016. Despite this, more than 300 patients died or became too sick to transplant on the lung transplant waiting list in 2016. These numbers don't even account for the large population of patients in need of a lung transplant who are never waitlisted because of the scarcity of donor organs relative to the number in need. Thus there is a critical need to expand the pool of lung donors in order to save more lives from end-stage lung disease.
The current treatment paradigm of HCV has evolved to the point that we should reconsider transplanting lungs from HCV-positive donors into HCV-negative patients in order to greatly increase the number of lifesaving lung transplants. The potential for liver disease, coupled with logistical and ethical intricacies of transplanting lungs from HCV-positive donors into HCV-negative recipients, highlight the need to conduct a controlled study to establish safety and efficacy, while investigating mechanisms of HCV transmission.

We expect that there will be a high degree of willingness of carefully selected, HCV-negative lung transplant patients to accept an organ from an HCV-positive donor, especially given the high HCV cure rates with current therapies. After completing this pilot study, the goal is to then apply for federal funding to perform a multi-center randomized controlled trial using HCV-positive lungs for HCV-negative recipients, with the hope to increase utilization of organs that are currently discarded more than 97% of the time.

This study will target lung transplant candidates that currently face challenges in receiving an HCV-negative transplant and have a substantial probability of health decline while on the waiting list. This could include several broad cohorts of patients, but particularly those with "low to medium" LAS scores (the scores used for waitlist priority), which would largely include patients with chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF), who in many scenarios derive the greatest benefit for lung transplantation. This is especially true for patients with CF, who are among the youngest lung transplant patients. Unlike the USHER study, this study will include pre-enrollment testing for hepatic fibrosis using a Fibroscan to ensure patients do not have significant underlying liver disease.

4.2. Rationale of the study

We will perform a pilot trial to prove feasibility of knowingly using HCV-positive organs for HCV-negative recipients, by transplanting up to 11 HCV-negative subjects with lungs from HCV-positive donors, and then treating these subjects with Zepatier, Epclusa, or another appropriate antiviral treatment in the early post-transplant phase in order to cure their HCV.

4.3. Zepatier for recipients of lung transplants from donors with genotype 1 or 4 HCV

Open-label Zepatier (grazoprevir 100 mg and elbasvir 50 mg) will be administered.[1,2] Zepatier is a fixed-dose combination tablet without ribavirin. GZR is an HCV NS3/4a inhibitor while EBR is an HCV NS5A inhibitor. Both grazoprevir and elbasvir are direct-acting antivirals, which together form an effective therapy for HCV and reduce the likelihood and effects of long-term liver-related HCV complications. GZR/EBR exhibits broad in vitro activity against most HCV genotypes and in vitro activity against many clinically relevant RAVs.[1,2]

Zepatier has been evaluated globally in multiple phase I, II, and III trials to treat HCV.[1,2] Randomized, placebo-controlled trials have been carried out, which led to FDA approval for Zepatier as a treatment for genotype 1 and 4 HCV.

As of July 1, 2015, a diverse population of over 1000 HCV patients has been exposed to Zepatier either as a single agent or in combination with ribavirin or sofosbuvir in phase I/II/III studies. Zepatier has been generally well tolerated at doses of 50-100 mg GZR and 50 mg EBR orally once daily. It has been comparably effective across all subgroups it has been tested in, including non-cirrhotic and/or treatment-naïve subjects.[1,2]

Headaches, fatigue, and nausea represent the most common adverse drug reactions with Zepatier.[1,2] Other drug-related adverse events have included arthralgia, insomnia, diarrhea, dizziness, pyrexia, and asthenia.[1,2] Drug-related serious adverse events are uncommon, but include allergic reactions, possible adverse interactions with other medications, or elevated liver enzymes. In past Zepatier trials, the majority of the adverse events were reversible. These adverse events are usually grade 1 or 2 mild or moderate events.

The dosage in our study (100/50 mg daily) is a commonly attainable dose in clinical practice. In the event dialysis is needed after transplant, Zepatier has shown to be safe for subjects with chronic lung disease or who are on hemodialysis. Less than 1% of Zepatier is excreted renally. In Merck C-SURFER, a phase 1 randomized, controlled Zepatier trial, subjects with advanced heart disease tolerated the drug well for the required 12 weeks and had no need for dose adjustments.[3]

Zepatier trials have demonstrated a 94-100% success rate achieving HCV RNA levels of <15 IU/ml after 12 weeks of treatment (SVR-12) among genotype 1 HCV patients.[1,2]

HCV genotype (either on donor sera or recipient sera) will be confirmed by the standard of care diagnostic test at the Hospital of the University of Pennsylvania.

4.4 Epclusa for recipients of lung transplants from donors with HCV infection that is genotype 2, 3, 5, or 6

For recipients transplanted with a lung from a donor with genotype 2, 3, 5, or 6, the treatment regimen will be 12 weeks of Epclusa (Sofosbuvir/Velpatasvir). This treatment regimen, similar to Zepatier, has demonstrated SVR-12 (cure) rates of genotype 1 and 4 HCV that exceeds 95%. However, Epclusa has also been shown to have cure rates of 95-100% in patients with genotypes 2, 3, 5, or 6, and is thus considered a pan-genotypic HCV regimen. [4,5] There are also multiple published case series of Epclusa being administered crushed and placed down an enteral feeding tube (e.g., NG feeding tube), including in lung transplant recipients acutely infected with HCV.[6,7] In addition to demonstrated efficacy when crushed and administered via an enteral feeding tube (which is commonly required in lung transplant recipients), Epclusa has been shown to be safe to be administered in patients with renal dysfunction.[8,9] Because of the interaction between Sofosbuvir and Amiodarone that can lead to fatal bradyarrythmias, patients on amiodarone pre-transplant will be excluded.

In the unlikely event that the patient has a contraindication for Epclusa, the investigators will identify and administer the safest and most effective alternative antiviral treatment.

In the unlikely event that neither the donor nor the recipient HCV can be genotyped, the investigators will identify and administer the safest and most effective alternative antiviral treatment.

5 CHAPTER 2: OBJECTIVES AND SPECIFIC AIMS

5.1. Objectives

This study is being conducted to determine safety and efficacy of transplanting lungs from HCV-NAT-positive donors into HCV-negative patients on the lung transplant waitlist, who will then be treated with Zepatier, Epclusa, or another appropriate antiviral treatment post-transplantation.

5.2. Specific aims

Primary aims:

1. Primary efficacy objective: To determine sustained virologic response (SVR) rates of open-label Zepatier, Epclusa, or another appropriate antiviral treatment in hepatitis C virus (HCV) negative patients who receive a lung transplant from an HCV-infected donor, leading to post-transplantation de-novo HCV infection.

2. Primary safety objective: To determine the safety of administration of open-label Zepatier, Epclusa, or another appropriate antiviral treatment among HCV-negative patients who receive a lung transplant from an HCV-infected donor and develop post-transplant HCV infection.

Secondary aims:

1. To determine 1-year graft survival rates of HCV-negative lung transplant patients who receive a lung transplant from an HCV-infected donor, including those who spontaneously clear HCV and those who receive open-label Zepatier, Epclusa, or another appropriate antiviral treatment upon development of de-novo HCV.

2. To evaluate rates of spontaneous clearance of HCV among HCV-negative patients who receive a lung transplant from an HCV-infected donor.

3. To compare the quality-of-life of HCV-negative patients receiving a lung transplant from a HCV-infected donor to those of similar patients remaining on the waitlist for a standard deceased donor lung transplant.

6 CHAPTER 3: SCREENING AND SUBJECT SELECTION

6.1. Recruitment: identification and screening process

The trial's phases can be categorized as "screening phase," (when patients are consented and will undergo testing and evaluation for enrollment), "waiting list phase" (when patients are enrolled and are waiting for an offer of transplantation) and "transplantation phase" (after a HCV-positive lung has been received and transplanted.

We will approach patients meeting the above criteria to receive a lung transplant from an HCV-positive donor. We anticipate needing to approach 50 patients in order to enroll the necessary 25-35 patients. We will continue to follow these patients for updates on transplant status even after initial review and noted as a part of study data.

Prior to consenting to be in the study, patients will be screened for any underlying liver diseases using serologic testing, and will be evaluated by a transplant hepatologist and abdominal transplant surgeon, to ensure that besides the underlying cardiac disease, the patient would meet criteria for listing for liver transplantation. Once patients are consented and enrolled, the lung transplant team will be made aware of the patient's enrollment, and he/she will then have his/her status on UNET changed to be eligible to receive a lung from an HCV-infected donor.

The overall study population will include an estimated 20-30 patients who we anticipate to consent to become eligible for HCV-infected lung offers while on the lung transplant waiting list. Out of this pool of consented patients, we will assemble the study population of interest: up to 11 patients who will receive a lung transplant from an HCV-infected donor (we may transplant more patients if not all of the original 11 patients become infected with HCV). It will be necessary to consent and enroll a greater number of patients that will be transplanted because transplantation may not ultimately be available to all wait-listed patients, given various barriers related to blood type, HLA matching, and donor and recipient size matching.
Patients who are screened will be tracked in a pre-screening log to facilitate the screening process. The study team has worked with their department's Information Technology Team and their recommendations for protecting potential subject health information will be put into place.

Subjects who are temporarily inactive and unable to receive any lung offers until reactivated will continue to be followed. If the subject is reactivated, his/her status based on the inclusion and exclusion criteria will be reviewed by the investigator team to ensure the patient is still eligible for the study.

Only subjects who would be hypothetically eligible for a liver transplant if HCV caused them to experience liver failure will be enrolled in this study.

6.1.1. Eligible subject pool after 10th transplant (Amendment 11/13/20)

The original study design called for 10 transplants. The nature of transplant requires a larger pool of eligible patients be assembled than can be transplanted within the framework of this protocol. In the likelihood that an eligible patient remains enrolled on the study waitlist after the "final" transplant (10th), we will keep them active for study transplant offers for an additional six weeks from IRB approval of this protcol amendment.

Study drug availability has been confirmed along with approval from the DSMB and Sponsor (Merck).

The remaining subject has been told the study is now closed to enrollment and that this exception will have to be approved for them to remain active on our study waitlist for an additional six weeks.

Organ offers happen sporadically at random. To ensure this subject has the best opportunity to transplant and is not kept in limbo, we consider this request highly-time sensitive. It is also imperative the subject know his/her study status in order to make an well-informed decision regarding non-study organ offers.

The original study design called for 10 transplants, which we just achieved. The nature of transplant requires a larger pool of eligible patients be assembled than can be transplanted within the framework of this protocol. At this time, we have only one remaining subject on our waitlist. This subject is highly motivated and we believe he/she can benefit from a chance at transplantation from our study. The needed study drug is available and the Sponsor and DSMB both support this goal.

6.2. Subject selection criteria

6.2.1. Inclusion criteria

- 18-67 years of age
- Obtained agreement for participation from the lung transplant team
- No evident contraindication to lung transplantation other than the underlying lung disorder
- Able to travel to the University of Pennsylvania for routine post-transplant visits and study visits for a minimum of 12 months after transplantation
- No active illicit substance abuse
- Women must agree to use birth control in accordance with Mycophenolate Risk Evaluation and Mitigation Strategy (REMS) following transplant due to the increased risk of birth defects and/or miscarriage
- Both men and women must agree to use at least one barrier method of birth control or remain abstinent following transplant due to risk of HCV transmission
- Inclusion criteria for treatment (not for entry as study patient) will include any detectable HCV RNA by week 4 post-lung transplantation
- Able to provide informed consent

6.2.2. Exclusion criteria

- Hepatocellular carcinoma
- HIV positive
- HCV RNA positive
- Hepatitis B surface antigen and/or DNA positive
- Any chronic liver disease (excluding non-alcoholic fatty liver disease (NAFLD) that is occurring in the setting of persistently elevated liver enzymes (patients with Alpha-1-antitrypsin lung disease without hepatic involvement are eligible)
- Significant fibrosis (≥F2 on the Fibroscan)—for patients with cystic fibrosis, the cutoff will be 11kPa (cutoff for F2 for patients with chronic cholestatic liver disease), whereas for all other patients the cutoff will be 8kPa (the cutoff for fatty liver disease used in the THINKER study)
- Pregnant or nursing (lactating) women
- Known allergy or intolerance to tacrolimus that would require post-transplant administration of cyclosporine, rather than tacrolimus given the drug-drug interaction between cyclosporine and Zepatier and Epclusa
- Pre-transplant use of Amiodarone given the drug-drug interaction between amiodarone and Epclusa

- Waitlisted for a multi-organ transplant
- Patients with underlying liver disease with or without liver cirrhosis
- Patients with cystic fibrosis who have underlying liver disease
- Re-transplant candidate
- Use of ECMO or mechanical ventilation as a bridge to lung transplantation
- Inability to provide study consent
- Chronic kidney disease with GFR<50

Relative contraindications for study subjects that will be reviewed on a case-by-case basis by the Lung Transplant Selection Committee and the Principal Investigators

- *Evidence of end organ damage due to diabetes (e.g. retinopathy, nephropathy, ulcerations) and /or brittle diabetes mellitus (e.g. history of diabetic ketoacidosis) and/or uncontrolled diabetes as evidence by a HgbA1C of 7.5-8.5.*
- *Hematologic: Significant coagulation abnormalities, and/or bleeding diatheses.*
- *Active or recent solid or liquid malignancy in the past 5 years (apart from select skin malignancies).*
- *Patient refusal to receive blood products or transfusions during lung transplant surgery.*
- *Psychosocial: Profound neurocognitive impairment with absence of social support.*
- *Active mental illness or psychosocial instability*
- *Inadequate insurance and/or financial support for post-transplant care.*
- *Evidence of drug, tobacco or alcohol abuse within the past six months and failure to satisfy recommended therapy/services/parameters as indicated by social work staff and/or consult team.*
- *History of chronic non-adherence to medical recommendations and/or medications*
- *PRA >10%.*
- *Severe malnutrition, BMI <18 kg/m^2*
- *Major chronic disabling comorbidity (e.g. lupus, severe arthritis, neurologic diseases, previous stroke with profound residual).*
- *Symptomatic or severe vascular disease (History of CABG, Aorta-femoral surgery)*

6.3. Donor Organ Selection Criteria

Broad goal: To include donors with confirmed HCV-infection expected to have acceptable post-transplant graft outcomes based on large retrospective lung transplant studies.

Inclusion criteria for donors

- Detectable HCV RNA
- Age ≤55 years
- PaO_2/FiO_2 ≥300 on FiO_2 = 100% and PEEP=5
- Cigarette use history ≤ 20 pack years
- No evidence of cirrhosis
- No prior treatment of HCV with a DAA-based therapy
- Can be isolated hepatitis B Core IgG positive, but cannot have a detectable HBV Core IgM, HBSAg, and/or HBV DNA (positive HBV NAT test)

Donor Exclusion Criteria

- Donation after circulatory death determination (DCDD)
- HIV positive

6.3.1. Donor Evaluation

We will ensure that subjects only receive a lung transplant from a confirmed HCV-infected donor as demonstrated by HCV NAT results reported by UNOS or the organ procurement organization.

6.3.2. Genotype guided treatment of HCV

We will accept donor or recipient HCV genotype results for guidance of appropriate antiviral therapy for recipients. The ability to obtain donor blood for HCV genotype testing prior to transplant will not be required.

Where available, donor genotyping will be performed on specimens provided to the Molecular Pathology Laboratory by LABS and Gift-of-Life, the local organ procurement organization. These specimens will be taken from potential lung donors once Gift-of-Life has been notified of the potential donor and will be qualified for testing by Gift-of-Life. Per standard of care, LABS will analyze specimens for the presence of HCV via serological testing and qualitative nucleic acid testing. If a specimen is positive for both HCV tests, it will be couriered to the University of Pennsylvania via a Gift-of-Life courier

In other instances, we will perform genotyping of the lung recipient in the first week after transplantation. The assay that will be used for HCV genotyping is a laboratory-developed assay that was validated by the HUP MPL under the guidance of Vivianna Van Deerlin, MD, PhD. The validation process entailed testing multiple past clinical samples with known HCV genotypes, as well as purchased HCV genotype controls, and assessing concordance between the results obtained and the expected results.[10] This assay (the eSensor® HCVg *Direct* Test, GenMark Diagnostics) has also been validated by multiple external laboratories with the following results: Covance Central Laboratory Services (482 samples, 98.6% concordance), University of Minnesota (135 samples, 96.4% concordance), and the University of Washington (77 samples, 97.4%).[11-13] In the HUP MPL, overall, the assay was able to genotype all purchased controls correctly (n=15, HCV genotypes 1 through 6, concordance = 100%). It was also able to correctly genotype the vast majority of prior clinical samples (n=56 of 61, HCV genotypes 1 through 6, concordance = 92%). Resolution of discordant samples showed that the limitations of the assay, as determined by the validation, included decreased ability to genotype samples with: low viral loads, mixed genotype infections, or HCV genotype 4f infection. These limitations are felt to be minor as low viral load specimens are not expected from HCV-untreated organ donors, and mixed genotype / genotype 4f specimens are very rarely encountered in the United States. The validation samples were picked to better understand the limitations of the assay and so had a higher proportion of mixed infection samples (n=6) and rare genotype samples (e.g., Type 4f, n=1) than what is encountered clinically. A retrospective review by the MPL of HCV genotypes resulted at HUP over a 14-month period (July 2014 to October 2015) by the previous MPL HCV genotyping assay (Siemens VERSANT HCV Genotype 2.0) found a total of 6 mixed infections and one genotype 4f infection out of 1,551 samples tested (~0.4% and 0.06%, respectively).

6.3.3. Drug Resistance Testing

Participants with Genotype 1a and Genotype 1 HCV infection with an unknown subtype will have baseline NS5A drug resistance assay testing checked at the start of treatment. The Hepatitis C Viral RNA Genotype 1 NS5a Drug Resistance test will be used to check for NS5A drug resistance. This test uses reverse transcription polymerase chain reaction (PCR) and DNA sequencing to detect mutations [resistance associated variants (RAVs)] in the NS5a inhibitors. It has not been cleared or approved by FDA but has been validated pursuant to the CLIA regulations. The test will be performed by a lab qualified by the Principal Investigator Team. It has an analytical sensitivity of >95% for viral loads ≥1800 IU/mL.[14] Reported results include mutations and polymorphisms

associated with NS5A inhibitor resistance (only if HCV genotype 1a, 1b, or 1 detected) as well as a patient specific interpretation:

- Resistance predicted: ≥1 mutation predicting NS5A inhibitor resistance detected
- Resistance not predicted: no mutations predicting NS5A inhibitor resistance detected

7 CHAPTER 4: TREATMENTS

7.1. Zepatier (grazoprevir and elbasvir) for lung recipients with HCV genotype 1 or genotype 4 infection

Zepatier tablets will be provided by Merck as part of this investigator-initiated protocol funded by Merck. Open-label Zepatier (grazoprevir 100 mg and elbasvir 50 mg) will be administered once daily by mouth for 12 weeks. An exception to the 12 week course of treatment will be if patients have polymorphisms at positions M28, Q30, L31, and/or Y93 as determined by the Hepatitis C Viral RNA Genotype 1 NS5a Drug Resistance test. In this case, treatment with Zepatier will be extended to 16 weeks and renally-adjusted Ribavirin will be initiated at the clinician's discretion, and continued for the remainder of therapy (until the 16 week mark). Such a strategy will provide optimal treatment, without delaying therapy prior to receipt of results of NS5A drug resistant testing. Grazoprevir (GZR)/ elbasvir (EBR) is a fixed-dose combination tablet without ribavirin.

GZR is an HCV ns3/4a inhibitor while EBR is an HCV NS5A inhibitor. Both are direct-acting antivirals, which together form an effective therapy for HCV virus and reduce the likelihood and effects of long-term liver-related HCV complications. GZR/EBR exhibits broad in vitro activity against most HCV genotypes and in vitro activity against many clinically relevant resistance-associated variants (RAVs).

Zepatier (GZR/EBR) has been evaluated globally in multiple phase I, II, and III trials to treat HCV. Randomized, placebo-controlled trials have been completed and led to obtain FDA approval for Zepatier as a treatment for genotype 1 and 4 HCV. As of July 1, 2015, a diverse population of over 1000 HCV patients has been exposed to Zepatier either as a single agent or in combination with ribavirin or sofosbuvir in phase I/II/III studies. Zepatier has been generally well tolerated at doses of 50-100 mg GZR and 50 mg EBR orally once daily. It has been comparably effective across all subgroups it has been tested in, including non-cirrhotic and/or treatment-naïve subjects.

Headaches, fatigue, and nausea represent the most common adverse drug reactions with Zepatier. Other drug-related adverse events have included arthralgia, insomnia, diarrhea, dizziness, pyrexia, and asthenia. Drug-related serious adverse events are uncommon, but include allergic reactions, possible adverse interactions with other medications, or elevated liver enzymes. In past Zepatier trials, the majority of the adverse events were reversible. These adverse events are usually grade 1 or 2 mild or moderate events.

The dosage in our study (100/50 mg qd) is a commonly attainable dose in clinical practice. In the event dialysis is needed after transplant, Zepatier has shown to be safe for subjects with chronic kidney disease or who are on hemodialysis. Less than 1% of Zepatier is excreted renally. In Merck C-SURFER, a phase 1 randomized, controlled Zepatier trial, subjects with advanced lung disease tolerated the drug well for the required 12 weeks and had no need for dose adjustments.

Zepatier trials have demonstrated a 94-100% success rate achieving HCV RNA levels of <15 IU/ml after 12 weeks of treatment (SVR-12) among genotype 1 and 4 HCV patients.

As of January 2016, Zepatier was approved by the Food and Drug Administration. It has been extensively studies in multiple large clinical trials. This drug regimen was chosen as first-line therapy, rather than other approved agents (i.e., Sofosbuvir/Ledipasvir, trade name Harvoni), as Zepatier has been shown to be safe and efficacious in patients with significant renal dysfunction. As a result, if a subject's lung function has not fully recovered when treatment is initiated, the investigational agents can safely be administered, unlike other approved agents.

7.1.1. Epclusa or another appropriate antiviral treatment for lung recipients with HCV genotypes 2, 3, 5 or 6

For recipients transplanted with a lung from a donor with genotype 2, 3, 5, or 6, we plan to administer a treatment regimen of 12 weeks of Epclusa (Sofosbuvir/Velpatasvir). This treatment regimen, similar to Zepatier, has demonstrated SVR-12 (cure) rates of genotype 1 and 4 HCV that exceeds 95%. However, Epclusa has also been shown to have cure rates of 95-100% in patients with genotypes 2, 3, 5, or 6, and is thus considered a pan-genotypic HCV regimen. [4,5] There are also multiple published case series of Epclusa being administered crushed and placed down an enteral feeding tube (e.g., NG feeding tube), including in lung transplant recipients acutely infected with HCV.[6,7] In addition to demonstrated efficacy when crushed and administered via an enteral feeding tube (which is commonly required in lung transplant recipients), Epclusa has been shown to be safe to be administered in patients with renal dysfunction.[8,9] Because of the interaction between Sofosbuvir and Amiodarone that can lead to fatal bradyarrythmias, patients on amiodarone (at enrollment or pre-transplant) will be excluded. The side effect profile of Epclusa is similar to that of Zepatier from the Epclusa registry trials.

7.1.2. Administration of Zepatier

Merck & Co will manufacture, package, and label Zepatier drug. There will be one bottle per subject containing a 28-day supply (28 capsules) of 100/50 mg Zepatier tablets. Daily dose will be one tablet.

The Investigational Drug Services (IDS) pharmacy, directed by Kenneth Rockwell, PharmD, will only be required to store and distribute Zepatier. Sofosbuvir and Ribavirin will be purchased and sourced locally. Both of these medications will be purchased and stored by the IDS pharmacy at Penn. Ribavirin will be generic and the manufacturer will vary depending on monthly price fluctuations.

Zepatier will be picked up from the investigational drug services (IDS) pharmacy by the research staff at 28-day intervals. The study staff will deliver the medication to the subjects at their study visits (patients expected to be at home by the time that HCV therapy is initiated and patients will be given medication at their scheduled post-transplant/study visit). Treatment with the study drug will begin within 4 weeks post-transplant. If hepatitis C is not cured after a subject has received Zepatier, he or she will be treated with a second regimen that includes Zepatier plus Sovaldi (Sofosbuvir) and Ribavirin. Any patient (male or female) receiving ribavirin as part of the first- or second-line regimen will be required to use two methods of birth control while on Ribavirin therapy, with continuing two forms of birth control for up to 6 months after the last dose of the study drug.

If patients have baseline NS5A drug resistance assay testing that demonstrates polymorphisms at positions M28, Q30, L31, and/or Y93, treatment with Zepatier will be extended to 16 weeks, rather than 12 weeks, and renally-adjusted Ribavirin at the clinician's discretion will be initiated, and continued for the remainder of therapy (until the 16 week mark). Such a strategy will provide optimal treatment, without delaying therapy prior to receipt of results of NS5A drug resistant testing.

7.1.3. Drug logistics and accountability

Study medication bottles must be stored at controlled temperature of 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F) in a locked, secure area. Study drug must be protected from moisture. The research staff or investigator will instruct the subject on the proper administration of Zepatier. Zepatier tablets should be taken once daily by mouth. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational agent using the drug accountability form. If a subject loses the bottle of study medication, the

research staff should contact Kenneth Rockwell, Pharmacist at the research pharmacy. A replacement bottle with the appropriate amount of study medication will be made available at the research pharmacy.

7.1.4. Destruction and return

At the conclusion of the study, remaining medication from the study patients (and left-over medication) will be destroyed at the clinical site, after approval is granted by the research pharmacy for the drug destruction plan. Destruction will be documented in the drug accountability form.

7.1.5. Zepatier Initial Treatment Failures

Study subjects with treatment failure, defined as virologic breakthrough (when an undetectable viral load while on treatment becomes detectable) or virologic relapse (undetectable viral load after completion of Zepatier treatment that during the 12-week post-treatment follow-up period becomes detectable) will be provided open-label Zepatier + Sofosbuvir (Sovaldi) 400 mg + Ribavirin (generic), renally dosed based on creatinine clearance per the manufacturer guidelines. Any subjects who experience treatment failure will repeat the original study lab visit and visit protocol once they begin their secondary treatment with Zepatier, sofosbuvir, and ribavirin, similar to subjects initiating HCV treatment following lung transplantation. Prior to initiating treatment with this regimen, patients will have serum NS5A resistance (RAV) testing.

7.2. Epclusa for lung recipients with genotype 2, 3, 5, or 6 HCV infections

Upon receiving the results of genotype testing of the donor and/or lung recipient showing HCV infection that is neither genotype 1 nor genotype 4 (genotypes 2, 3, 5 or 6), PIs will begin Epclusa that will be locally sourced by the hospital pharmacy. In the unlikely event that the patient has a contraindication to Epclusa, another optimal antiviral regimen will be selected.

The Hospital of the University of Pennsylvania (HUP) will provide the antiviral treatment and coordinate the application to the subjects insurance company for coverage of the antiviral treatment. In the event that the subject's insurance company denies coverage for the antiviral treatment, HUP will provide the entire HCV treatment regimen at no charge to the subject. In the event that the subject fails to be cured of HCV with the initial treatment regimen and the subject's insurance declines to pay for a second antiviral treatment, HUP will provide the second HCV treatment regimen at no charge to the subject.

8 CHAPTER 5: DATA COLLECTION

8.1. Study visits

Study visits are scheduled to occur following subjects' standard post-transplant follow-up visits. Since treating cardiologists do not always require stable post-transplant patients to attend these visits, subjects may be asked to come in solely for study visits. These visits will be encouraged, but not required unless the study drug is being dispensed that day. For all other study visits, a missed visit by a stable subject who has had necessary labs drawn will not be considered a protocol violation.

8.1.1. Informed consent

During the screening phase, potentially eligible, interested subjects will be invited to attend an informational session. The following procedures will be performed during the screening process:

- Sign and date the ICF and HIPAA authorization
- Review of inclusion/exclusion criteria
- Schedule for screening visit

After completing the informational session and signing the informed consent, the subject will be scheduled for a screening visit within 56 days if the subject meets inclusion/exclusion criteria thus far. The study staff will call the subject 1-2 days prior to the screening visit and send a reminder letter as well if the screening visit is not conducted within the 2 weeks following consent. The study staff will instruct the subject to not eat or drink (except water) and to avoid heavy exercise for 3 hours prior to the study visit in order to ensure accuracy of the Fibroscan test that requires 3 hours of NPO prior to testing. According to the recommendations of use and based on safety and efficacy matters; patients with ascites (fluid in the abdomen), persons with active implantable medical devices, and persons with a waist size more than 100cm will be excluded from having a Fibroscan performed.

8.1.2. Screening

The following procedures and activities will be performed during the screening process, after the informed consent is signed:

- Review medical history
- Vital signs
- Physical exam
- Fibroscan
- Review current medications
- Labs/phlebotomy: hepatic function panel, HCV RNA, HBV DNA, and HIV antibody
    - HBV Core Antibody will be checked in patients during screening, if not checked previously.
- Serum chg. pregnancy test (for women of childbearing potential)
- Completion of health status questionnaire (RAND-36)
- Provide instructions on recording of new medications and dose changes

8.1.3. Post-Lung Transplant

8.1.3.1. Post-Lung Transplant Visits

Patients, after receiving a lung transplant are followed very closely by both the surgical and nephrology team. As a part of standard of care visits, the following procedures activities will be performed:

- Phlebotomy
- Vital signs
- Physical exam

The study staff will follow procedures and activities closely along with transplant team and this information (vital signs, physical exam, and phlebotomy results) will be collected as a part of data collection. In addition to these standard of care procedures and activities, the study team will also perform specific research related activities at specific time points.

8.1.3.2. Post-Lung Transplant Research Phlebotomy

Research laboratory blood draws will take place along with standard of care blood draws outlined in Section 8.2.1. The study staff will call the research subject to coordinate research blood draws appropriately. In addition, study staff will assess for adverse events/side effects and obtain current medication data.

As outlined in Section 8.2.1, patients with a positive HBV Core Antibody, HBV-DNA levels will be checked every 6 weeks while on Zepatier and LFTs will be closely monitored. HBV therapy may be considered the transplant team as medically appropriate.

Additional laboratory testing will be done if the PIs feel it is necessary for patient safety.

8.1.3.3. Visit 1: Post-Lung Transplant (between days 2 - 7)

The study staff will meet the subject in their HUP hospital room, three days after their lung transplant.

<u>Initiating antiviral treatment</u>
Treatment with the study drug will begin when the patient has a detectable and quantifiable HCV RNA post-transplantation and the donor and/or recipient have had an HCV genotype ascertained to guide treatment. As appropriate, subjects being discharged will be provided with a sufficient supply of the study drug.

As with any scientific protocol, safety will be considered before treating the patients. The treating physician will evaluate the patient's overall condition and make a judgment on whether initiating treatment is safe.

The following research procedures and activities will be performed:

- Assess for Adverse Events
- Obtain medication data
- Research Phlebotomy, including the NS5A drug resistance assay testing as appropriate (See Section 8.2.1 for complete list)
- Dispense study drugs

8.1.3.3.1. Management of patients with genotype 1 HCV and NS5A resistance variants

Patients with Genotype 1a and Genotype 1 with an unknown subtype will have baseline NS5A drug resistance assay testing. This will be checked at start of treatment. If patients have polymorphisms at positions M28, Q30, L31, and/or Y93, treatment with Zepatier will be extended to 16 weeks, rather than 12 weeks, and renally-adjusted Ribavirin at the clinician's discretion will be initiated, and continued for the remainder of therapy (until the 16 week mark). Such a strategy will provide optimal treatment, without delaying therapy prior to receipt of results of NS5A drug resistant testing. Under such a scenario, all of the study procedures referenced above and below will be extended by 4 weeks. Any patient (male or female) receiving ribavirin as part of the first- or

second-line regimen will be required to use two methods of birth control while on Ribavirin therapy, with continuing two forms of birth control for up to 6 months after the last dose of the study drug.

8.1.3.3.2. Management of patients with positive HBV Core Antibody

For patients with a positive HBV Core Antibody, HBV-DNA levels will be checked every 6 weeks while on Zepatier (or Epclusa or another appropriate antiviral treatment) and LFTs will be closely monitored. HBV therapy may be considered the transplant team as medically appropriate.

8.1.3.4. Visit 2: Post-Lung Transplant (day 10 ± 1 day)

Visit #2 should occur two weeks (10 ± 2 days) after the subject's lung transplant and coincide with the subject's regularly scheduled post-transplant follow-up visit. The staff will call the subject 1-2 days before the visit. During this phone call, the research staff will remind the subject where to go for the study visit, to take their routine and study medications as they usually would prior to the visits and if a fibroscan is needed, inform the subject and remind him/her to not eat or drink for three hours before the study visit.

The subject will arrive at the study site outpatient clinic. The following procedures and activities will be performed:

- Assess for Adverse Events
- Obtain medication data
- Research Phlebotomy (See Section 8.2.1 for complete list)
- Pill count and verbal assessment for drug adherence
- Schedule appointments for follow-up visits

8.1.3.5. Visit 3: Post-Lung Transplant (day 21 ± 3 days)

Visit #3 should occur three weeks (21 ± 3 days) after the patient's lung transplant and coincide with the subject's regularly scheduled post-transplant follow-up visit. The staff will call the subject 1-2 days before the visit. During this phone call, the research staff will remind the subject where to go for the study visit, to take their routine and study medications as they usually would prior to the visits and if a fibroscan is needed, inform the subject and remind him/her to not eat or drink for three hours before the study visit.

The subject will arrive at the study site outpatient clinic. The following procedures and activities will be performed:

- Assess for Adverse Events
- Obtain medication data
- Research Phlebotomy (See Section 8.2.1 for complete list)
- Pill count and verbal assessment for drug adherence
- Schedule appointments for follow-up visits

8.1.3.6. Visit 4 Post-Lung Transplant (day 28 ± 3 days)

Visit #4 should occur 4 weeks (28 ± 2 days) after the subject's lung transplant and coincide with the subject's regularly scheduled post-transplant follow-up visit. The staff will call the subject 1-2 days before the visit. During this phone call, the research staff will remind the subject where to go for the study visit, to take their routine and study medications as they usually would prior to the visits and if a fibroscan is needed, inform the subject and remind him/her to not eat or drink for three hours before the study visit.

The subject will arrive at the study site outpatient clinic. The following procedures and activities will be performed:

- Assess for Adverse Events
- Obtain medication data
- Research Phlebotomy (See Section 8.2.1 for complete list)
- Fibroscan (elastography of liver)
- Health Status Questionnaire (RAND-36) (to assess changes in health status from pre- to post-transplant)
- Pill count and verbal assessment for drug adherence
- Replenish study drug as appropriate with the DAA prescribed from the specialty pharmacy
- Schedule appointments for the follow-up visits

HCV Non-Transmission

It is possible that a subject may not develop chronic HCV infection, either due to non-transmission or spontaneous clearance of HCV by week 4 (defined as an initial positive HCV RNA and subsequent undetectable HCV RNA without treatment). If a subject has an undetectable HCV RNA based on the week 4 HCV RNA, a repeat HCV RNA will be checked at week 8 to ensure non-infection with HCV, rather than a false-negative HCV RNA. If the week 8 HCV RNA confirms lack of infection (undetectable week 8 HCV RNA), then no further treatment will be needed. Subjects will be assessed at a study visit and HCV RNA levels re-checked at week 16 and 28 post-lung transplantation. Should any subject spontaneously clear HCV without treatment, another subject will replace them in order to meet our planned treatment sample size.

8.1.3.7. Visits 5-7: Post-Lung Transplant (day 42±7, day 56±7, day 70±7)

Visit #5 should occur 6 weeks (42±7 days) after the subject's lung transplant and will coincide with the subject's regularly scheduled post-transplant follow-up visit**.** Visit #6 should occur 8 weeks (56±7 days) after the subject's lung transplant and will immediately follow the subject's regularly scheduled post-transplant follow-up visit**.** Visit #7 should occur 10 weeks (70±7 days) after the subject's lung transplant and will immediately follow the subject's regularly scheduled post-transplant follow-up visit**.**

For both visits, the staff will call the subject 1-2 days before the visit to remind subject of visit. During this phone call, the research staff will remind the subject where to go for the study visit, to take their routine and study medications as they usually would prior to the visits and, if a fibroscan is needed, inform the subject and remind him/her to not eat or drink for three hours before the study visit.

The following procedures and activities will be performed:

- Assess for Adverse Events
- Obtain medication data
- Research Phlebotomy (See Section 8.2.1 for complete list)
- Replenish study drug
- Pill count and verbal assessment for drug adherence
- Schedule appointments for follow-up visits

The staff will replenish the subject's 28-day supply of the Zepatier study drug or Epclusa or another appropriate antiviral therapy sometime during visits #5 & 6, depending on when the subject began treatment.

8.1.3.8. Visits 8 & 9: Post-Lung Transplant (day 84 ±7, day 112 ±14)

Visit #8 should occur 12 weeks (84 ±7) after the subject's lung transplant and will coincide with the subject's regularly scheduled post-transplant follow-up visit**.** Visit #9 should occur 16 weeks (112 ±14) after the subject's lung transplant and will immediately follow the subject's regularly scheduled post-transplant follow-up visit**.**

Midway between these study visits, subjects will be phoned in order to ensure drug adherence, if necessary

For both visits, the staff will call the subject 1-2 days before the visit to remind subject of visit. During this phone call, the research staff will remind the subject where to go for the study visit, to take their routine and study medications as they usually would prior to the visits and, if a fibroscan is needed, inform the subject and remind him/her to not eat or drink for three hours before the study visit.

The following procedures and activities will be performed:

- Assess for Adverse Events
- Obtain medication data
- Research Phlebotomy (See Section 8.2.1 for complete list)
    - Note: Timing for HCV RNA viral load, post treatment, should, as best possible, follow the important data collection points post treatment. These are as follows:
        - Post-treatment: This should occur after the subject has completed treatment of the study drug.
        - SVR 4: This should occur ~4 weeks after the subject has completed treatment.
        - SVR 8: This should occur ~ 8 weeks after the subject has completed treatment.
        - SVR 12: This should occur ~12 weeks after the subject has completed treatment.
        - SVR 24: This should occur ~24 weeks after the subject has completed treatment.
- Fibroscan (elastography of liver) for one visit only
- Health Status Questionnaire (RAND-36) (to assess changes in health status from pre- to post-transplant)
- Pill count and verbal assessment for drug adherence
- Replenish study drug
    - Note: The staff will replenish the subject's supply of the Zepatier or Epclusa or another appropriate antiviral therapy between visits 7 & 8, if necessary. This is based on management of patients NS5A resistance variants, in any were are present. The staff will also remind the subject how to take the medication, for those subjects still on study medication.

8.1.3.9. Visit 10 Post-Lung Transplant (day 168 ±14)

Visit #10 should occur 24 weeks (168 ±14) after the subject's lung transplant and will coincide with the subject's regularly scheduled post-transplant follow-up visit**.**

For this visit, the staff will call the subject 1-2 days before the visit. During this phone call, the research staff will remind the subject where to go for the study visit, to take their routine and study medications as they usually would prior to the visits and if a fibroscan is needed, inform the subject and remind him/her to not eat or drink for three hours before the study visit.

The following procedures and activities must be performed:

- Assess for Adverse Events
- Research Phlebotomy (See Section 8.2.1 for complete list)
    - Note: Timing for HCV RNA viral load, post treatment, should, as best possible, follow the important data collection points post treatment. These are as follows:

  - Post-treatment: This should occur after the subject has completed treatment of the study drug.
  - SVR 4: This should occur ~4 weeks after the subject has completed treatment.
  - SVR 8: This should occur ~ 8 weeks after the subject has completed treatment.
  - SVR 12: This should occur ~12 weeks after the subject has completed treatment.
  - SVR 24: This should occur ~24 weeks after the subject has completed treatment.
- Fibroscan (elastography of liver)
- Health Status Questionnaire (RAND-36) (to assess changes in health status from pre- to post-transplant)

8.1.3.10. Visit 11 Post-Lung Transplant (day 365 ±14)

Visit #10 should occur 52 weeks (365 ±14 days) after the subject's lung transplant and will coincide with the subject's regularly scheduled post-transplant follow-up visit**.**

For this visit, the staff will call the subject 1-2 days before the visit. During this phone call, the research staff will remind the subject where to go for the study visit, to take their routine and study medications as they usually would prior to the visits and, if a fibroscan is needed, inform the subject and remind him/her to not eat or drink for three hours before the study visit.

The following procedures and activities must be performed:

- Assess for Adverse Events
- Research Phlebotomy (See Section 8.2.1 for complete list)
- Fibroscan (elastography of liver)
- Health Status Questionnaire (RAND-36) (to assess changes in health status from pre- to post-transplant)

The Research Staff should fill out the **Study Closeout Form.** This form must be signed by the principal investigator.

8.1.3.11. Additional Visits

Additional visits will only be necessary in the case of treatment failures. If treatment failure occurs, subjects with genotype 1 or 4 infections will be treated with Zepatier and two other hepatitis C medications, Sofosbuvir (Sovaldi), and Ribavirin for an additional 12 weeks. All study and lab visits will be repeated during this secondary treatment period. NS5A resistance (RAV) testing will be checked again (a second time) prior to initiating second-line therapy.

If treatment failure occurs for patients with non-genotype 1 and non-genotype 4 infections (i.e. genotypes 2, 3, 5, or 6), the PIs will evaluate these patients for second treatment regimen that will be paid for either by the patient's insurance company or provided by HUP if the insurance company denies payment.

8.1.4. Long-term outcomes and Future research

We will collect long-term outcome data beyond the end of the 12-month active study participation period. We will passively monitor care through the electronic medical record in order to identify and track problems with organ function or other health problems that may develop, related to the transplant and study participation. This data will be stored safely like all other data, with all necessary precautions.

Subjects will also be approached to provide optional blood sample for testing of viral kinetics (HCV RNA), donor and recipient IL-28B polymorphisms, and alloimmune responses (T- and B-cell function). Samples will be stored in a locked freezer, using encrypted patient IDs.

De-identified samples from subjects may be sent to other investigators for their research. These samples may include information such as sex, age, health history, or ethnicity. These samples will not be sold. Some future studies may need health information (such as smoking history or present health status) that may require contacting the subject to obtain.

8.2. Study schedule of procedures

8.2.1. Visits, lab testing, and other clinical testing

See next page for table.

		Visit Schedule			Research Visit Activities					Research Labs								Standard of Care				
Week(s) post-KT	Day(s) post-KT	Visit	Study Visits	Lab-Only	Informed Consent	Assess Adverse Events	Current Medications	Fibroscan	RAND-36 Questionnaire	HBV DNA HIV AB & LFTs	HBV Core Antibody	Urine Preg Test	Urine Protien/Cre Ratio	HCV RNA	Viral Kinetics (optional)♦	NS5A Resistance**	Genotyping of donor andor recipient	Vitals & Physical Exam	Surveillance biopsy	CMP*	CBC	Tacrolimus
Screening					✓	✓	✓	✓	✓	✓	✓	✓		✓				✓				
1 (Begin treatment)	Day 2 - 7	V1	✓			✓	✓				✓▪			✓	✓	✓	✓	✓	✓	✓	✓	✓
1	7 ± 1 day			✓			✓							✓	✓					✓	✓	✓
2	10 ± 1 day	V2	✓			✓	✓							✓	✓			✓	✓	✓	✓	✓
2	14 ± 1 day			✓			✓							✓	✓				¥	✓	✓	✓
3	21 ± 3 day	V3	✓			✓	✓							✓	✓			✓		✓	✓	✓
4	28 ± 3 day	V4	✓			✓	✓	✓	✓				✓	✓	✓			✓	✓	✓	✓	✓
6	42 ± 7 day	V5	✓			✓	✓				✓▪			✓	✓			✓	✓	✓	✓	✓
8	56 ± 7 day	V6	✓			✓	✓							✓	✓			✓	✓	✓	✓	✓
10	70 ± 7 day	V7	✓			✓	✓								✓				✓	✓	✓	✓
12	84 ± 7 day	V8	✓			✓	✓				✓▪		✓	✓	✓			✓	✓	✓	✓	✓
13 (End treatment)†	91 ± 7 day			✓			✓								✓							
16 (SVR 4)†	112 ±14 day	V9	✓†			✓	✓		✓					✓	✓			✓†	✓	✓	✓	✓
20 (SVR 8)	140 ±7 day			✓										✓	✓				✓	✓	✓	✓
24 (SVR 12)	168 ±14 day	V10	✓			✓		✓	✓				✓	✓	✓			✓	✓	✓	✓	✓
28†	196 ±7 day			✓											✓				✓	✓	✓	✓
32	224 ±7 day			✓											✓				✓	✓	✓	✓
36 (SVR 24)	252 ±7 day			✓									✓	✓	✓				✓	✓	✓	✓
40	280 ±14 day			✓											✓				✓	✓	✓	✓
52	365 ±14 day	V11	✓			✓		✓	✓				✓	✓	✓			✓	✓	✓	✓	✓

* CMP=comprehensive metabolic panel which includes basic metabolic panel and liver function tests ** As appropriate ♦Viral Kinetics testing can be done anytime there is a standard of care blood draw

	†If patients require the 16 weeks of therapy, the last 4 weeks would be the same as weeks 9-12 of therapy ■Only if HBV Core Antibodies are positive.

8.2.2. Blood sampling volumes

Maximum Post-Transplant Blood Draw Totals								
Week Post-KT	CBC	CMP	Tacrolimus/ Cyclosporine	HBV Core Antibody	HCV RNA	Viral Kinetics (optional)♦	NS5A Resistance	Blood Draw Total
1	4	4.5	4	4	6	6	2	28.5
1	4	4.5	4	0	6	6	0	24.5
2	4	4.5	4	0	6	6	0	24.5
2	4	4.5	4	0	6	6	0	24.5
3	4	4.5	4	0	6	6	0	24.5
4	4	4.5	4	0	6	6	0	18.5
6	4	4.5	4	4	6	6	0	24.5
8	4	4.5	4	0	6	6	0	24.5
10	4	4.5	4	0	0	6	0	18.5
12	4	4.5	4	4	6	6	0	28.5
16	4	4.5	4	0	6	6	0	24.5
20	4	4.5	4	0	6	6	0	24.5
24	4	4.5	4	0	6	6	0	24.5
28	4	4.5	4	0	0	6	0	18.5
36	4	4.5	4	0	6	6	0	24.5
40	4	4.5	4	0	0	6	0	18.5
52	4	4.5	4	0	6	6	0	24.5
Total	68	76.5	68	0	84	102	2	400.5

♦ Lung transplant recipients have twice a week labs including tacrolimus or cyclosporine levels, CBC and a CMP after discharge for the first 6-8 weeks

♦There may also be additional blood draws due to optional Viral Kinetics lab testing increasing the total sample volume.

8.3. Subject retention and drug adherence

We will enforce subject retention in several ways. We will record extensive contact information for each subject at their enrollment in the trial. This will include home, work, and cellular telephone numbers. The research staff will call before each study visit to remind the subject to attend. We will also obtain contact information of a family member or friend so that we can contact him/her if the subject does not answer his/her regular phone number.

An adequate record of receipt, distribution, and return of all study drugs must be kept. Subject adherence with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations.

The research staff and physician will explain the importance of adherence with the study protocol at each subject contact. If a subject fails to comply with a study visit, the staff will contact him or her by telephone. If this fails, the staff will send two certified express letters one week apart, to request follow-up.

We have considered how to minimize non-adherence with therapy. We will strongly emphasize the importance of complying with the study drug treatment. Nonetheless, we will perform pill counts at visits and record episodes when medication is withheld for any reason. If a subject has a serious adverse event (SAE) (whether

related to study drugs or not), we will continue to follow-up with the subject for study assessments to assist with safety monitoring and to avoid the problems introduced by missing data. The inclusion of such follow-up data will allow for analysis by intention-to-treat. If a study subject withdraws consent, he/she will no longer be followed.

9 CHAPTER 6: ASSESSMENT OF EFFICACY AND OUTCOME MEASURES

9.1. Assessments of Efficacy

The primary aims of the study are to determine sustained virologic response rates (SVR) of open-label Zepatier, Epclusa, or another appropriate antiviral treatment administered to HCV-negative patients with lung failure who receive a lung transplant from an HCV-infected donor, leading to post-transplant de-novo HCV infection.

9.1.1. Sustained Virologic Response (SVR)

SVR will be based on the standard definition of SVR-12, defined as an undetectable HCV RNA in a subject's serum 12 weeks after completing treatment for HCV (12 weeks after the subject takes the last dose of Zepatier, Epclusa, or another appropriate antiviral treatment).

9.2. Secondary Outcome Measures

- To determine safety of administering Zepatier, Epclusa, or another appropriate antiviral treatment to lung transplant recipients who were previously HCV-negative, but developed de-novo HCV after receiving a lung transplant from an HCV-infected donor
- To determine 1-year graft survival rates of HCV-negative lung transplant patients who receive a lung transplant from an HCV-infected donor, including those who spontaneously clear HCV and those who receive open-label Zepatier, Epclusa, or another appropriate antiviral treatment upon development of de-novo HCV.
- To evaluate rates of spontaneous clearance of HCV among HCV-negative patients who receive a lung transplant from an HCV-infected donor.

9.2.1. Safety

Subject safety and adverse events will be based in CTCAE Version 4 criteria, listed in Section 13, and will include adverse events and serious adverse events, related both to receipt of a lung transplant from an HCV-positive donor among HCV-negative subjects with lung failure, and adverse events related to administration of Zepatier, Epclusa, or another appropriate antiviral treatment.

9.2.2. Graft Survival

Graft survival will be based on standardize United Network for Organ Sharing (UNOS) criteria, with a graft failure defined as subject death, or re-transplantation within the first year post-transplantation.

9.2.3. Spontaneous Clearance or Non-Transmission of HCV

Spontaneous clearance or non-transmission of HCV will be based on an undetectable HCV RNA level at post-transplant weeks 1-4 in the absence of treatment among HCV-negative subjects who receive a lung transplant from a confirmed HCV-infected donor. Any subject who experiences spontaneous clearance of HCV or non-transmission of HCV will still be tested for HCV RNA at weeks 8, 16, and 28, to ensure that their levels are still undetectable.

10 CHAPTER 7: STATISTICAL CONSIDERATIONS

10.1. Study Design

This open-label trial involves one primary and several secondary objectives. Post-transplant HCV status will be monitored, and patients will be treated with 12-16 weeks of therapy with Zepatier, Epclusa, or another appropriate antiviral treatment, after which time, treatment will be complete, barring instances of treatment failure, which would require an additional course of therapy.*

10.2. Disposition of Subjects and Baseline Comparisons

Summaries of all subjects screened, recruited, and enrolled will be provided, according to the CONSORT guidelines. The treatment groups will be evaluated at baseline with respect to demographics and baseline measurements related to efficacy and safety without formal statistical testing.

10.3. Analyses of Outcome Measures

The primary analysis will evaluate SVR-12 rates of HCV-negative lung transplant recipients who receive a lung from an HCV-infected donor and subsequently develop de-novo HCV. All patients will be assessed for toxicity and included in the safety analysis. This analysis will include summaries of the incidence and grade of toxicities. Patients will be evaluated for serious adverse events. Safety interim analyses will be performed and reported at each DSMB meeting.

10.4. Missing Data and Dropouts

We will attempt to minimize missing data, however we have planned for its occurrence. For subjects lost to follow-up, we will use all of the information available until the end of follow-up. Subjects who withdraw consent will no longer be followed in this protocol. Patients will receive care from the patients' clinicians.

For patients lost to follow-up, we will use all the information available up to the time of loss to follow-up. For the primary end point, we will perform an analysis of completers only. We will also perform additional sensitivity analyses using imputation to assess the impact of missing data for the primary and secondary end points.

10.5. Protocol Violations

Serious protocol deviations such as discontinuation of experimental treatment unrelated to adverse events (AEs) will be carefully recorded and regularly reviewed by co-Principal Investigators. Remedial changes in procedure will be recommended where feasible to reduce the incidence of such deviations. The causes and circumstances of all violations will be documented where known for purposes of future secondary analyses and interpretation. Because all primary analyses will be intent-to-treat, it is essential that violations be kept to a minimum, especially where it is possible to influence their rate of occurrence. A missed study visit will not be considered a protocol violation unless the study drug was scheduled to be dispensed at the visit, the subject did not have necessary labs done, or the subject has not been stable.

10.6. Safety Analysis

All patients will be assessed for toxicity and included in the safety analysis. This analysis will include summaries of the incidence and grade of toxicities. Safety interim analyses will be performed at days 14, 30, 60, 90, 118, and 184, and will be reported at each DSMB meeting. SAEs will be evaluated by the DSMB.

11 CHAPTER 8: QUALITY CONTROL AND DATA HANDLING

11.1. Personnel Training

Prior to enrolling the first subject in the study protocol, the Principal Investigators will ensure that the Investigator staff has completed appropriate training and that all documentation including IRB approval is completed and available. The purpose of training is to ensure that study personnel are carrying out the protocol in a consistent way and adhering to good clinical practice guidelines. Staff will have current Human Subjects

Training Certification on file. Before enrollment begins, study staff who will perform the outcome assessments will be trained in all procedures, including completion of the REDCap database.

The co-PIs and research staff will constitute the first line of monitoring of the safety of the human participants. Surveillance for AEs will consist of questioning subjects about potential AEs at every study contact, having subjects report any AE to the study team, and having subjects undergo vital sign checks and physical exams during each study visit. Laboratories will be performed at selected visits and checked.
All study personnel are required to read the consent form, the protocol, and the IB.

11.2. Data Quality

The co-PIs and research staff will perform continuous monitoring of data quality and completion of CRFs. All consent forms and screening logs will be subject to audit by the University of Pennsylvania. Summary statistics from the screening logs will be sent to Merck quarterly or as requested. Finally, Merck staff reviews the reporting, documentation and follow-up of SAEs to assure that these events were handled according to required study procedures. All data on AEs and SAEs will be made available to the DSMB, as per the timeline outlined in the DSMB Charter.

11.3. Audit and Inspection

Inspections may be carried out by regulatory health authority representatives [i.e., FDA] as well as the IRB.

11.4. Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request. Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

12 CHAPTER 9: PARTICIPANT SAFETY AND CONFIDENTIALITY

12.1. Informed Consent

Informed Consent will be obtained for enrollment from participants. For each consent process, study personnel will discuss the details of the study, the risks and benefits, and the subject's rights and responsibilities if they choose to participate in the trial and their right to refuse to participate. It will be made clear that their clinical care will not be affected by their decision.

Each subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only after the subject consents voluntarily and agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will sign and date the form. The subject will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or

If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The ICF and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written ICF. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC/IRB's approval in advance of use.

12.2. Institutional Review Board Process

Study staff will obtain IRB approval before any study procedures are initiated.

12.3. Insurance

The lung transplant itself will be paid for by subjects' insurance carriers, and does not require any additional pre-authorization because of the potential to receive a lung from a hepatitis C-positive donor. The costs of all visits and tests described above will be billed to the insurance carrier, except for: 1) the blood draw for research purposes (which includes the hepatitis C genotype test, which is based on a laboratory-developed test using materials purchased from the commercial entity that developed this test, and will be paid for by the research team), and 2) the study drug Zepatier in the event of infections with genotype 1 or genotype 4 HCV, which will be provided by Merck, and 3) other antiviral therapies for infections with HCV that are neither genotype 1 nor genotype 4; these therapies will be provided by HUP until such time that the subject's insurance provides coverage for the drug. In the event that the subject's insurance denies coverage for the treatment, HUP will provide the full course of appropriate HCV therapy as well as a second treatment course of antiviral therapy for HCV if the first treatment fails.

Subjects are still responsible for any deductibles or applicable co-pays for routine office visits, blood work and procedures. We do not expect subjects to have health insurance coverage/payment issues due to becoming infected with hepatitis C, per se, and the study is designed so subjects do not require additional study visits post-transplant, provided there are no adverse events.

12.4. Laboratory Values

The following clinical laboratory tests will be measured and repeated at time points specified in schedule of procedures (section 8.2.1) and as clinically indicated.

12.4.1. Chemistry

- Hepatic function panel including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin, and albumin.
- Basic metabolic panel including BUN and creatinine.

12.4.2. Serum virologic testing

- HCV RNA (with Genotyping per protocol)
- Hepatitis B surface antigen
- HIV antibody testing.
- HBV Core Antibody (as needed)

12.4.3. Pregnancy Testing

Blood and urine pregnancy tests will be performed (as appropriate) per the schedule of procedures (section 5.2).

12.4.4. Hepatitis C Viral Kinetics

Each time standard of care laboratories are drawn, subjects may have one additional purple -top tube drawn (4cc of blood). This blood test is optional. The research coordinator will process the tube and store it in a -80◦ freezer in the Perelman Center for Advanced Medicine 7th Floor Gastroenterology Research Office. Each month, these tubes will be shipped to Abbott Pharmaceuticals so they can test for HCV antibodies, HCV core antigen, and HCV RNA. These additional tests will be included in the informed consent process for all subjects. Abbott will perform these tests free of charge to University of Pennsylvania once both are able to reach a Material Transfer Agreement (MTA).

12.5. Zepatier Related Laboratory Abnormalities and Drug Interactions

Laboratory Abnormalities
The following laboratory abnormalities were observed in studies done with Zepatier:

Late elevations in aminotransferase levels greater than 5 times the upper limit of normal generally occurred in around 1-3% of patients in previous Zepatier clinical trials; these increases were rarely associated with hyperbilirubinemia. These abnormalities were reversible and had no major clinical consequences.

Effects of Zepatier on antiretrovirals:

- Atazanavir/ritonavir 300/100mg co-administered with MK-5172 200mg daily somewhat increased atazanavir exposure (AUC increased 43%, Cmax increased 12%, C24 increased 23%). Co-administration of these medications is not recommended.

- Darunivir/ritonavir 600/100 mg co-administered with MK-5172 200 mg was not significantly altered by either MK-5172 or MK-8742. However, due to DRV/r effects on Zepatier exposure, co-administration is not recommended.
- Efavirenz was not significantly impacted when co-administered with Zepatier, though it may negatively impact Zepatier exposure.
- Lopinavir/ritonavir exposures were not significantly impacted when co-administered with Zepatier. However, due to LPV/r effects on Zepatier exposure, co-administration is not recommended.

Effect of Antiretrovirals on Zepatier:

- Atazanavir/ritonavir 300/100mg co-administered with MK-5172 200mg significantly increased exposure of MK-5172 (AUC increased 10.58-fold, Cmax increased 6.24-fold, and C24 increased 11.6-fold). These findings were similar when ATV/r was combined with 50mg MK-8742. MK-8742 AUC geometric mean ratio (GMR) was 4.76, probably due to ATV/r CYP3A4/Pgp inhibition and possible inhibition of OATP-mediated disposition of MK-8742. Co-administration of these medications is not recommended.
- Exposures of MK-5172 were significantly increased when MK-5172 200 mg was co-administered with darunavir/ritonavir 600/100 mg daily. MK-5172 AUC increased 7.5-fold, Cmax increased 5.27-fold, and C24 increased 8-fold. MK-8742 exposures were also significantly increased when combined with DRV/r 600/100 mg daily. MK-8742 AUC GMR following co-administration was 1.66. This increase is likely caused by CYP3A4/Pgp inhibition by DRV/r and possibly inhibition of OATP-mediated disposition of MK-8742. For these reasons, co-administration of Zepatier and DVR/r is not recommended.
- Efavirenz 600mg co-administration with MK-5172 200 mg decreased MK-5172 AUC by 84%, most likely due to CYP3A4 induction. The same dose EFV combined with MK-5172 50 mg also decreased MK-8742 AUC 54% for the same reasons. Co-administration of these medications may cause sub-therapeutic MK-5172 exposure.
- Lopinavir/ritonavir 400/100 mg co-administered with MK-5172 200 mg significantly increased MK-5172 exposure. MK-5172 AUC increased 12.86-fold, Cmax increase 7.31-fold, and C24 increased 21.7-fold. When the same dose of LPV/r was administered with MK-8742 50 mg, MK-8742 AUC GMR was increased to 3.71. LPV/r likely impacts MK-8742 exposures due to CYP3A4/Pgp inhibition and possible inhibition of OATP-mediated disposition. Co-administration of these medications is not recommended.

Effect of Zepatier on Other Drugs:

- Rosuvastatin 10 mg co-administered with Zepatier 200/50 mg increased rosuvastatin exposure. Rosuvastatin AUC and Cmax were increased 59% and 325% respectively when exposed to MK-5172 alone and 126% and 449% when exposed to the combined Zepatier pill. The most likely cause of the increase is pre-systemic inhibition of rosuvastatin efflux in the liver and/or gut due to BCRP inhibition. Clinicians may want to avoid co-administration of Zepatier and rosuvastatin.
- Midazolam 2 mg/mL combined with multi-dose MK-5172 200 mg daily decreased midazolam AUC to 34%. MK-5172 is likely a weak CYP3A4 inhibitor.
- Multiple oral doses of rifampin did not significantly affect MK-5172 AUC, but reduced C24h by 85%. This decrease was presumably due to the combined effect of OATP inhibition and CYP3A4/Pgp induction by chronic rifampin administration. Clinicians should avoid co-administration of these medications until further data becomes available.

Effect of Other Drugs on Zepatier:

- Rosuvastatin 10 mg co-administered with Zepatier 200/50 mg did not significantly alter MK-5172/8742 exposure. However, due to Zepatier effects on rosuvastatin exposure, clinicians may wish to avoid co-administration.

- Ketoconazole (CYP3A4 and P-gp inhibitor) approximately tripled MK-5172 AUC. In healthy male subjects taking 400 mg multi-dose ketoconazole, MK-8742 AUC increased by 31%.
- Combining MK-5172 200 mg and a single dose of 600 mg IV rifampin caused a 12.6-fold increase in MK-5172 AUC, compared to an 8.35-fold increase with a single dose of oral rifampin 600 mg. This is likely due to P-gp and OATP inhibition by rifampin. Clinicians should avoid co-administration of these medications until further data becomes available.

12.6. Epclusa Related Laboratory Abnormalities and Drug Interactions

Effects of Epclusa on Other Drugs:

- Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1. Coadministration of Epclusa with drugs that are substrates of these transporters may increase the exposure of such drugs.
- Fluctuations in INR values may occur in patients receiving warfarin concomitant with HCV treatment, including treatment with Epclusa. Frequent monitoring of INR values is recommended during treatment and post-treatment follow-up.

Effects of Other Drugs on Epclusa:

- Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 (the predominant circulating metabolite of sofosbuvir) is not. In vitro, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed.
- Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to reduced therapeutic effect of Epclusa. The use of these agents with Epclusa is not recommended. Epclusa may be coadministered with P-gp, BCRP, and CYP inhibitors.

Established and Potentially Significant Drug Interactions:

- See Table on next page.

Table: Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
Acid Reducing Agents:	↓ velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		Separate antacid and EPCLUSA administration by 4 hours.
H_2-receptor antagonists[c] (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from EPCLUSA at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g., omeprazole)		Coadministration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to coadminister, EPCLUSA should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton pump- inhibitors has not been studied.
Antiarrhythmics: amiodarone	Effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown	Coadministration of amiodarone with EPCLUSA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with EPCLUSA is not recommended; if coadministration is required, cardiac monitoring is recommended *[see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*.
digoxin[c]	↑ digoxin	Therapeutic concentration monitoring of digoxin is recommended when coadministered with EPCLUSA. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancers: topotecan	↑ topotecan	Coadministration is not recommended.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin[c] rifapentine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HIV Antiretrovirals:		
efavirenz[c]	↓ velpatasvir	Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir DF	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving EPCLUSA concomitantly with a regimen containing tenofovir DF. Refer to the prescribing information of the tenofovir DF-containing product for recommendations on renal monitoring.
tipranavir/ritonavir	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Herbal Supplements: St. John's wort *(Hypericum perforatum)*	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: rosuvastatin[c]	↑ rosuvastatin	Coadministration of EPCLUSA with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with EPCLUSA at a dose that does not exceed 10 mg.
atorvastatin	↑ atorvastatin	Coadministration of EPCLUSA with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG- CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.

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

12.7. Other Events

We will not discontinue study drug for clinical events not thought to be serious drug-related AEs. For example, a hospitalization for clinical worsening may or may not result in cessation of trial participation. Such events could result in missing data for primary and secondary endpoints, comprising the integrity of the analysis. This trial does prohibit certain therapies, thus there may be a reason to stop study drug participation under such circumstances. Even if subjects are withdrawn from the study drug, outcome assessments will continue, allowing analysis by intent-to-treat.

12.8. Safety and Adverse Events

12.8.1. Definitions

Adverse event (AE): Any untoward medical occurrence associated with the protocol procedures, whether or not considered product or process related. Any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Inter-current illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious AE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious adverse event (SAE): Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-subject hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All AEs that do not meet any of the criteria for serious should be regarded as ***non-serious AEs***.
Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug/investigational product caused the adverse event. For reporting purposes, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug/investigational product and the adverse event.

Unanticipated Adverse Device Effect (ADE): is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any

other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

12.8.2. Classifying Adverse Events

Severity

The intensity of the AE is classified according to the CTCAEv4.0.[15] Grade refers to the severity (intensity) of the AE:

- **CTCAEv4 Grade 1**: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.
- **CTCAEv4 Grade 2:** moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- **CTCAEv4 Grade 3:** severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **CTCAEv4 Grade 4:** life-threatening consequences; urgent intervention is indicated.
- **CTCAEv4 Grade 5:** death due to an AE.

Expectedness

AEs must be assessed as to whether they were expected to occur or were unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label.
Expected: an AE/ADE known to be associated with the intervention or condition under study.
Unexpected: an AE/ADE for which the nature or severity is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.

OHRP defines an **unexpected AE** as any AE occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

1) the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and b) other relevant sources of information, such as product labeling and package inserts; or
2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

Relatedness

1) Definite: the AE/ADE is clearly related to the research procedures
2) Probably: the AE/ADE is likely related to the research procedures
3) Possible: the AE/ADE may be related to the research procedures
4) Unlikely: the AE/ADE is doubtfully related to the research procedures
5) Unrelated: the AE/ADE is clearly not related to the research procedures

For each identified AE/ADE, an entry on the AE/ADE form will be completed. Reporting procedures should be started immediately upon learning of a SAE/ADE.

12.8.3. Interpretation of Definitions

AE Reporting Period

The study period during which AEs must be reported is normally defined as the time of consent to the end of the study treatment follow-up. However, for this study, the AE reporting period will be divided based on the three phases of the study.

a. **Screening phase:** When all screening tests have been done, we will assess for any AEs related to the screening tests at the time of communication with the subject about whether he/she is official eligible or ineligible for the study.
   Preexisting Condition: A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

b. **Waitlist phase**: We will only capture AEs that are pertinent to the study. Specifically the following will be captured:
   1. Patient death,
   2. Patient develops a condition that would exclude them from the study,
   3. Patient is de-listed (taken off the lung transplant waitlist),
   4. Patient is made inactive on the transplant waitlist,
   5. Patient is transplanted with a non-HCV lung.

   In order to ascertain these events, we will review the patient's medical record once a month, and will contact the patient (by phone, e-mail, or in-person) every 6-8 weeks.

c. **Post-transplant phase**: All AEs will be assessed at every clinic visit when the subject is seen by a member of the study team.

d. **Post-study:** At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.
   All unresolved AEs considered possibly, probably or definitely related to the study drug should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. The investigator should notify the IRB of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The IRB will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

General Physical Examination Findings (screening, post-transplant, and post-study phases)
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

Abnormal Laboratory Values (post-transplant, and post-study phases)
A clinical laboratory abnormality should be documented as an AE if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is considered clinically significant by the local PI and is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery (post-transplant and post-study phase)
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a serious AE unless specifically instructed otherwise in this protocol, with the exception of hospitalization at the time of a lung offer and/or lung transplant. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for and AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

12.8.4. Reporting Procedures for Unanticipated Problems, Adverse Events, and Adverse Device Effects

Principal investigators should notify and local IRB, in an expedited manner, of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. Researchers should submit reports of the following problems:

Any AE/ADE or UP (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator, the event was more likely than not to be caused by the research procedures.)

AND

Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Additionally, all adverse events/adverse device effects shall be documented by the PI team, assessed, and shared with. All Serious Adverse Events will be forwarded to **Merck Worldwide Product Safety.**

What Event is Reported	By Whom is Event Reported	To Whom is Event Reported	When is Event Reported
Fatal unexpected, suspected serious adverse event *(SAE/ADE – death that is unexpected and poss/prob/def related to the research)*	Investigator	Local IRB	Within **24 hours** of initial receipt of information

Life-threatening unexpected, suspected serious adverse reactions *(SAE/ADE- life-threatening, unexpected, poss/prob/def related to the research)*	Investigator	Local IRB	Within **3 calendar days** of initial receipt of information
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions *(SAE/ADE – unexpected, poss/prob/def related, non-life-threatening hospitalization, prolonged hospitalization, disability/incapacity/birth defects, important medical event)*	Investigator	Local IRB	
Unanticipated Problem that is not an SAE *(AE/ADE or non-AE, unexpected, poss/prob/def related and suggests greater risk of harm)* *e.g. Development of moderate hypersomnia that resolve after discontinuing drug. This AE/ADE although not-serious, is not listed as an expected event in the consent. Thus it is an AE that is unexpected, possibly related (resolved after coming off drug), and places subject(s) at greater risk of harm than previously known*	Investigator	Local IRB	Within **10 calendar days** of initial receipt of information

12.8.4.1. Reporting Process

UPs posing risks to subjects or others as noted above will be reported to local IRB using a Medwatch or CIOMS report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation) will be completed.

All Serious Adverse Events, regardless of causal relationship to the investigational product, will be forwarded to **Merck Worldwide Product Safety** via fax (**215-993-1220**) within 2 working days of the investigator becoming aware of the event and no later than 3 calendar days.

The Principal Investigator is expected to provide as much of the following information:

- Protocol name and number
- Subject identifiers (no PHI will be shared with the IRB, unless requested)
- Demographic data
- Nature of the event
- Severity of the event
- Probable relationship (causality) of AE to study procedure
- Date and time of AE onset
- Date and time of AE resolution, if available
- Concomitant medications that the participant was taking for an underlying medical condition or disease and the therapeutic agents used for the treatment of the adverse event
    - Clinical assessment of participant conducted at time of SAE/AE
    - Results of any laboratory and/or diagnostic procedures, and treatment
    - Follow-up plan
    - Outcome
    - Autopsy findings (if appropriate)

The Principal Investigator will provide details about the AE/ADE as they become available. If additional information cannot be obtained for whatever reason, this will be documented. The Principal Investigator should inform the IRB when no other information is expected. The Principal Investigator should provide the IRB with a logical, complete, and accurate narrative description of the SAE based upon the above information.

The Principal Investigator should promptly determine an assessment of causality

The IRB determines if any corrective actions should be initiated as a result of any known specific or collective SAE/AE(s) and inform the principal investigator of the corrective action (e.g., revision of informed consent form, protocol, CRF).

The Principal Investigator/designee should keep originals or photocopies of all relevant documentation, including facsimile confirmations, and file them in the participant's file.

The Principal Investigator should ensure that all routine AE(s) are reported as part of the periodic or annual reporting requirements to the IRB of record.

The Principal Investigator should file copies of all correspondence with the IRB in the appropriate section of the Regulatory Master File or site study file.

Other Reportable Events:
The following events are also reportable to the IRB:

- Any adverse experience that, even without detailed analysis, represents an unexpected SAE that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis).
- Any AE that would cause a modification to the investigators brochure, protocol or ICF, or would prompt other action by the IRB to assure protection of human subjects.

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

Unanticipated Problem Involving Risks to Subjects or Others (UPRSO): Any incident, experience, or outcome that meets **all** of the following criteria:

1)Unexpected (in terms of nature, severity, or frequency) given a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document, or investigators brochure; and b) the characteristics of the subject population being studied;

2)Related or possibly related to participation in the research (possibly related to participation in the research means there is a reasonable possibility that the AE, experience, or outcome may have been caused by the procedures involved in the research.); and

3)Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

12.9. Subject Withdrawal

A subject has the right to withdraw from the study entirely at any time for any reason without prejudice to future medical care by the investigator or other physician. The investigator also has the right to withdraw subjects from the study in the event of concurrent illness, AEs, or other reasons deemed to be in the subject's best interest.

Subjects **must be withdrawn** from the trial (treatment and procedures) for the following reasons:

- Subject withdraws consent for study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

- Subject becomes pregnant while undergoing treatment with Zepatier—therapy will be stopped as there are no human safety data of Zepatier during pregnancy. There are no adequate and well-controlled studies with Zepatier in pregnant women. No effects on embryo-fetal development were observed in rats or rabbits at grazoprevir or elbasvir exposures higher than exposures in humans at the recommended clinical dose. Because animal reproduction studies are not always predictive of human response, Zepatier should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because the transmission rates of HCV from mother to fetus are very small, and HCV can be treated after pregnancy and delivery, therapy will not be continued during pregnancy. Patients will continue with the regularly scheduled study visits, but will not be eligible to receive continued Zepatier therapy.
- Zepatier is no longer produced by the company, or if a decision is made to stop the study patients will not receive study drug, but will continue with study visits as scheduled.
- Subject becomes pregnant while undergoing treatment with Epclusa—therapy will be stopped.
- Epclusa is no longer produced by the manufacturer, or if a decision is made to stop the study patients will not receive study drug, but will continue with study visits as scheduled.

Subject develops a condition that it is life threatening or any other significant risk as judged by the Investigators. Patients will not receive study drug, but will continue with study visits as scheduled.
Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

In order to preserve the integrity of the intention-to-treat analysis, even if the subject is withdrawn from the treatment portion of the protocol (either due to subject, physician, or investigator decision), it is imperative to continue with the scheduled follow-up assessments both for the safety of the subject and for completeness of data collection. This will be explained to potential subjects at the time of informed consent. The importance of adherence with study visits will be reinforced throughout the trial. If the treatment is permanently withdrawn, the subject will return to the center for safety assessment (history, physical examination, and clinical laboratories, if necessary).

12.10. Confidentiality of Study Data

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12.11. Potential Risks

12.11.1. Risks of Study Procedures

There are several areas of potential risk in this study. We will obtain several blood samples from each subject. There is a risk of bruising, hematoma, and infection after phlebotomy, which are possible but not considered serious AEs. Fainting may occur, which is unlikely but considered a serious AE. The removal of <70 cc of blood every 1-4 weeks during the 40-week post-transplant period is a potential risk; however this amount is routinely taken from subjects for clinical indications without adverse effect. Study medications will be delayed until after phlebotomy on each study day.

Because we may store subjects' blood samples, there may be confidentiality risks associated with the storage and analysis of those samples or the information resulting from the analysis of those samples. Samples may be used for genetic testing. Under some circumstances, it can be a risk for genetic information to be known. To help ensure confidentiality, samples will be coded and stored in a secured facility. While situations cannot be foreseen where potentially sensitive genetic information is revealed or where people who should not have this information could obtain it (representing a loss of confidentiality), however, it is possible that presently unforeseen situations may arise where this could happen.

The risk of undergoing screening includes potential identification of new health problems that subjects were unaware of. If we discover new health problems, we will answer subjects' questions and try to arrange appropriate treatment if any is needed. If new health problems are discovered, it is possible that subjects would not be able to enter this study. It is also possible that subjects would no longer be eligible for lung transplantation based on the results.

The risks of lung transplant surgery include blood loss, infections, and deep vein thrombosis. There are also risks related to immunosuppression and standard anti-infective therapy.

The risks of any transplant include primary graft non-function, delayed graft function, acute rejection, and death. Re-admissions within 30 days after a lung transplant are expected in approximately 40% of patients.

There may also be a small risk of developing Focal and Segmental Glomerulosclerosis (FSGS) after receiving a lung from a HCV positive donor. However, this condition can also develop in patients who do not have HCV. After transplant, we will monitor all patients for FSGS and similar conditions.

12.11.2. Risk of Genotyping Failure

There is a risk of failure of the Genotyping LDT in that no result is obtained. In that case, the investigators will use their judgment to select the most appropriate empirical treatment regimen.

There is also a risk of the Genotyping LDT giving an incorrect genotype. The risk to the recipient participant, in this event, is that they receive the transplant, but are possibly unable to be adequately treated for HCV positivity. Failure of the LDT to give an accurate genotype could be due to a mixed infection (e.g. genotype 1 and 2) or HCV genotype 4f infection in the donor sample.

12.11.3. Risk of NS5a Drug Resistance Test Failure

The potential risks of the NS5a resistance testing are false negative and false positive test results. The risk of a false negative test result would be if the test does not report any one of the four pertinent polymorphisms, even though they are present (the presence of which would be rare). In this case, the patient would receive only 12 weeks of Zepatier (rather than 16 weeks of Zepatier + renal-dosed Ribavirin), and potentially fail first-line therapy, requiring second-line therapy.

A false positive result is less likely to happen than a false negative result. The risk of a false positive test result would be if the test reports a polymorphism when the subject does not have one. Hence, the subject would be exposed to Zepatier for 4 weeks longer than needed as well as Ribavirin, and potentially experiencing the products' side effects.

12.11.4. Risk of Study Drugs

Zepatier
In subjects receiving Zepatier for 12 weeks, the most commonly reported adverse reactions of all intensity (greater than or equal to 5% in placebo-controlled trials) were fatigue, headache, and nausea. In subjects receiving Zepatier with ribavirin for 16 weeks, the most commonly reported adverse reactions of moderate or severe intensity (greater than or equal to 5%) were anemia and headache. [16-18]The greatest risk is failure to achieve SVR12 after treatment with Zepatier, leading to chronic HCV.

There is a risk of fetal harm and birth defects should any woman taking Zepatier become pregnant while on the drug.[16-18] Due to the age of the participants, this is a small risk, as all will be over 40 and unlikely to become pregnant. However, to mitigate this risk, all pre-menopausal women with a uterus will be screened for pregnancy before enrollment and instructed to use a highly effective form of birth control (e.g. abstinence, intrauterine device, etc.). Highly effective forms of birth control will be defined by the Mycophenolate Risk Evaluation and Mitigation Strategy (REMS), a standard protocol used for post-transplant patients at Penn being treated with Mycophenolate.

Sovaldi (Sofosbuvir)
The most common adverse events (incidence greater than or equal to 20%, all grades) observed with Sovaldi in combination with ribavirin were fatigue and headache. The most common adverse events observed with Sovaldi in combination with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia and anemia.[19]

Ribavirin
The hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant.[20]

Epclusa
The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with Epclusa for 12 weeks are headache and fatigue. The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with Epclusa and ribavirin for 12 weeks in patients with decompensated cirrhosis are fatigue, anemia, nausea, headache, insomnia and diarrhea.

12.11.5. Risks of Developing HCV

The risks of chronic HCV include severe acute inflammation of the liver that could lead to liver failure requiring a liver transplant. HCV may also cause a severe type of acute infection called fibrosing cholestatic HCV, that can cause severe liver injury, jaundice (yellowing of the eyes and skin), and progressive liver dysfunction.

There is a small risk of transmission of HCV from the study subject to intimate partners during sexual activity. This risk is very low and should be reduced even further due to requirements for subjects to use barrier protection during sexual activity.

12.12. Potential Benefits

The results from the study could be applied in the future to subjects (including those in the study) who stand to benefit from the information. Subjects will experience clinical benefits as their lung function and quality of life should vastly improve following transplant. The study involves the risks of phlebotomy, development of chronic HCV, and loss of confidentiality, but there is a potential for future benefit for both subjects in the study and for future subjects, the risk/benefit ratio is favorable.

12.13. Alternatives

The use of the medications for this study requires that certain other medications not be used. Therefore, the alternative is to not participate in this study and to continue having the option to take these medications.

12.14. Ethical Considerations

The main ethical considerations in this trial are non-maleficence, respect for persons, and autonomy. Our selection criteria are designed to select subjects who are at substantial risk of death and health complications because of lung failure. Transplantation with a HCV-positive lung and then treatment for HCV also involve risks, but it is plausible that survival and quality of life will still improve after transplantation compared to the alternative of remaining on the list. Our informed consent procedures are designed to enable individuals to make decisions that are consistent with their values. We will enumerate the many possible risks and plausible benefits. The processes of informed consent in this study will be conducted so that patients can ask questions, confer with their primary cardiologists and develop a full understanding of the trial procedures and risks, all of which is consistent with respect for persons. Lastly, subjects in the trial will retain the ability to consider organ offers and decide whether to accept an organ based on their own judgment about the value of that particular organ and after getting advice from their transplant team.

13 CHAPTER 11: GOOD CLINICAL PRACTICE

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, University of Pennsylvania requirements, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to the FDA and a properly constituted IRB in agreement with local legal prescriptions for formal approval of the study conduct. The principal investigators will not commence the study until the IRB has issued written approval to the PIs.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

14 CHAPTER 12: REFERENCES

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