Kidney Transplants in Hepatitis C Negative Recipients With Hepatitis C Viremic Donors

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JHM IRB - eForm A – Protocol

Kidney transplants in hepatitis C negative recipients with hepatitis C viremic donors. An open-label, non-randomized pilot study to determine the safety and efficacy of two weeks of fixed-dose glecaprevir and pibrentasvir as pre- and post-exposure prophylactic therapy.

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1. Abstract

Due to an organ shortage crisis, many individuals with end-stage renal disease will die or become too sick to undergo transplantation before receiving a kidney transplant. At the same time, many high quality kidneys from hepatitis C infected (HCV+) donors are discarded every year because there is no HCV+ waitlist candidate available to accept the organ. New HCV therapies are highly effective and well tolerated, with cure rates of nearly 100%. This study is a single center, open-label, pilot interventional trial of glecaprevir/pibrentasvir for 10 HCV- nonviremic recipients of kidneys from HCV-infected deceased donors at Johns Hopkins Hospital (JHH).

The primary hypothesis is that prophylactic treatment with glecaprevir/pibrentasvir before and after transplant will prevent the establishment of HCV infection in the recipients of kidneys from HCV-infected deceased donors. The safety hypothesis is that grade 3-4 AE related to G-P will occur in ≤ 10% of participants. Based on the success of preliminary studies, the objective of this study is to evaluate the safety and efficacy of two weeks of glecaprevir/pibrentasvir as prophylactic therapy for HCV D+/R- kidney transplantation.

2. Objectives

Primary objectives:
The primary objectives of this study are to evaluate the safety and efficacy of glecaprevir 300 mg/pibrentasvir 120 mg (G-P) treatment in HCV-nonviremic transplant recipients (HCV R-) of a kidney from an HCV-infected deceased donor (HCV D+). G-P will be administered on-call to the operating room (OR) for the kidney transplant procedure and continued for 2 weeks after the kidney transplant.

- The primary efficacy outcome will be the proportion of HCV D+/R- renal transplant recipients with undetectable HCV plasma RNA at 12 weeks after treatment (14 weeks after kidney transplant).
- The primary safety outcome will be the incidence of adverse events (AE) related to G-P.

Secondary outcomes:

- Proportion of kidney transplant recipients who have undetectable HCV plasma RNA at 1, 2, 4 and 12 weeks after discontinuation of therapy.
- Proportion of kidney transplant recipients who become reactive for HCV antibodies following transplant.
- Kidney allograft function at 6 and 12 months and 24 months following transplantation, including creatinine, glomerular filtration rate and assessment of protein in the urine.

3. Background

As of March 20, 2020, there are 94,874 individuals awaiting a life-saving kidney transplant in the United States; however, due to a shortage of donor organs, only 23,400 kidney transplants were performed in 2019 [1]. Waiting times in the United States for a kidney transplant average 5 years and up to half of all individuals on the waiting list will die or become too sick to undergo the procedure. Mortality on the kidney transplant waiting list is 6% per year with significant variation depending on patient characteristics and the geographic location where the patient lives. The death rate on the kidney waiting list for older individuals and for individuals with diabetes is approximately 10% per year. Therefore, a patient over 60 years of age with an estimated waitlist time of five years for a kidney has a 50% chance of death before a kidney becomes available [2,3].

Kidneys from hepatitis C-infected (HCV+) donors are currently underutilized. From 2014-16, over 40% of kidneys from HCV+ deceased donors were discarded, compared to 18% of kidneys from HCV-uninfected (HCV-) donors. Many of these HCV+ organs are of excellent quality, but are frequently discarded due to a lack of hepatitis C-infected waitlist candidates [4].

One strategy to expand the kidney donor pool is to transplant HCV+ donor kidneys into HCV- recipients (HCV D+/R- transplant) in combination with direct-acting antivirals (DAAs) to treat HCV. In 2016, we performed the first study in the world using this strategy at Hopkins (EXPANDER: An open-label study to determine the efficacy and safety of fixed-dose grazoprevir/elbasvir treatment in hepatitis C uninfected recipients of renal transplants from hepatitis C infected deceased donors. IRB 00089751; NCT# 02781649). This study was a pilot trial of this approach in 10 HCV-uninfected kidney transplant recipients using DAAs as pre- and post-transplant prophylaxis. Depending on the donor HCV genotype, the DAAs grazoprevir/elbasvir with or without sofosbuvir were used. In this trial, HCV- recipients were given the first dose of DAAs just prior to the transplant procedure and were subsequently treated with standard treatment durations of 12-16 weeks (depending on donor HCV genotype) of DAAs after transplant. The length of DAA therapy was based on the kidney donor's HCV genotype. Ten HCV D+/R- transplants were performed at Johns Hopkins and this approach was successful in preventing chronic hepatitis C infection in all 10 recipients. The DAAs were well tolerated and there were no grade 3 or grade 4 serious adverse events noted [5].

In addition to the study described above, a similar study at the University of Pennsylvania treated 10 HCV negative participants receiving an HCV+ donor kidney with elbasvir-grazoprevir for 12 weeks and reported SVR in all 10 participants at week 12 post treatment [6]. In contrast to the Hopkins EXPANDER study where a prophylactic strategy was used to treat donor-derived hepatitis C infection in recipients, the Penn study used a pre-emptive approach, waiting for recipients to have detectable HCV RNA in the blood prior to initiating DAA therapy. In that trial, 10/10 patients had detectable HCV RNA in peripheral blood by day 3. All patients were cured with 12 weeks of DAA therapy [6].

An important finding in the EXPANDER study was the short duration and low level of viremia observed in transplant recipients when DAA treatment was initiated just prior to the transplant procedure. In contrast, the U Penn group observed much higher levels of persistent hepatitis C viremia in their study where DAA therapy was delayed for several days. We hypothesized that shorter duration DAA therapy would be successful and tested this hypothesis in a recently completed study (Renal transplants in hepatitis C negative recipients with nucleic acid positive donors, IRB00174409; NCT#03627299). In this study we used the once daily, fixed-dose combination of the NS3/4A protease inhibitor glecaprevir

(G) and the NS5A inhibitor pibrentasvir (P) as the DAA. This medication was newly approved for the treatment of all hepatitis C genotypes (1-6) and is not metabolized by the kidneys. Thus, it was felt to be the best regimen to use as pre- and post-exposure prophylaxis in the early post-kidney transplant period [7].

In this recently completed study with 4 weeks of DAA treatment, all ten recipients completed 4 weeks of G-P following transplantation as well as 12 weeks of follow-up after completing DAA therapy. All 10 patients cleared hepatitis C and remained HCV negative throughout the follow-up period. All 10 patients had excellent kidney graft function through 6 months of follow-up; however, one patient did lose kidney transplant function approximately 8 months after transplantation due to a late renal vein thrombosis that was unrelated to hepatitis C or to DAA treatment. Of note, only 5 of 10 recipients showed any evidence of hepatitis C viremia during the early post-op period and the highest quantifiable viral loads observed were on postoperative day 1 in three patients (post-operative day 1 hepatitis C viral loads: 161, 153, and 87 IU/ml). All recipients were clear of hepatitis C after the first week following transplantation [8].

Based on the success of these preliminary studies, the objective of our current study is to evaluate the safety and efficacy of two weeks of glecaprevir/pibrentasvir as prophylaxis for HCV D+/R- kidney transplantation.

4. Study Procedures

This is a single center, open-label, pilot trial of glecaprevir/pibrentasvir for 10 HCV- nonviremic recipients (R-) of kidneys from HCV-infected deceased donors (HCV D+) at Johns Hopkins Hospital (JHH). Individuals who meet the inclusion criteria will be offered enrollment. Informed consent will be obtained by a physician on the study team and those who provide informed consent will be enrolled. All participants will be initiated on oral, once-daily, fixed-dose G-P starting on call to the operating room for the kidney transplant.

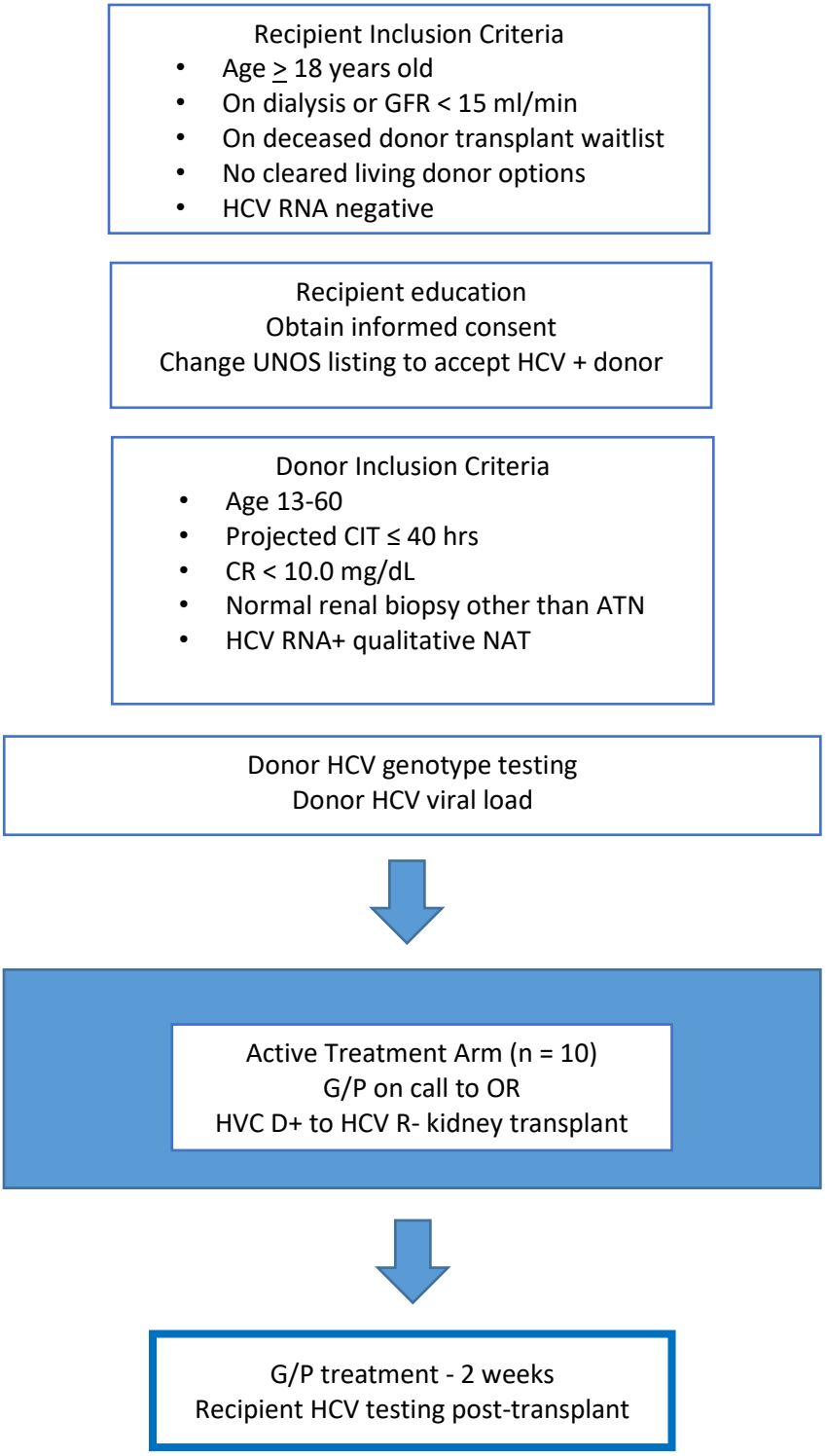
Screening Phase: HCV RNA negative individuals on the kidney transplant waiting list at Johns Hopkins Hospital (JHH) will be recruited and screened for eligibility. Individuals who are interested in the study will give informed consent. We will approach HCV negative individuals on the deceased donor kidney transplant waitlist who meet the recipient inclusion criteria. Currently there are over 500 individuals meeting these criteria at JHH. At JHH, approximately 50% of current waitlist candidates will accept Infectious Risk Donors (IRDs). We anticipate a lower acceptance rate of HCV+ deceased donors and estimate a 20% participation rate. Thus, we estimate having a pool of at least 50 eligible screened participants and our consenting target is 25, with 10 subjects enrolled and transplanted. Once a patient signs a consent form, a unique baseline number will be assigned for identification purposes. Prior to transplantation, data on demographics (age, sex, race, etc.), medical history, social history, and renal biopsy diagnosis (when available) will be collected.

We estimate 2 months for screening and consenting a pool of 20 eligible patients. At JH the approximate wait time for an HCV+ deceased donor is approximately 6 months. Therefore, we anticipate an average of one HCV D+/R- transplant per month, with an accrual period of 12 months. Total study duration will therefore be 24 months.

Accrual Objective: 10 participants **Accrual Period:** 12 months **Total Study Duration:** 24 months
Long-term follow-up at 2-years: 24 months

HCV+ Donor Identification: Those who provide informed consent for the study will be listed in the United Network for Organ Sharing (UNOS) with a status of "willing to accept an HCV+ organ". The JHH transplant team will then receive HCV+ donor kidney offers for the study participant from Organ Procurement Organizations (OPOs). If an HCV+ donor who meets the inclusion criteria is identified, the study participants will be offered the organ and, if they accept, they will become an active treatment participant. A donor blood sample will be obtained from the OPO for the purposes of this study. Currently, offering OPOs only perform a qualitative HCV RNA by nucleic acid testing. HCV quantification and genotyping are not performed on donors, and no FDA approved assays exist for this indication in organ donors. Donor HCV RNA quantification and HCV genotyping will be performed in parallel with the transplantation and initiation of treatment. The OPO will ship a donor blood sample to JHH for HCV genotyping and HCV RNA quantification. Plasma will be banked for future resistance testing if needed.

Screening, enrollment and treatment (Figure 1)



Active Phase, Transplant and Treatment: At the time of transplant admission, the kidney recipient will undergo the standard pre-operative work-up, including laboratory testing, chest X-ray, EKG, and urinalysis (if applicable). In addition, a sample for baseline HCV serology will be drawn if not performed within the past 12 months. Donor and recipient crossmatch will be performed using T cell and B cell complement-dependent cytotoxicity crossmatch. In addition, quantitative assessment for the presence of donor specific antibody will be performed by solid phase assay (Luminex) and confirmed to be below a flow positive level. Once a recipient is deemed appropriate to undergo the kidney transplant procedure and the HCV+ donor organ has been examined and found to be acceptable for transplant, the recipient will be called to the operating room. The initial dose of G-P will be administered to the recipient when called to the operating room (see treatment strategy below).

The deceased donor kidney transplant procedure will be performed in the standard manner under general anesthesia with appropriate monitoring lines. Intraoperative medications will include intravenous cefazolin, heparin, mannitol, and furosemide. Anesthetic medications include inhalational agents, muscle relaxant, and narcotic pain medication. Other standard medications will be administered as well. Induction immunosuppression administered in the operating room will consist of intravenous Solumedrol (500 mg) and intravenous rabbit anti-thymocyte globulin (1.5 mg/kg) (Thymoglobulin, Genzyme). During the transplant operation, a surgical drain(s), ureteral stent, and urinary catheter will be placed.

Postoperative care will be performed in the standard manner in a monitored, step-down intensive care unit setting. Ongoing induction immunosuppression with daily Solumedrol and Thymoglobulin for three post-operative doses each will be administered per JHH protocol. In addition, maintenance immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and prednisone will be initiated. Tacrolimus dosing will be adjusted to obtain a serum trough concentration between 7-10 ng/ml for the first three months postoperatively and then 6-8 ng/ml beyond three months. Mycophenolate mofetil will be administered in divided doses for a total dose of 1000-2000 mg daily. Prednisone will be initiated at a dose of 20 mg daily once the initial course of Solumedrol is completed and gradually tapered to 5 mg daily by 6-12 weeks.

Standard post-transplant prophylaxis strategies will be used in subjects for the prevention of opportunistic infections. These include trimethoprim-sulfamethoxazole (Bactrim) for pneumocystis pneumonia prophylaxis, valganciclovir for cytomegalovirus infection in cases of CMV seropositive donors and/or recipients, and fluconazole for fungal prophylaxis.

Additional postoperative care will be performed in the standard manner and include intravenous fluids to replace urine output for the first 24 hours postoperatively. Early mobilization and ambulation will be encouraged. Diet advancement will start with clear liquids several hours after surgery and progress to a regular diet by approximately 24 hours after surgery. The urinary catheter will remain in place for 3-7 days after surgery, depending on the condition of the patient's bladder at the time of the transplant operation. Surgical drain(s) placed at the time of the transplant procedure remain(s) in place until daily output is below 50 ml per day. The ureteral stent is removed by cystoscopy approximately 4-8 weeks after surgery.

Discharge from the hospital is typically between 5 and 10 days postoperatively, once renal transplant function is established, the patient is tolerating a regular diet, having normal bowel and bladder function, and has a satisfactory understanding of post-transplant care. During the hospitalization, teaching of

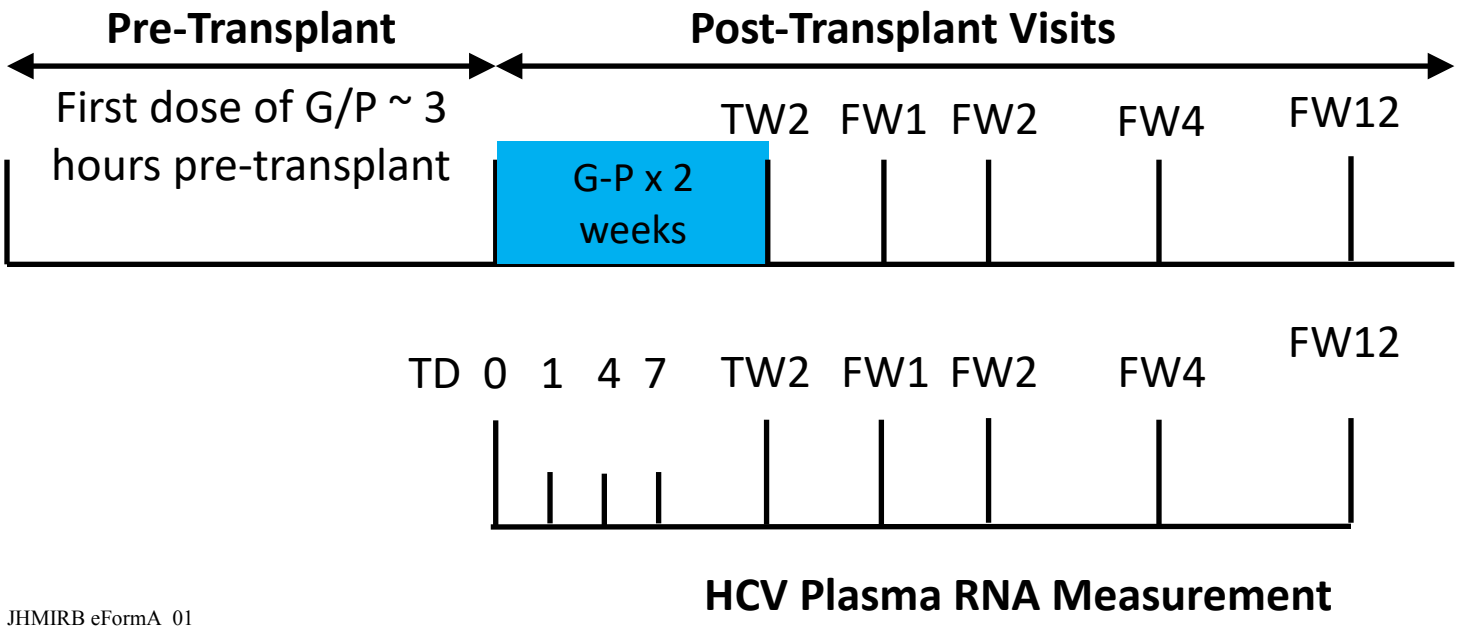
transplant medications and planned follow-up will occur on several occasions. Included in this teaching will be the medication and follow-up labs and visits related to the study protocol.

Treatment Strategy: The study participant will be admitted to the hospital and undergo standard recipient admission work-up. Once this work-up is completed, crossmatch results are available, and relevant donor kidney information is available (including examination of the kidney in the operating room to confirm anatomic suitability for transplantation), the first dose of G-P will be administered when the recipient is called to the operating room (typically 1-3 hours prior to start of surgery). Post-transplant, G-P will be continued daily at 10 AM to correspond with the inpatient daily dosing nurse medication administration. To ensure timely delivery daily at 10 AM, the first dose post-operatively may occur before, but not after, 36 hours. For example, if the participant received the first dose pre-transplant at 2:00 PM, the second dose will take place 20 hours later on post-operative day #1 at 10:00 AM. Most renal transplant recipients are extubated in the operating room and able to take oral medications within eight hours after the transplant procedure. During the hospitalization, G-P will be given once daily.

Visit Schedule: Study visits will occur at days 0, 1, 4, 7, treatment week 2, and follow-up weeks (FW) 1, 2, 4 and 12 for all participants. Post-transplant data collection will include the laboratory data indicated in the Schedule of Events (Table 1). We will also collect immunosuppression regimen, tacrolimus trough, creatinine level, acquisition of opportunistic infections, graft survival and patient survival. Allograft biopsies will be performed if there is concern for rejection or other causes of graft dysfunction. Allograft biopsies will be classified by the Banff criteria.

Year 2 Long-Term Follow-Up: As of August 18, 2022, all 10 subjects were accrued and completed the 1-year study. The study team proposes a minimal risk long-term follow-up in order to capture survival, rejection, graft failure, and eGFR data from the EMR at 2-years post-transplant. We will call previously enrolled subjects that consented for Future Contact to gauge their interest and obtain oral consent for the collection and use of their health information through the 24 month timepoint. No procedures are involved; chart review only. We will use an oral consent script.

Treatment and follow-up strategy (Figure 2)



TD = treatment day, TW = treatment week, FW = follow-up week

Schedule of Events (Table 1)

	Baseline	POD 1, 4, 7	TW 2	FW 1	FW 2	FW 4	FW 12
Donor HCV genotype[a]	X						
Donor HCV quant RNA[b]	X						
Recipient HCV RNA[b]	X	X	X	X	X	X	X
Recipient HCV Serology[c]	X						X
Recipient Hematology[d]	X	X	X	X	X	X	X
Recipient Chemistry[e]	X	X	X	X	X	X	X
Recipient Physical exam	X		X		X	X	X

POD post-operative day; TW treatment week; FW follow up week
[a]HCV genotype and subtype will be determined
[b]HCV RNA will be measured using an FDA approved assay in a CLIA certified lab.
[c]HCV antibody testing using an FDA approved assay in a CLIA certified lab.
[d]Hematocrit, Hemoglobin, platelet count, red blood cell count, white blood cell count– standard of care
[e]Alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, creatinine, total bilirubin, glucose, potassium, and sodium– standard of care

Adverse Event Reporting: Adverse event reporting will follow the requirements outlined below. Adverse events will also be recorded and tracked in a safety monitoring database by the investigators. Serious adverse events will be reported to the Institutional Review Board at Johns Hopkins University according to IRB guidelines and to the sponsor.

Participants undergoing solid organ transplantation will be expected to have frequent adverse events (AEs) related to the organ transplant surgery and immunosuppressants, which are not the subject of this protocol. This protocol focuses on the use of G-P. Grade 3 and Grade 4 AEs and SAEs related to the use of G-P will be collected.

All Grade 3 or 4 AEs and all SAEs will be reviewed by the principal investigator as they occur in a timely manner. All serious adverse events (SAEs) will be reported to the IRB. Grade 3 or higher AEs that are possibly or definitely related to G-P will be reported to the IRB.

Adverse Event (AE) Definition
Any untoward or unfavorable medical occurrence associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Participants or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with, but not limited to:

1. Worsening (change in nature, severity or frequency) of conditions present at the onset of the study
2. Intercurrent illnesses
3. Infections

4. Abnormal laboratory values (significant shifts from baseline within the range of normal that the investigator considers to be clinically important)
5. Clinically significant abnormalities in physical examination, vital signs, weight, and/or tests and procedures
6. Surgical complications

Serious Adverse Event (SAE) Definition

An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of the investigator, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital anomaly or birth defect
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above

Grading and Attribution of Adverse Events

Grading Criteria:

AEs will be graded according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.
Grade 2 = moderate adverse event.
Grade 3 = severe and undesirable adverse event.
Grade 4 = life-threatening or disabling adverse event.
Grade 5 = death.

Events grade 3 or higher that are possibly or definitely related to study procedures or intervention will be collected on AE case report.

Attribution Definitions:

The relationship, or attribution, of an adverse event to the study intervention or study procedures will initially be determined by the investigator. For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Unrelated: The adverse event is clearly not related; there is insufficient evidence to suggest a causal relationship.

Possibly Related: The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.

Definitely Related: The adverse event is clearly related.

Collection and Recording of Adverse Events

Collection Period

Serious adverse events will be collected from the time of first dose of study medication until a participant completes study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent) or is withdrawn from the study. Grade 3 or higher AEs will be reviewed by the investigator and will be reported if they are possibly or definitely related to the study medication.

Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

1. Observing the participant
2. Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.]
3. Receiving an unsolicited complaint from the participant
4. In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 2.9.3, Grading and Attribution of Adverse Events

Recording Adverse Events

Throughout the study, the investigator will review all grade 3 or higher AEs and if potentially related to a study medication, will report them to the IRB. All SAEs will be reported to the IRB.

Once reported, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent) or is withdrawn from the study, whichever occurs first.

Reporting of Serious Adverse Events and Adverse Events

Adverse Events and Serious Adverse Events Exempt from Reporting:

1. Any AE lower than grade 3

Reporting of Other Safety Information

An investigator shall promptly notify the site IRB when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event

5. Inclusion/Exclusion Criteria

Recipient Inclusion Criteria

1. Participants ≥ 18 years old
2. On the deceased donor kidney waitlist at Johns Hopkins Hospital
3. Awaiting a first or second kidney transplant
4. No cleared living kidney donors

5. On hemodialysis or peritoneal dialysis or stage 5 CKD defined as a glomerular filtration rate <15 ml/min for ≥ past 90 days
6. HCV- nonviremic (by HCV RNA PCR) and without any behavioral risk factors for contracting HCV other than being on hemodialysis
7. Calculated panel reactive anti-HLA antibody (flow cPRA) below 80%

Recipient Exclusion Criteria

1. Plan to receive a multi-organ transplant
2. Plan to receive a dual kidney transplant (including en bloc)
3. Participating in another study that involves an intervention or investigational product
4. Plan to receive a blood type incompatible kidney
5. History of human immunodeficiency (HIV), hepatitis C (HCV), or active hepatitis B (HBV) infection, defined as being on active antiviral treatment for HBV, detectable hepatitis B surface Ag or detectable hepatitis B DNA
6. Unable to safely substitute or discontinue a medication that is contraindicated with the study medication
7. Psychiatric or physical illness that in the opinion of the investigator would make it unsafe to proceed with transplantation or interfere with the ability of the subject to participate in the study

Donor Inclusion Criteria

1. Donor age 13-60 years
2. Donation after brain death or donation after cardiac death donor
3. Projected cold ischemia time of 40 hours or less
4. Terminal creatinine less than 10.0 mg/dL
5. No evidence of significant chronic pathologic findings on pre-implantation biopsy
6. HCV positive by nucleic acid (RNA) testing

6. Drugs/ Substances/ Devices

Co-formulated glecaprevir 300 mg/pibrentasvir 120 mg will be provided by the study, dispensed from the Investigational Drug Service (IDS). The G-P orally will be initiated on call to the operating room for kidney transplantation. Dosing will continue every 24 hours postoperatively through week 2 after transplantation for donors with any genotype of HCV (genotypes 1-6).

Rescue Treatment

With the availability of a pan-genotypic HCV medication that is safe to use with renal dysfunction, we expect all recipients to be adequately treated with G-P. However, we will perform genotyping on the donor blood sample in order to help guide therapy if there is a treatment failure. Based on the results of our initial studies using this strategy (EXPANDER, REHANNA), we expect 70 percent of donors to have genotype 1 and the other 30% to be have genotype 2 or 3.

If a treatment failure were to occur, recipient genotype and mutation analysis would be performed and the most recent AASLD/IDSA HCV treatment guidelines (hcvguidelines.org) would be followed to select the most appropriate regimen to use in any cases of HCV infection. This would be considered clinical care.

7. Study Statistics

A. Primary Outcome Variable:

- The primary outcome will be the proportion of kidney transplant recipients with undetectable plasma HCV RNA at 12 weeks after stopping treatment.

B. Secondary Outcome Variables:

- Detection of HCV antibodies
- Allograft function at 6 and 12 months
- If there are transplant recipients with detectable plasma HCV RNA after treatment or if there is viral breakthrough on treatment, we will measure prevalence of NS3 and NS5A mutations in HCV from the recipient plasma. Mutation testing will be guided by the HCV genotype that is present.

C. Statistical plan including sample size justification and interim data analysis:

The Johns Hopkins group will be responsible for collecting data, maintaining the database, and data analysis. Both our transplant surgery and transplant infectious disease group have extensive experience leading hepatitis C treatment studies and multicenter NIH-funded studies examining outcomes in transplant.

Our Transplant Infectious Disease Group has an active prospective database collecting outcomes, including infectious complications, on the JH cohort of all solid organ transplant recipients. The cohort design facilitates use of standardized outcomes definitions, prospective capture of event-driven data, and collection of information after discharge from the referral center. Expanding on these existing protocols and infrastructure, we will leverage infrastructure and resources from the Department of Surgery clinical research unit and the JH Comprehensive Transplant Center (CTC) for the planned study. Moreover, the JH Transplant and Oncology Infectious Diseases Clinical Research Coordinating Center (Infectious Diseases) has committed support for document development and regulatory support. These groups have staff dedicated to regulatory oversight and development and compliance with reporting requirements and we have successfully collaborated already in generating the preliminary data shown above.

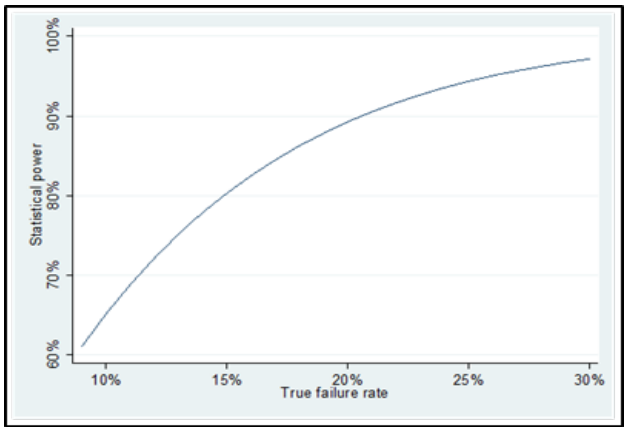
Data Collection Mechanism:

Data collection will be performed using the REDCap electronic data collection and storage hosted by Johns Hopkins University. All data in REDCap will be de-identified. Each site will maintain a record of which subject corresponds to subject numbers assigned by REDCap. This file will be password protected if electronic or kept in a locked location if in the subject binder.

In brief, the REDCap Consortium consists of 84 institutional partners from CTSA, GCRC, RCMI and other institutions, in which JH is an active participant. It was developed by CTSA partners at Vanderbilt, with the goal of enabling investigator research through the establishment of a more user-friendly database system. This consortium supports two secure web-based applications designed to enable data capture for research studies. The software contains an intuitive interface for collecting data with data validation commands, allows for automated export procedures to statistical packages (e.g. SAS) and provides advanced features that allow for branching logic, file uploading, etc. The system itself is supported on MySQL, an open source database similar to SQL/Oracle, and operates on a web-based system. All servers are backed-up at each data center (institution) and include password protection to provide enhanced security while maintaining accessibility via the internet.

Data Monitoring:
Upon enrollment of subjects, the REDCap database constructs a calendar of anticipated events, which includes completion of follow-up case report forms, with electronic reminders

Power/Sample Size:
Figure 4. We hypothesize that the treatment strategy will be 100% effective and that the HCV RNA<LLOQ in all 10 patients. Given that this is a pilot study with no comparison group, the power to detect a difference depends on the true efficacy. For example, if the true efficacy is 79%, then we will have at least one observed outcome 90.53% of the time (1-.79^10). Figure 4 demonstrates the relationship between the true efficacy and the power of the proposed study.



8. Risks

A. Medical Risks:

Although it has not been reported, due to acute infection with hepatitis C, there is a slight risk of acquiring hepatitis C, fulminant hepatitis, and death.

Glecaprevir/Pibrentasvir:
The most common side effects with these drugs are nausea, headache, and fatigue.

Blood Draw:
Taking blood may cause discomfort, bleeding or bruising where the needle enters the body. In rare cases, it may result in fainting. There is a small risk of infection.

Pregnancy: To date there is no adequate human data available to establish whether or not the study drug poses a risk to an embryo or fetus. To ensure patient safety, study treatment must be discontinued and the subject withdrawn if pregnancy occurs while the patient is on study treatment. Women, and men with female partners capable of becoming pregnant, must use effective methods of birth control.

B. Steps taken to minimize the risks:

Medication Side Effects:

Participants will be monitored closely and instructed to report any change in their medical condition promptly. Side effects will be assessed and managed as clinically indicated.

Blood Draw:
Only properly trained clinical staff will draw blood. The amount of blood collected is the minimal amount for proper analysis.

Pregnancy:
Women only:
Women who can get pregnant should not take study drug(s) unless they and their partner do not have intercourse ever or are using 2 methods of birth control for the duration of the study (starting 3 weeks prior to the Day 1 visit) and for a minimum of 6 months after last dose of study drug or longer as directed by your study doctor.

At least one method of birth control must be a condom.

Women who can get pregnant must have a negative pregnancy test at time of admission for transplant, and prior to taking the first dose of study drug.

Female subjects must notify the study team if they become pregnant while in this study and for 6 months after stopping the study drug, or for as long as directed by the study doctor to use contraception. In the event of a positive urine pregnancy result, subjects will be instructed to return to the study clinic as soon as possible for a serum (blood) pregnancy test.

Men only:
If male subjects have a female partner who cannot become pregnant, they must still consistently and correctly use a condom.

If male subjects have a female partner who can become pregnant, subject must use two forms of birth control for the entire study and for a minimum of 6 months after the last dose of study drug.

Male participants must also agree not to donate sperm from the time of first dose of study drug until 6 months after the last dose of study drug.

C. Plan for reporting unanticipated problems or study deviations:

Recording Adverse Events:
Throughout the study, the investigator will review all grade 3 or higher AEs and if potentially related to a study medication, will report them to the IRB. All SAEs will be reported to the IRB. Once reported, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent) or is withdrawn from the study, whichever occurs first.

Reporting of Other Safety Information:
An investigator shall promptly notify the site IRB when an “unanticipated problem involving risks to participants or others” is identified, which is not otherwise reportable as an adverse event.

D. Legal risks such as the risks that would be associated with breach of confidentiality:

The principal legal risk regarding a breach of confidentiality of subjects on this study concerns responsibility for potential retribution by the subject's employer or insurance company to their medical condition and risks associated with this research. A variety of mechanisms have been established to protect the confidentiality of medical records and data procured in this project. Access to the database is controlled through passwords. Access to the work site is controlled through passkeys. Although the study team will maintain a password-protected spreadsheet linking subject numbers to identifiable patient information, any research generated will be completely de-identified for reporting purposes.

E. Financial risks to the participants:
The subject will receive the Insurance and Research Participant Financial Responsibility Information Sheet, which will include the procedures and tests that will be paid for by the study, as well as those billed to the subject's health insurer. If the subject has health insurance, they will be responsible for any co-pays or deductibles not covered by their insurance.

9. Benefits

Participants may receive an organ offer for an HCV-infected organ sooner than if they waited for an HCV-uninfected organ. This may have a survival benefit to the participant.

10. Payment and Remuneration

Study participants will receive either a parking voucher for each outpatient study visit or similar compensation in the form of a gift card. Total compensation for participation in the study will not exceed $50.

11. Costs

Research blood draws and study drug will be paid for by the Department of Surgery (no cost to the participant). All other procedures, test, and drugs are part of standard clinical care for organ transplantation and will be billed to the participant and/or their health insurer.

12. References

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4. Bowring MG, Kucirka LM, Massie AB, et al. Changes in utilization and discard of HCV-antibody positive deceased-donor kidneys in the era of direct-acting antiviral therapy. Transplantation 2018 Dec; 102(12):2088-2095.

5. Durand CM, Bowring MG, Brown DM, et al. Direct-acting antiviral prophylaxis in kidney transplantation from hepatitis C virus-infected donors to noninfected recipients: an open-label nonrandomized trial. Ann Intern Med 2018 Apr 17; 168(8):533-540.

6. Goldberg DS, Abt PL, Blumberg EA, et al. Trail of transplantation of HCV-infected kidneys into uninfected recipients. N Engl J Med 2017; 377(11):1105-1106.

7. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. N Engl J Med 2017; 377(15):1448-55.

8. Durand CM, Barnaba B, Yu S, et al. Four-week direct-acting antiviral prophylaxis for kidney transplantation from hepatitis C-viremic donors for hepatitis C-negative recipients: An open-label non-randomized study. Submitted and under review.