OPEN-LABELED TRIAL OF ZEPATIER FOR TREATMENT OF HEPATITIS C NEGATIVE PATIENTS WHO RECEIVE HEART TRANSPLANTS FROM HEPATITIS C POSITIVE DONORS (USHER)

Test drug:	**Zepatier**
Clinical study phase:	**II**
Sponsor:	**University of Pennsylvania**
Funder:	**Merck**
IND#	**Exempt**
IRB#	**826708**
NCT#	
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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 Zepatier For Treatment Of Hepatitis C-Negative Patients Who Receive Heart Transplants From Hepatitis C-Positive Donors
Clinical study phase	II
Study objectives	This study is being conducted to determine safety and efficacy of transplanting hearts from HCV virus (HCV)-positive donors into HCV-negative patients on the heart transplant waitlist, who will then be treated with Zepatier status post-single heart transplantation. **Primary aim:** 1. Primary efficacy objective: to determine sustained virologic response (SVR) rates of open-label Zepatier in HCV-negative patients who receive a heart transplant from a genotype 1 or 4 HCV-positive donor, leading to post-transplantation de-novo HCV infection. 2. Primary safety objective: to determine the safety of administration of open-label Zepatier among HCV-negative patients who receive a heart transplant from a genotype 1 or 4 HCV-positive donor and develop post-transplant HCV infection. **Secondary aims:** 3. To determine 1-year graft survival rates of HCV-negative heart transplant patients who receive a heart transplant from a genotype 1 or 4 HCV-positive donor, including those who spontaneously clear HCV (and those who receive open-label Zepatier upon development of de-novo HCV. 4. To evaluate rates of spontaneous clearance of HCV among HCV-negative patients who receive a single heart transplant from a genotype 1 HCV-positive donor.
Indication	Chronic HCV post-heart transplantation
Diagnosis and main criteria for inclusion	*Inclusion criteria* • New York Heart Association (NYHA) Class III or IV CHF refractory to maximal medical therapy (ACE inhibitor, B-blocker, digoxin and diuretics, resynchronization therapy or ICD when applicable) and/or conventional surgery AND/OR Inoperable coronary artery disease with intractable anginal symptoms AND/OR Malignant ventricular arrhythmias unresponsive to medical or surgical therapy • 40-65 years of age • Obtained agreement for participation from the transplant cardiology team • No evident contraindication to liver transplantation other than the underlying cardiac disorder • Able to travel to the University of Pennsylvania for routine post-transplant visits and study visits for a minimum of 6 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-heart transplantation • Able to provide informed consent *Exclusion criteria* • Hepatocellular carcinoma • HIV positive • HCV antibody positive and/or RNA positive • Hepatitis B surface antigen, core antibody, and/or DNA positive • Any other chronic liver disease (excluding non-alcoholic fatty liver disease (NAFLD) with abnormal liver enzymes • Persistently elevated liver transaminases • Congenital heart disease • Fibrosis by liver biopsy or total bilirubin > 2.5 with associated evidence of synthetic dysfunction. • 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 • Waitlisted for a multi-organ transplant • 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. • Chronic bronchitis, chronic obstructive pulmonary disease, inability to stop smoking. • Hematologic: Significant coagulation abnormalities, bleeding diatheses. • Psychosocial: Profound neurocognitive impairment with absence of social support. • Active mental illness or psychosocial instability • Inadequate insurance or financial support for post-transplant care. • Evidence of drug, tobacco or alcohol abuse within the past six months and completion of recommended therapy/services or meets satisfied parameters as indicated by social work staff and/or consult team. • History of chronic non-compliance. • Amyloidosis (restricted to cardiac only, without evidence of extra cardiac involvement) • BMI ≥38 • Active peptic ulcer disease. • Severe malnutrition.

	• Major chronic disabling illness (e.g. lupus, severe arthritis, neurologic diseases, previous stroke with profound residual). • Pulmonary infarction within the past 6 weeks • Severe pulmonary hypertension as evidenced by a fixed pulmonary vascular resistance of greater than 4 Wood units on appropriate medical therapy. • Patient refusal to receive blood products or transfusions during heart transplant surgery. • Severe chronic obstructive pulmonary disease • Current clinical sepsis. • Symptomatic or severe vascular disease. • Chronic Kidney Disease Stage IV, GFR < 30 • History of Mantle radiation. • Asymptomatic renal cell carcinoma <1 year from curative treatment. • Symptomatic renal cell carcinoma <5 years from curative treatment. • Prostate cancer <2 years from curative treatment. • Uterine or cervical cancer <2 years from curative treatment. • Any other cancer other than the above including malignant melanoma, < 5 years from treatment apart from other skin malignancies.
Study design	Open-labelled pilot clinical trial of Zepatier (MK-5172 and MK-8742/Grazoprevir + Elbasvir) in 10 HCV-negative subjects with heart failure receiving a heart transplant from a HCV-positive donor. Eligible subjects will receive a heart transplant from a deceased-donor with genotype 1 or 4 HCV, and then will receive 12 weeks of Zepatier after heart transplantation when infection with HCV is confirmed in these heart transplant recipients. 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. • HCV RNA prior to treatment, on treatment, and 4 and 12 weeks after completing Zepatier.
Type of control	None
Number of subjects	Estimated 10 HCV-negative subjects transplanted with a heart from an HCV-positive 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-heart transplant patients. • Evaluate 1-year heart graft survival in HCV-negative patients who receive a heart transplant from an HCV-positive donor • Determine the rates of spontaneous HCV clearance among HCV-negative patients with heart failure receiving a heart 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 therapy) / (number of subjects treated with Zepatier post-heart transplantation)

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3 ABSTRACT

Since 2006, there has been a 50% increase in the number of adults added to the heart transplant waitlist in the US. Yet the persistent organ donor shortage has led to only a 25% increase in the number of transplants, and a 25% increase in the number of patients removed from the heart transplant waitlist because of death or becoming too sick to transplant, reaching nearly 700 patients in 2015. It has been suggested that the donor supply could be increased by utilizing hearts from older donors or those with more medical co-morbidities, but the increased risk of graft failure prevents their broader use. Despite advances in ventricular assist devices (VADs), which can prolong patient survival and improve quality-of-life, they are not a panacea. Long-term survival is superior for patients receiving a heart transplant, and VADs are not an option for patients with several forms of end-stage heart disease (i.e., arrhythmia disorders). Thus there is a critical need to expand the pool of heart donors in order to save more lives from end-stage heart disease.

We will perform a pilot trial to prove feasibility of knowingly using HCV-positive organs for HCV-negative recipients, by transplanting 10 HCV-negative subjects with hearts from HCV-positive donors, and then treating these subjects' with Zepatier 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 10 HCV-negative subjects who receive a heart transplant from an HCV-positive donor, develop HCV, and are then treated for their HCV with Zepatier.

4 CHAPTER 1: BACKGROUND AND SIGNIFICANCE

4.1. Background

Since 2006, there has been a 50% increase in the number of adults added to the heart transplant waitlist in the US. Yet the persistent organ donor shortage has led to only a 25% increase in the number of transplants, and a 25% increase in the number of patients removed from the heart transplant waitlist because of death or becoming too sick to transplant, reaching nearly 700 patients in 2015. It has been suggested that the donor supply could be increased by utilizing hearts from older donors or those with more medical co-morbidities, but the increased risk of graft failure prevents their broader use. Despite advances in ventricular assist devices (VADs), which can prolong patient survival and improve quality-of-life, they are not a panacea. Long-term survival is superior for patients receiving a heart transplant, and VADs are not an option for patients with several forms of end-stage heart disease (i.e., right ventricular dysfunction, hypertrophic cardiomyopathy). Thus there is a critical need to expand the pool of heart donors in order to save more lives from end-stage heart disease. The current treatment paradigm of HCV has evolved to the point that we should reconsider transplanting hearts from HCV-positive donors into HCV-negative patients in order to greatly increase the number of lifesaving heart transplants. The potential for liver disease and coronary vasculopathy, coupled with logistical and ethical intricacies of transplanting hearts 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 and de-novo coronary vasculopathy.

We expect that there will be a high degree of willingness of carefully selected, HCV-negative heart 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 hearts 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 cardiac 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. These capture two broad groups of patients: 1) patients with end-stage systolic heart failure with lower probabilities of transplant, and higher risk of waitlist mortality; and 2) patients with arrhythmia disorders, as these patients don't receive the highest priority (status 1a) because inotropic support may lead to worsened arrhythmias and/or LVAD support may not ease the arrhythmic burden. With respect to group 1, as one example, patients with blood group O have known longer waiting times and lower transplant rates—from 2005-2014, there were 29,488 adults added to the heart transplant waitlist in the US, with significantly higher risks of waitlist removal for death or clinical deterioration and lower transplant rates in patients with blood group O who were "bigger": a) Blood group O, height ≥6 feet, weight <100kg: 56.8% transplanted, 17.4% died/too sick; b) Blood group O, height <6 feet, weight ≥100kg: 43.2% transplanted, 22.2% died/too sick; c) Blood group O, height ≥6 feet, weight ≥100kg: 42.2% transplanted, 21.3% died/too sick; d) all other patients on waitlist: 65.3% transplanted, 14.4% died/too sick.

These discrepancies are even more pronounced in certain parts of the country; for example, in UNOS region 2 (PA, MD, WV, DE, and NJ), 41.1%-56.5% of blood group O patients who are ≥6 feet and/or ≥100kg are transplanted, as compared to 70.5% of all other patients on the waitlist during this time period.

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 10 HCV-negative subjects with hearts from HCV-positive donors, and then treating these subjects with Zepatier in the early post-transplant phase in order to cure their HCV.

4.3. Zepatier

Open-label Zepatier (grazoprevir 100 mg and elbasvir 50 mg) will be administered in this study.[3,4] 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.[3,4]

Zepatier has been evaluated globally in multiple phase I, II, and III trials to treat HCV.[3,4] 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.[3,4]

Headaches, fatigue, and nausea represent the most common adverse drug reactions with Zepatier.[3,4] Other drug-related adverse events have included arthralgia, insomnia, diarrhea, dizziness, pyrexia, and asthenia.[3,4] 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 heart 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.[8]

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.[3,4]

All donor hearts in this trial will come from confirmed genotype 1 or 4 HCV-positive donors. Genotype will be confirmed by the standard of care diagnostic test at the Hospital of the University of Pennsylvania.

5 CHAPTER 2: OBJECTIVES AND SPECIFIC AIMS

5.1. Objectives

This study is being conducted to determine safety and efficacy of transplanting hearts from genotype 1 or 4 HCV-positive donors into HCV-negative patients on the heart transplant waitlist, who will then be treated with Zepatier post-transplantation.

5.2. Specific aims

Primary aim:

1. Primary efficacy objective: To determine sustained virologic response (SVR) rates of open-label Zepatier in hepatitis C virus (HCV) negative patients who receive a heart transplant from a genotype 1 or 4 HCV-positive donor, leading to post-transplantation de-novo HCV infection.

2. Primary safety objective: To determine the safety of administration of open-label Zepatier among HCV-negative patients who receive a heart transplant from a genotype 1 or 4 HCV-positive donor and develop post-transplant HCV infection.

Secondary aim:

1. To determine 1-year graft survival rates of HCV-negative heart transplant patients who receive a heart transplant from a genotype 1 or 4 HCV-positive donor, including those who spontaneously clear HCV and those who receive open-label Zepatier upon development of de-novo HCV.

2. To obtain preliminary data on the distribution of changes in circulating biomarkers of endothelial damage and coronary vasculopathy in HCV-negative patients transplanted with hearts from HCV-positive donors prior to HCV treatment, after viral clearance, and after SVR.

3. To evaluate rates of spontaneous clearance of HCV among HCV-negative patients who receive a heart transplant from a genotype 1 or 4 HCV-positive donor.

4. To identify the viral reservoirs leading to HCV transmission in HCV-negative patients receiving a heart transplant from a HCV-positive donor based on endomyocardial biopsies, measures of HCV antigens in peripheral mononuclear blood cells, and histological examination of arterial and venous tissue surrounding the transplanted heart.

5. To compare the quality-of-life of HCV-negative patients receiving a heart transplant from a HCV-positive donor to those of similar patients remaining on the waitlist for a standard deceased donor heart 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 heart has been received and transplanted.

We will approach patients meeting the above criteria to receive a heart 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 apart 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 heart 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 heart from an HCV-positive donor.

We expect to screen 200 subjects, including patients being newly evaluated for a heart transplant, and those that are already on the waitlist. Of these, we expect 100 to meet inclusion/exclusion criteria, of whom 35 will consent to be screened, and 25 will remain eligible following all screening tests.

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 heart 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 eligible for a liver transplant if HCV caused them to experience liver failure will be enrolled in this study. To be deemed eligible for a liver transplant at Penn, all patients (not only study subjects) must be examined by both a hepatologist and a liver transplant surgeon.

6.2. Subject selection criteria

6.2.1. Inclusion criteria

- New York Heart Association (NYHA) Class III or IV CHF refractory to maximal medical therapy (ACE inhibitor, B-blocker, digoxin and diuretics, resynchronization therapy or ICD when applicable) and/or conventional surgery AND/OR Inoperable coronary artery disease with intractable anginal symptoms AND/OR Malignant ventricular arrhythmias unresponsive to medical or surgical therapy
- 40-65 years of age
- Obtained agreement for participation from the transplant cardiology team
- No evident contraindication to liver transplantation other than the underlying cardiac disorder

- Able to travel to the University of Pennsylvania for routine post-transplant visits and study visits for a minimum of 6 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-heart transplantation
- Able to provide informed consent

6.2.2. Exclusion criteria

- Hepatocellular carcinoma
- HIV positive
- HCV antibody positive and/or RNA positive
- Hepatitis B surface antigen, core antibody, and/or DNA positive
- Any other chronic liver disease (excluding non-alcoholic fatty liver disease (NAFLD) with abnormal liver enzymes
- Persistently elevated liver transaminases
- Congenital heart disease
- Fibrosis by liver biopsy or total bilirubin > 2.5 with associated evidence of synthetic dysfunction.
- 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
- Waitlisted for a multi-organ transplant
- 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.
- Chronic bronchitis, chronic obstructive pulmonary disease, inability to stop smoking.
- Hematologic: Significant coagulation abnormalities, bleeding diatheses.
- Psychosocial: Profound neurocognitive impairment with absence of social support.
- Active mental illness or psychosocial instability
- Inadequate insurance or financial support for post-transplant care.
- Evidence of drug, tobacco or alcohol abuse within the past six months and completion of recommended therapy/services or meets satisfied parameters as indicated by social work staff and/or consult team.
- History of chronic non-compliance.
- Amyloidosis (restricted to cardiac only, without evidence of extra cardiac involvement)
- BMI ≥38
- Active peptic ulcer disease.
- Severe malnutrition.
- Major chronic disabling illness (e.g. lupus, severe arthritis, neurologic diseases, previous stroke with profound residual).
- Pulmonary infarction within the past 6 weeks

- Severe pulmonary hypertension as evidenced by a fixed pulmonary vascular resistance of greater than 4 Wood units on appropriate medical therapy.
- Patient refusal to receive blood products or transfusions during heart transplant surgery.
- Severe chronic obstructive pulmonary disease
- Current clinical sepsis.
- Symptomatic or severe vascular disease.
- Chronic Kidney Disease Stage IV, GFR < 30
- History of Mantle radiation.
- Asymptomatic renal cell carcinoma <1 year from curative treatment.
- Symptomatic renal cell carcinoma <5 years from curative treatment.
- Prostate cancer <2 years from curative treatment.
- Uterine or cervical cancer <2 years from curative treatment.
- Any other cancer other than the above including malignant melanoma, < 5 years from treatment apart from other skin malignancies.

6.3. Donor Organ Selection Criteria

General criteria (although there can be exceptions on a case-by-case basis)

- Detectable HCV RNA
- Genotype 1 or 4 HCV
- Age <=55 years
- No history of coronary artery disease
- No congenital heart disease except a repaired atrial septal defect (ASD) provided the patient has normal right ventricular function
- No history of arrhythmia (atrial fibrllation, atrial flutter or VT) except during resuscitation from fatal event.
- No evidence of cirrhosis

Echocardiographic criteria

- Left ventricular ejection fraction (LVEF) >=50%
- Normal right ventricular function
- No left ventricular hypertrophy (LVH) – septal wall thickness <1 cm
- No left ventricular hypertrophy (LVH)– posterior wall thickness <1 cm
- No significant valvular heart disease – more than mild tricuspid regurgitation, more than mild mitral regurgitation, more than trace aortic regurgitation. No mitral or aortic stenosis.
- No congenital heart disease – transposition of the great vessels, ventricular sepatal defect (VSD), ASD, and/or single ventricle (Fontan)

Right heart catheterization criteria

- Right atrial pressure <=10mmHg
- Pulmonary capillary wedge pressure <=18mmHg
- CI >=2.1 l/min/m2
- Pulmonary hypertension is allowed if the patient has normal right ventricular function and a normal tricuspid valve

6.3.1. Donor Genotyping

We will ensure that subjects only receive a heart transplant from a confirmed Genotype 1 or 4 HCV-positive donor by testing the HCV genotype using the standard of care assay at the Hospital of the University of Pennsylvania.

To briefly outline this procedure, 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 heart 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, only if and after the donor's authorizing next-of-kin has given authorization for donation and research. The Molecular Pathology Laboratory (MPL) at the Hospital of the University of Pennsylvania (HUP) will then determine the HCV genotype(s) present in the specimen. Once resulted, a printed copy will be sent to Gift-of-Life and the study investigators, and will be kept in the locked research file by the study investigators.

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.[9] 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%).[10-12] 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).

6.3.2. Drug Resistance Testing

Participants with Genotype 1a and Genotype 1 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.13 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)

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 heart 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 patient with significant renal dysfunction. As a result, if a subject's heart function has not fully recovered when treatment is initiated, the investigational agents can safely be administered, unlike other approved agents.

7.1.1. Administration of study medication

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 the study drug. 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.

7.1.2. 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.

7.1.3. 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.

7.1.4. 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 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 heart transplantation. Prior to initiating treatment with this regimen, patients will have serum NS5A resistance (RAV) testing.

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.

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
- 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-Heart Transplant

8.1.3.1. Post-Heart Transplant Visits

Patients, after receiving a heart transplant are followed very closely by both the surgical and nephrology team. As apart 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 apart 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-Heart 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-Heart Transplant (day 3 ± 1)

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

Initiating treatment with Zepatier

Treatment with the study drug will begin when the patient has a detectable and quantifiable HCV RNA post-transplantation. All subjects will be provided with a 28-day supply of the study drug and instructed to begin treatment once HCV RNA is confirmed, which may occur any time between weeks 1-4. When the subject begins treatment for HCV with Zepatier, the staff will notify the subject's primary cardiologist and primary care physician.

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 (See Section 8.2.1 for complete list)
- Dispense study drugs

Blood samples for immunologic t-cell assays will be processed and banked or shipped.

8.1.3.3.1. Management of patients with NS5A resistance variants

Once HCV infection is confirmed, patients will have their HCV genotype reconfirmed. 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 and LFTs will be closely monitored. HBV therapy may be considered the transplant team as medically appropriate.

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

Visit #2 should occur two weeks (10 ± 2 days) after the subject's heart 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.

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 drug diary assessed for adherence
- Schedule appointments for follow-up visits

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

Visit #3 should occur three weeks (21 ± 3 days) after the patient's heart 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.

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 drug diary assessed for adherence
- Schedule appointments for follow-up visits

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

Visit #4 should occur 4 weeks (28 ± 2 days) after the subject's heart 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.

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)
- Health Status Questionnaire (RAND-36) (to assess changes in health status from pre- to post-transplant)
- Pill count and drug diary assessed for adherence

- Replenish study drug
- 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-heart 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-Heart Transplant (day 42±7, day 56±7, day 70±7)

Visit #5 should occur 6 weeks (42±7 days) after the subject's heart 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 heart 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 heart 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.

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 drug diary assessed for adherence
- Schedule appointments for follow-up visits

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

8.1.3.8. Visits 8 & 9: Post-Heart Transplant (day 87 + 7, day 115 + 14)

Visit #8 should occur 12 weeks (87 + 7 days) after the subject's heart transplant and will coincide with the subject's regularly scheduled post-transplant follow-up visit**.** Visit #9 should occur 16 weeks (115 + 14 days) after the subject's heart 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.

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.
- Health Status Questionnaire (RAND-36) (to assess changes in health status from pre- to post-transplant)
- Pill count and drug diary assessed for adherence
- Replenish study drug
    - Note: The staff will replenish the subject's supply of the Zepatier study drug 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-Heart Transplant (day 171 ±7 days)

Visit #10 should occur 24 weeks (171 ±7 days) after the subject's heart 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.

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.
- Health Status Questionnaire (RAND-36) (to assess changes in health status from pre- to post-transplant)

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

Visit #10 should occur 52 weeks (365 ±14 days) after the subject's heart 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.

The following procedures and activities must be performed:

- Assess for Adverse Events
- Research Phlebotomy (See Section 8.2.1 for complete list)
- 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 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.

8.1.4. Future research

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**	**RAND-36 Health Status Questionnaire**	**HBV DNA HIV AB & LFTs**	**HBV Core Antibody**	**Urine Preg Test**	**Urine Protien/Cre Ratio**	**HCV RNA**	**Viral Kinetics (optional)♦**	**NS5A Resistance**	**Genotyping**	**Vitals & Physical Exam**	**Surveillance biopsy**	**CMP***	**CBC**	**Tacrolimus**
Screening					✓	✓	✓	✓	✓	✓	✓		✓				✓				
1 (Begin treatment)	**3 ± 1 day**	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 ♦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	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

♦ There may 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 administered to HCV-negative patients with heart failure who receive a heart transplant from a genotype 1 or 4 HCV-positive 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).

9.2. Secondary Outcome Measures

- To determine safety of administering Zepatier to heart transplant recipients who were previously HCV-negative, but developed de-novo HCV after receiving a heart transplant from an HCV-positive donor
- To determine 1-year graft survival rates of HCV-negative heart transplant patients who receive a heart transplant from a genotype 1 or 4 HCV-positive donor, including those who spontaneously clear HCV and those who receive open-label Zepatier upon development of de-novo HCV.
- To evaluate rates of spontaneous clearance of HCV among HCV-negative patients who receive a heart transplant from a genotype 1 or 4 HCV-positive 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 heart transplant from an HCV-positive donor among HCV-negative subjects with heart failure, and adverse events related to administration of Zepatier.

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 heart transplant from a confirmed genotype 1 or 4 HCV-positive 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 Zepatier therapy, after which time, treatment will be complete, barring instances of treatment failure, which would require an additional 12 weeks 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 heart transplant recipients who receive a heart from an HCV-positive 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 heart 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 heart from a hepatitis C-positive donor. The costs of all visits and tests described above will be billed to the insurance carrier, except for 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 the study drug, which will be paid for by Merck. 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).

12.4.5. IL28B Genotype Testing

At the time of the subject's heart transplant, both donor and recipient will have one tube of blood drawn to be used for IL28B Genotype Testing. Donors' families will have already agreed to this test when they consent to research testing. Recipients must sign an additional consent form before this test is performed.

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. 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.

12.7. Safety and Adverse Events

12.7.1. 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.

12.7.2. Classifying Adverse Events

Severity

The intensity of the AE is classified according to the CTCAEv4.0.[14] 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.

12.7.3. 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 heart transplant waitlist),
   4. Patient is made inactive on the transplant waitlist,
   5. Patient is transplanted with a non-HCV heart.

   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 heart offer and/or heart 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.

12.7.4. 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

12.7.4.1. 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.

12.8. 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.
- 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.
- 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.

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).

12.9. 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.

12.10. Potential Risks

12.10.1. 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 heart transplantation based on the results.

The risks of heart 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 heart 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 heart 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.

12.10.2. Risk of Genotyping Failure

There is a risk of failure of the Genotyping LDT in that no result is obtained. However, the risk to the recipient participant, in this event, is that they would not receive the transplant. Hence, the related risk is losing the opportunity to use the organ. Failure of the LDT could be due to an instrument or cartridge failure or issues with the sample (e.g., the sample contains a very low level of virus). To minimize the study impact of a failed cartridge, the HUP Molecular Pathology Laboratory will run the study samples in duplicate due to there not being enough time to repeat the test (as would be done with a sample in clinical care). The duplicate sample

testing will serve to provide additional confirmation of the result because the RNA extraction will be performed twice. Thus, confirmation testing will be performed on every sample in the study with a single result generated.

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.

12.10.3. 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.

12.10.4. 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. [15-17]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.[15-17] 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.[18]

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.[19]

12.10.5. 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.

12.11. 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 heart 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.

12.12. 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.

12.13. 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 heart failure. Transplantation with a HCV-positive heart 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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