Official title: A proof of concept study of preemptive treatment with grazoprevir and elbasvir for donor HCV positive to recipient HCV negative kidney transplant

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Partners Human Research Committee Detailed Protocol

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT 3

Original Protocol Date:	**11 January 2017**
Amendment 1 Date:	**07 February 2017**
Amendment 2 Date:	**12 June 2017**
Administrative Amendment 1 Date:	**13 July 2017**
Amendment 3 Date:	**20 September 2017**

Rationale	Herein is a summary of the major changes made to the protocol dated 13 July 2017 and reflected in Amendment 2 dated 12 June 2017: • The donor inclusion and exclusion criteria have been simplified. Our goal was to ensure that the donor was high quality. This is best done by setting an upper limit of the KDPI (the kidney donor profile index) at 0.65. We have removed other criteria as they are actually captured in the KDPI (which takes into account age, donation after cardiac death, race, comorbidities, terminal creatinine). • We now allow recipients to be pre-dialysis as long as their GFR is low enough at the screening visit (<15mL/min/1.73m2) to suggest that dialysis is imminent without a transplant. • We have extended the amount of accrued wait-time to 1095 days that a recipient may have if they are blood type B or O (between 5-6years). This is because these blood types have substantially longer wait times than blood type A (between 3-5 years)

	• We have modified the patient education session in response to feedback from our Nephrology Patient Advisory Committee to make the session more patient-friendly • We have increased the total number of subjects that can be screened for this study from 30 to 40 because we have found that so far many of the patients who are screened end up being ineligible for transplant after they undergo "transplant readiness evaluation" by the transplantation unit. This is typically due to medical or psychiatric comorbidities that were not detected at original listing for transplant. Thus we expect to need to screen 40 patients to find 11 that are able to undergo transplant • We now clarify that the "second visit" in the screening period is either a phone or in-person visit per patient request. This allows the investigators an opportunity to answer all questions and confirm patient eligibility, but allows for flexibility in regards to where this visit takes place, it can be done by phone if that is the patients preference. This has been clarified in the informed consent

I. Background and Significance

Currently in the United States, there are 133,925 patients waiting for organ transplants and 109,136 of those await kidney transplants. In 2014, 17,105 kidney transplants took place, with only 13,299 donors in total for that year. Thus, there is a definite shortage of transplant viable organs in the U.S. In a survey of kidney donations between 1995 and 2009, of the 93,825 HCV-positive deceased donors (potentially 187,650 kidneys), over 50% were discarded. In Region 1, which encompasses the New England states and 4,050 patients on the national Waitlist, the discard rate of HCV-positive kidneys is 36% (data per New England Organ Bank). Furthermore, for the past decade, total kidney donors per year in the U.S. have reached a plateau of approximately 13,000 donors each year,[5] suggesting that kidney donations have reached a ceiling and that the kidney donor pool is fixed at present levels.

It is well established that there exists a significant survival benefit for patients with ESRD who receive a well-functioning kidney transplant, as compared to those remaining on dialysis and the kidney waitlist. Wait list time and duration of dialysis contribute greatly to outcomes for kidney transplants, with greater waiting and dialysis times associated with poorer post-transplant

outcomes. Therefore, it is of paramount importance and in accordance with the OPTN Final Rule that available resources are used efficiently;[8] namely, that all potentially transplantable organs are recognized for their enormous value as scarce resources and should be utilized to their maximum potential for the maximum benefit (the principle of Utility).[9]

Transplantation of HCV-positive donor kidneys to HCV-positive recipients has been performed for some twenty years with increasing evidence of long-term safety; some argue that it is an underutilized option. One major advantage is a decrease in wait time and the potential to decrease waitlist mortality. However, a major concern with donor HCV-positive to HCV-positive recipients is that high viral loads contributing to accelerated allograft damage or an increased rate of post-transplant diabetes. However, it is important to note that the above risks associated with transplantation of HCV-positive kidneys were all determined prior to the current era of HCV treatment.

In contrast, traditional anti-HCV therapy depended on Interferon as the linchpin of single or combination therapy. Not only has Interferon been generally poorly tolerated, the risk of serious systemic side-effects has limited its use. When used in combination with transplant immunosuppression, acute HCV flare-ups have been reported including acute fulminant hepatitis.[16] In addition, Interferon can elicit induction of class II antigen expression on renal tubules, which theoretically can lead to acute kidney rejection episodes (AR). Induction of AR and the requirement for a further increase in net immunosuppression to treat AR can cause an increase in viral replication, setting off a vicious cycle. This concern about AR has been one of the most formidable arguments against Interferon use in the immediate post-transplant setting. Finally, previous treatments with Interferon-based HCV regimens have been prone to complications, as enumerated above, even after a 6 month post-transplant waiting period. Overall, Interferon-based treatments have not been well tolerated and have produced underwhelming cure rates of approximately 50% (genotype 1).[17] Because of this, it was generally recommended that patients with kidney transplants do not receive interferon-based HCV therapies.

In the present era, direct-acting antiviral (DAA) therapies produce exceptionally high cure rates and are well tolerated. DAAs have dramatically improved treatment options for patients with HCV. A recent study of kidney transplant recipients with HCV showed that 10 out of 11 patients receiving DAAs post-transplant were cured and treatment was well tolerated in all cases except for one.[18] Modern DAAs offer exceedingly high cure rates (upwards of 95% for genotype 1), with minimal side-effects as compared to previous forms of treatment, especially those that were Interferon-based.[19]

Grazoprevir, an inhibitor of the HCV NS3/4A protease and elbasvir, a NS5A inhibitor, in combination have been shown to be highly effective and well tolerated in patients with advanced

kidney failure. We believe this is the best choice for treatment in this population not only because it has been most extensively studied in renal failure, with 99% SVR12 (sustained virological response at 12 weeks), but also because of its minimal side effect profile, with only 2% of patients discontinuing the regimen due to adverse effects. This regimen is able to powerfully suppress viral load – with no on-treatment virologic breakthrough at 12 weeks of therapy[19]. Furthermore, this regimen has no significant interactions with commonly used immunosuppressant regimens.

The optimal dosing of elbasvir and grazoprevir post transplant is determined based on data from the phase III C-EDGE trial, which assessed the efficacy and safety of elbasvir/grazoprevir for 12 weeks in treatment-naïve adults (genotypes 1, 4, and 6). The sustained virologic response rate (cure rate) at 12 weeks (SVR12) was 92% in genotype 1A, 99% in genotype 1b (129/131) patients receiving 12 weeks of elbasvir/grazoprevir. When genotype 1A was evaluated more closely, it became clear that patients who had baseline high level resistance associated variant (RAVs) had lower rates of cure, this was overcome by adding weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]) and extending the treatment course to 16 weeks. NS5A RAVs were identified at baseline in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study of which 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RAVs receiving 12 weeks of elbasvir/grazoprevir. It is now recommended that patients with high-level baseline RAVs prolong duration of treatment to 16 weeks and add ribavirin; this is based on extrapolation of data from the C-EDGE TE trial. In this phase III open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, among 58 genotype 1a patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures. Subsequent analysis of the elbasvir/grazoprevir phase II and III trials have demonstrated SVR12 rates of 100% (6 of 6 patients) in genotype 1 patients with pre-treatments NS5A RAVs treated with elbasvir/grazoprevir for 16/18 weeks plus ribavirin. Because of this we will perform NS5A resistance testing for any donor with genotype 1a infection to determine treatment duration and need for addition of ribavirin to treat the recipient. If baseline RAVs are present, i.e., polymorphisms at amino acid positions 28, 30, 31, or 93, treatment will be extended 16 weeks with the addition of weight-based ribavirin to decrease the likelihood of transmission.

In light of these recent advances in HCV therapy, we believe that elbasvir/ grazoprevir have the potential to play an important role in curtailing the current high discard rates for HCV-positive kidneys, an antiquated and wasteful practice, and one antithetical to the Final Rule. We hypothesize that elbasvir/grazoprevir therapy could prevent or eliminate HCV infection that could occur after transplantation of a HCV-positive kidney into a HCV naïve host.

If this approach proves successful, it has the potential to result not only in a large increase *in the number* of organs available in the kidney donor pool but also an overall increase *in the quality* of organ offers. The reason for this is that, unfortunately, many potential donors who are HCV

positive belong to a young demographic, aged 18 to 35 years, who are now caught up in the national epidemic of opioid and intravenous drug abuse, their deaths resulting from drug overdosing. Sadly, despite availability of curative HCV therapies, very few intravenous drug users are able to access this care, due to fragmented healthcare and payers unwilling to cover DAA medications in anyone with a positive drug screen. Thus, it is estimated that the HCV epidemic will continue to spread amongst young IVDU; currently there are over 2,000 new cases of HCV infection per year. Thus, we believe the pool of HCV-positive donors will continue to exist for decades. HCV-positive donor kidneys originating from this potential donor cohort, by virtue of their young age and statistical estimates of projected allograft performance after transplantation, are the most robust in the kidney donor pool. Demonstration that preemptive treatment of HCV can prevent HCV transmission would greatly expand the viable kidney donor pool and could result in a substantial reduction in long-term healthcare costs for patients being treated with dialysis who suffer from ESRD co-morbid complications.

II. Specific Aims

Primary Objective

- Determine if the administration of grazoprevir and elbasvir (with or without ribavirin) for 12-16 weeks after kidney transplantation prevents the spread of Hepatitis C virus (HCV) infection from a donor kidney with known Hepatitis C genotype 1 or 4 infection to a Hepatitis C negative recipient as evidenced by a negative HCV viral RNA at 12 weeks post treatment

Secondary Objectives

- Evaluate the safety and tolerability of grazoprevir and elbasvir (with or without ribavirin) in patients undergoing kidney transplantation
- Determine the proportion of subjects with undetectable serum HCV RNA at study day 7, 14, 28, 56, 84, 112, 168, 252, and 365 in kidney transplant recipients receiving grazoprevir and elbasvir (with or without ribavirin) in combination with a kidney transplant from an HCV infected donor.

III. Subject Selection

The study will consist of 11 subjects to receive a transplant.

This is a proof of concept, open-label single center study for the donation of HCV positive kidneys to HCV negative patients, with preemptive, interventional treatment to prevent HCV transmission upon transplantation. Patients will be selected based on having a significantly long waitlist time in order to maximize possible benefit from early transplantation.

To ensure maximal benefit for the recipient, only high quality donor kidneys will be accepted; we will only accept those with low Kidney Donor Profile Index (KDPI) score. The KDPI is a numerical measure that combines ten dimensions of information about a donor, including clinical parameters and demographics, to express the quality of the donor kidneys relative to other donors. The KDPI is a cumulative percentage scale, based on a variety of donor factors used to compute the relative risk of graft failure after kidney transplant. Lower KDPI values are associated with increased donor quality; higher KDPI values are associated with lower donor quality. For instance, a donor with a KDPI of 80% has a higher expected risk of graft failure than 80% of all kidney donors recovered in the previous year. Kidneys with lower KDPI scores are associated with better post-transplant survival[20]. The chosen recipient may not otherwise have access to such high quality kidneys.

1. Donor Inclusion/Exclusion Criteria
1A. Donor Inclusion Criteria:
a. Detectable HCV RNA, with HCV Genotype 1 or 4 infection – Genotyping will occur prior to transplantation.
c. KDPI score is less than ≤ 0.650

1B. Donor exclusion criteria
a. Donor has been known to have previously received HCV treatment with a direct-acting antiviral agent
b. Confirmed HIV
c. Confirmed HBV positive (surface antigen or HBV DNA positive)
d. Kidney anatomical damage or significant pathology noted during recovery
e. Significant liver disease or signs of liver decompensation (splenomegaly, ascites) noted during recovery (advanced fibrosis or cirrhosis)
f. Any standard contra-indication to donation noted in donor (significant malignancy, unusual infection)

2. Recipient Inclusion/Exclusion Criteria

2a. Recipient Inclusion Criteria
a. Recipient Age is 40-70 years old
b. Met MGH transplant center criteria and already listed for isolated kidney transplant
c. No available living kidney donor
d. Has ≤ 730 days (2 years) of accrued transplant waiting time if blood type A and ≤ 1095 days of accrued transplant waiting time if blood type B or O.
e. On chronic hemodialysis or peritoneal dialysis or has a glomerular filtration rate <15mL/min/1.73m2 at the time of screening
f. Must agree to birth control. Women must agree to use birth control in accordance with Mycophenolate Risk Evaluation and Mitigation Strategy and at least one barrier method
g. Weigh at least 50kg
h. Serum ALT within normal limits with no history of liver disease
i. Able to sign informed consent

2b. Recipient Exclusion Criteria:
a. AB blood type (given expected short waiting time on the transplant list)
b. BMI > 35
c. Any liver disease in recipient
d. Pregnant or nursing (lactating) women
e. Known allergy or intolerance to tacrolimus that would require administration of cyclosporine rather than tacrolimus given the known drug-drug interaction between cyclosporine and Zepatier™
f. Cardiomyopathy (LV ejection fraction < 50%)
g. Albumin < 3g/dl or platelet count < 75 x 10^3/mL
h. Positive crossmatch or positive donor specific antibodies
i. HIV positive
j. HCV RNA positive
k. Hepatitis B surface antigen positive
l. Any known liver disease or elevated liver transaminases
m. Patients with primary focal segmental glomerulosclerosis (FSGS), FSGS recurring after previous transplant or disease process with increased risk of causing early graft failure as assessed by the transplant nephrologist and/or the investigator team
n. Any contra-indication to kidney transplantation per our center protocol

Patients will initially sign informed consent to be “waitlisted” for a HCV-positive kidney under this protocol. We will include up to 3 patients per blood type, exclusive of AB blood type. At the time that the kidney transplant becomes available, the “waitlisted” patients will be contacted and again sign surgical informed consent for transplantation (standard of care).

Upon selection a patient will receive a preemptive treatment regimen of grazoprevir 100mg /elbasvir 50mg coformulated, given orally on the day of transplantation. Daily dosing will continue for 12-16 weeks post-transplantation. Dosing may vary depending on patient viral specifics:

Genotype 1a: without high-level NS5A polymorphisms – grazoprevir/elbasvir x 12 weeks. With high level baseline NS5A polymorphisms - Grazoprevir/ elbasvir/ribavirin x 16 weeks

Genotype 1b: grazoprevir/elbasvir x 12 weeks

Genotype 4: grazoprevir/elbasvir x 12 weeks

Rationale for age range of recipients:
We are excluding young people because they are likely to have less comorbidity and have a high likelihood of surviving until transplant on the waitlist. Rationale for excluding elderly > 70 years old is that this technique is possibly riskier in this population who may have more comorbidities, require more concomitant medications and more likely to have side effects.

Full biochemical profiles of the patient will be performed at various stages throughout the study. On-Treatment safety monitoring schedule – (See standard of care post-transplant visit appendix) On-treatment safety labs include Baseline LFTs, CBC, comprehensive metabolic panel. LFTs will be monitored week 2, 4, 8, 12, and 16 for any patient on 16 weeks of therapy.

Standard of care at Partners includes confirming that female patients are not pregnant at the time of organ transplantation. Pregnant patients are not eligible for organ transplantation, regardless of their participation in the study. We will review the subjects standard of care pregnancy test to confirm they are not pregnant at the time of transplant/study entry but will not repeat a study specific pregnancy test at the time of transplant.

Study visits post-kidney transplantation will occur on days 1, 3, 7, 14, 28, 42, 56, 70, 84, 91, 95, 112, 168, 252, 365

Subjects who need to receive 16 weeks of therapy due to the presence of baseline RAVs will have an extra on-treatment visit at the end of therapy (Day 112) and will have their follow-up visits scheduled for 4 weeks post-treatment (day 140), 12 weeks post treatment (day 196), 24 weeks post-treatment (Day 280) and day 365. They will also complete a 1 year follow-up visit.

Targeted physical assessment, vital sign measurements, emergence of adverse events and concomitant medication usage will be assessed at scheduled visits and as needed at the time of any unscheduled contact during the 84 day (or 112 day) study period and/or the 365 day post-dosing

safety follow-up. For women of childbearing potential, a urine pregnancy test will be performed at all visits while taking the study medication. A negative result will be required prior to continuing study treatment.

40 subjects will be enrolled study wide. We plan to enroll all 40 subjects at MGH.

IV. Subject Enrollment

This is a proof of concept, single center study for the donation of HCV positive kidneys to HCV negative patients, with preemptive, interventional treatment to prevent HCV transmission upon transplantation.

Any patient interested in learning about HCV infection and this study will be invited to voluntarily attend a one-on-one information session (See Attachment) where they will be provided information about HCV, current treatments, current role in kidney transplantation, and have the opportunity to ask questions. After the session patients will be given the informed consent information to review at home. If interested they will return for a screening visit (Visit 1).

A study physician investigator will obtain informed consent. The consent form and protocol will be reviewed with the potential subject and any questions will be answered. The subject may be seen in a private area located on Renal Associates Clinic, 165 Cambridge St. Subjects will again have the option to take the consent form home with them for at least 24 hours to decide whether or not they wish to participate.

In the case that an identified patient is a part of the medical practice of one of the investigators, this patient will have an information session and screening visit conducted by a different physician investigator.

Ability to provide informed consent will be determined by the study investigator in discussion with the subjects treating physician. Subjects who cannot provide informed consent due to their clinical presentation will not be included. Surrogate consent will not be allowed in this study.

V. Study Procedures

Laboratory analyses, adverse effects, vital signs, and concomitant medications will be monitored at screening and all subsequent study visits through the end of the study. Serum pregnancy tests (for all females of childbearing potential) will be conducted at screening. At MGH, a serum pregnancy test will be done immediately prior to transplantation for all women of reproductive age as a standard of care.

In the case of isolated HBV cAb we will first ensure that this finding is worked up fully before transplant listing. Ordinary protocol is to monitor HBV DNA levels and this will be done, periodic HBV DNA post transplant per MGH kidney transplant standard of care and treatment started if DNA becomes positive. Patients with isolated HBV cAB positive will still be included and will follow standard of care monitoring.

The screening visit will take place within an estimated 6 months prior to kidney transplantation.

Day 0 of this study represents the day of kidney transplantation and study drugs will begin on this day.

Each subject will receive their study drugs (elbasvir 50mg and grazoprevir 100mg) daily for the duration of the study period.

With the prior approval of the patients treating MD team, statin use will be suspended while on elbasvir/grazoprevir and will be started no sooner than 2 weeks after treatment discontinuation. If there is an urgent need for statin use during the administration of grazoprevir/elbasvir as determined by treating physicians then we will request that pravastatin or pitavastatin be used as there is no clinically significant interactions of these two statins with Zepatier™.

Genotyping and Resistance-associated variant (RAV) testing will take place on the kidney donor's serum at the time of organ procurement. Rapid Genotyping is part of our allocation algorithm and is a component of the pre-transplant donor testing prior to organ implantation. This testing will be conducted in collaboration with the New England Organ Bank. Only patients with genotype 1 (1a or 1b) or genotype 4 are eligible to be transplanted. NS5A RAVs appear to have impact on treatment response with regimens that include an NS5A inhibitor and this impact occurs primarily with genotype 1a. NS5A variants with potential clinical significance include variant amino acids at positive 28, 30, 31, and 93 (HCVguidelines.org, accessed September 6, 2016). It is expected that 12% of donors with genotype 1A infection will have high level baseline RAVs. Any patient who receives a kidney transplant from a donor with donor with high level RAVs will have weight-based ribavirin (daily dose 1000 mg for those <75 kg and 1200 mg for those ≥75 kg) added to their regimen and the treatment course will be extended to a total of 16 weeks. Should any new RAVs be discovered during the duration of this study we will follow the most up to date recommendations based on HCVguidelines.org.

RAV testing will be performed on donor serum. Because this test cannot be done rapidly, it will be performed from serum taken at the time of organ procurement. Transplant of an organ will

take place without knowledge of RAV status. The RAV testing is necessary ONLY for patients with genotype 1A and results should return within 7-13 days and at that point, if needed based on the finding of high level RAVs, ribavirin will be added (by day 14 post transplant) and the patient will be informed that their planned treatment course will be extended to 16 weeks.

NS5A polymorphism testing will be a send-out test to Monogram Biosciences (South San Francisco, CA) via LabCorp. This is a CLIA-Approved lab. Results expected in 7-13 days with initiation of ribavirin if needed by day 14.

If worst case scenario arises and the patient is intolerant to ribavirin, published studies still show that the cure rate of HCV is still reasonable in those with high level RAVs who receive just elbasvir and grazoprevir for a traditional course. Dose reductions for ribavirin related adverse events would be given per the package insert recommendations as outlined in section 2.3 and 2.4 of the attached document.

Assessments *(also see Appendix 1)*

Pre-screening workup

Informed consent for evaluation
Completed education session with RN and MD
Complete medical history
Complete physical exam
Laboratory screening (HCV, HIV HBV testing, Comprehensive Metabolic panel, LFTs, CBC with differential, Coagulation tests)
Blood sample for storage
ECG monitoring
Quality of life assessment (SF36)
Phone call from study physician prior to transplant

Baseline testing (at transplant, day 0)

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential, Coagulation tests, blood sample for storage.
Review of concomitant meds

Week 1 (Visits on Days 1, 3, 7) -
Window for on treatment study visits will be +/- 3 days

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential
Blood sample for storage
Adverse event reporting

Standard of care post-transplant visit (see transplant protocol)
ECG monitoring
Review of concomitant meds

Week 2 (Day 14)
Window for on treatment study visits will be +/- 3 days

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential
Blood sample for storage
Adverse event reporting
Standard of care post-transplant visit (see transplant protocol)
Review of concomitant meds

Week 4 (Day 28)
Window for on treatment study visits will be +/- 3 days

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential
Blood sample for storage
Adverse event reporting
Standard of care post-transplant visit
ECG monitoring
Review of concomitant meds

Week 6 (Day 42)
Window for on treatment study visits will be +/- 3 days

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential
Blood sample for storage
Adverse event reporting
Standard of care post-transplant visit – (see transplant protocol)
Review of concomitant meds

Week 8 (Day 56)
Window for on treatment study visits will be +/- 3 days

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential

Blood sample for storage
Adverse event reporting
Standard of care post-transplant visit – (see transplant protocol)
Review of concomitant meds
Quality of life assessment (SF36)

Week 10 (Day 70)
Window for on treatment study visits will be +/- 3 days

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential
Blood sample for storage
Adverse event reporting
Standard of care post-transplant visit – (see protocol)
Review of concomitant meds

Week 12 (Day 84)
Window for on treatment study visits will be +/- 3 days

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential, Coagulation testing
Blood sample for storage
Adverse event reporting
Standard of care post-transplant visit – (see protocol)
ECG monitoring
Review of concomitant meds

Week 13 (Day 91 and Day 95) Laboratory Only Visit (may be done off-site)

Kidney function tests
Tacrolimus level monitoring

Week 16 (if needed based on baseline RAV testing of donor) (Day 112)
Window for on treatment study visits will be +/- 3 days and +/- 5 for post treatment visits.

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential
Blood sample for storage
Adverse event reporting

Standard of care post-transplant visit – (see protocol)
ECG monitoring
Review of concomitant meds

SVR 4 Visit (Day 112, or Day 140 if on 16 week course)
Window for study visits will be +/- 5 days for post treatment visits.

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential
Blood sample for storage
Adverse event reporting
Standard of care post-transplant visit – (see protocol)
Review of concomitant meds

SVR12 Visit (Day 168 or Day 196 if on 16 week course)
Window for study visits will be +/- 5 days for post treatment visits.

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential
Blood sample for storage
Review of concomitant meds
Quality of life assessments (SF36)

SVR 24 Visit (Day 252 or Day 280 if on 16 week course)
Window for study visits will be +/- 5 days for post treatment visits.

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential
Blood sample for storage
Review of concomitant meds

1 year visit (Day 365)
Window for study visits will be +/- 5 days for post treatment visits.

HCV RNA, Comprehensive Metabolic panel, LFTs, CBC with differential,Coagulation tests
Blood sample for storage
Review of concomitant meds
Quality of Life assessment (SF36)

Version 4.1 Dated: 20 September2017, inclusive of administrative amendment 1

Plan For Intensive Monitoring

Three situations will prompt beginning an intensive monitoring study visit schedule.

1. Medical need to begin a medication with known interaction with Zepatier™
2. Need to begin a transplant medication that has not been studied in combination with Zepatier™
3. Any patient experiencing a study drug related side-effect

If, for example, an azole is needed, tacro levels will be monitored twice weekly until stability is established, as is clinically indicated whenever an azole is added to a tacrolimus level. Co-administration with mTOR inhibitors has not been studied to our knowledge. We would adhere to the best standard-of-care currently practiced, which entails frequent monitoring of drug levels on this or any class of immunosuppressant, in addition to monitoring eGFR. Any patient with unforeseen need for a medication with a known interaction with elbasvir/grazoprevir (including azoles) would be subjected to a change in study visit schedule and would come weekly for the duration of Zepatier™ treatment.

Plan For Management of Patient Requesting Early Termination From the Study

If a subject decides to stop taking part in the study after the treatment period for any reason, we will ask them to make a final study visit, called the Early Termination Visit. They will need to return all unused study drug at this visit. The final study visit will take about 30 minutes. At this visit, we will:

- Give a physical exam and check on any new symptoms or new medications since their last visit
- Measure their weight
- Record their vital signs
- Draw some blood samples to measure if there is any Hep C virus in their blood, and the amount of anti-rejection medicine in their body, and for routine lab tests

If the patient decides to stop taking part in the study during Zepatier™ treatment, we have the following plan in place:

Although we would attempt to avoid this by fully informing the subject ahead of protocol participation, including an information session, detailing the immediate and downstream risks inherent in potential HCV transmission if medication is stopped, should a patient request study drug termination: We would immediately convene an intervention group that included the following to make sure that all attempts are made to address any potential issues that are leading to patients wanting to drop out of the study.

1. A study MD investigator

2. A Non-study related treating MD (ie the patients primary MD or Nephrologist)
3. The patients family member or close personal friend
4. A patients advocate/social worker

Finally, if the worst-case scenario was to play out and they were to get HCV, we now know that HCV is a treatable disease, no longer a death sentence. If transmission occurred, we would re-group and determine a successful therapeutic strategy to eradicate HCV. Although complications of HCV take decades to develop, we would help the patient become quickly connected to appropriate HCV care providers.

In the event of a possible HCV Seroconversion. We will pair sofosbuvir and ribavirin with elbasvir and grazoprevir for a repeat course. With established HCV infection, we would apply to the insurer for coverage of course of antiviral therapy.

Sofosbuvir use has not been well studied with eGFR < 30. At this point the patient would be > 12 weeks from transplant and the incidence of ongoing delayed graft function is low making it unlikely that the patients would have persistent severe renal impairment (eGFR < 30). Chances of eGFR < 30 at 12 weeks given the excellent kidney quality being selected for this study (see inclusion criteria) is < 10% at 3mo mark. Additionally, there are other regimens that are not renally excreted that could be used for this population soon available on the market (by 2017) that could be applied for through their insurance.

Plan for Patients That Develop a HCV Infection

The primary investigator, Dr. Chung, will advocate on behalf of the subject using his expertise to advise the appropriate salvage therapy. Every effort will be made with the insurer first and then the drug companies to secure effective treatment in this situation.

Plan for Waitlisted Patients After Study Completion

If the enrollment for this study closes (i.e. 11 patients have been participated and received a transplant), then patients will be notified that this protocol is over by phone call. We expect that with positive results from this study and others that there would be new larger studies of this technique (treating post transplant) with this and other anti-HCV regimens.

VI. Biostatistical Analysis

Variables/Time Points of Interest

The primary variable of interest will be HCV RNA at the multiple time-points assessed during and after treatment.

The primary efficacy outcome "Prevention of HCV Transmission" will be determined by a negative HCV RNA

The safety outcomes include summation of treatment related adverse events and transplant rejection or patient mortality. On treatment eGFR, proteinuria, hemoglobin, and liver function tests will be summarized to assess safety.

Statistical Methods
The first case will be described as a case report. Should HCV transmission be prevented with this protocol then a cohort of 10 patients will be recruited.

Patient characteristics for the follow-up cohort (N=10) will be presented with summary statistics for baseline demographics, clinical variables. The SVR12 rate will be presented and 95% CI constructed with the exact test. Mean and standard deviation for on-treatment laboratory values will be presented to analyze safety.

Power/Sample Size:
This is a pilot study. The first patient will be enrolled and complete the protocol as a proof of concept. Provided transmission does not occur, N=10 more patients will be enrolled in this pilot study.

VII. Risks and Discomforts

Psychological risk

Participation in research may result in undesired changes in thought process or emotion (episodes of depression, stress, guilt). Patients may experience discomfort when being asked questions about their medical history that they deem to be private.

Risks related to transplantation with a HCV kidney

Liver problems

It is possible that Zepatier™, which cured > 95% with HCV, will not work as well after a kidney transplant as it has worked in patients who did not have a transplant. It is also possible that after kidney transplant, a HCV infection could cause serious health problems, including liver failure or death. HCV can cause a rare but severe liver inflammation in the first few weeks to months after transplant. In the short term, infection with HCV can cause a flu-like illness that includes fatigue, nausea, fever, abdominal pain, vomiting, joint pain, and yellowing of the skin (jaundice). Although

it is very rare, infection with HCV can cause severe inflammation of the liver or even liver failure, including a condition called fibrosing cholestatic hepatitis. The risk of this complication in patients without HCV who receive a transplant from a donor with HCV is unknown. This complication can be treated and cured in some cases with the HCV medications that the study will be providing.

Cirrhosis of the liver can cause someone to experience leg swelling, yellow skin, skin itching, abdominal bleeding, shortness of breath, and the abdomen to fill with fluid (ascites). Liver failure can also cause death. Based on the limited data available, it would be extremely rare for someone in the study to experience liver failure in the first few months after transplantation because the study will be giving HCV treatment right away. However, because liver failure is possible, the study is only enrolling individuals in this study who would potentially be eligible to receive a liver transplant if they developed liver failure after a kidney transplant, which is why the screening process for this study requires that you have good heart function on the echocardiogram you underwent as a part of your transplant workup.

If the patient develops HCV infection despite getting Zepatier™, and it cannot be cured with the 2nd line treatment given through this trial, over time, there may be continued inflammation and scarring of the liver that over many years (10-30) can lead to cirrhosis. If HCV causes cirrhosis, the patient is at increased risk of developing liver cancer, liver failure requiring a liver transplant, or death.

Additional risks of HCV:
HCV can cause other types of inflammation in the body, such as arthritis, rash, anemia, nerve pain and inflammation damage to your kidney transplant. These problems are rare, and affect < 2% of people who have HCV. These problems should respond to effective treatment for the HCV.

Risks of the test used to determine the HCV virus genotype
The study intends only to transplant organs from patients with HCV – genotype 1 or 4. There is less than a 1% chance that the test the study uses to identify the virus might not be accurate. If the test gives the wrong result and the patient receives a kidney that has a different genotype of virus in it, the patient will still be treated, but the chances of cure may be lower.

Risks Related to Study Medications

Risks of Zepatier™
Elbasvir/grazoprevir is an FDA approved regimen for treating HCV infection and thousands of patients have received this medication. Based on the type of HCV the donor was infected with, some patients will also need to take ribavirin. Ribavirin is also approved by the FDA to treat HCV infection.

In patients receiving elbasvir/grazoprevir for 12 weeks the most common side effects were fatigue, headache and nausea (occurring in approximately 1 in 10 patients). Only 1 in 100 patients had side effects so severe that had to stop treatment due to a side effect.

In patients treated with elbasvir/grazoprevir plus ribavirin for 16 weeks the most commons side effect was anemia (8 in 100) and headache (6 in 100). Three in 100 patients had to stop treatment due to side effects.

The safety and tolerability of Zepatier™ after kidney transplantation have also not been studied. It is possible that taking immunosuppressant medications needed after kidney transplant may change the effectiveness or side effects of Zepatier™.

This drug regimen was chosen as first-line therapy for this study rather than other approved agents because this investigational agent is unique in that it can be safely used in patients with abnormal kidney function. The cure rates for patients with known HCV and chronic kidney disease (including being on dialysis) are similar to rates of patients without kidney disease. As a result, if kidney function has not fully recovered when treatment is initiated after transplant, the investigational agents can be safely given to you even if it takes some time for the kidney transplant to start working properly.

Risks of Ribavirin (Applies only to the minority with genotype 1a and positive resistance testing)

Ribavirin has been marketed for the treatment of HCV infection administered in combination with other HCV drugs (ribavirin is not effective against HCV infection when given by itself). Side effects which may be experienced with RBV include: Nausea, anorexia, vomiting, diarrhea, dyspepsia, abdominal pain, insomnia and rash. Hemolytic anemia can occur. The breakdown of red cells may lead to increased levels of bilirubin, and uric acid. The hemolytic anemia may cause worsening of heart disease which may lead to heart attacks and, sometimes, death.

A small percentage of patients may need ribavirin (expected to be 6.7% of all study participants, since 67% expected to be genotype 1A and 33% expected to be genotype 1B and only 10% of genotype 1A recipients have RAVs requiring additiona of RBV). In this small percentage, there is a risk of worsening anemia, particularly those with delayed graft function. Erythropoetin stimulating agents will be continued in the post-transplant period if needed. In general, anemia in the setting of delayed graft function (DGF) does not have to be treated in the short term. Because the anticipated graft function in this cohort of donors is expected to be quite robust, we would not expect DGF to endure longer than one to two weeks post-operatively.

Significant birth defects if pregnancy occurs while taking the drug or pregnancy occurs up to 6 months after taking the drug.

Risk of allergic reaction

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or serious, and can even result in death in some cases. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing.

Risk of developing Resistance of the virus to other HCV treatments
If Zepatier™ does not prevent HCV infection, there is a risk that the virus will develop resistance to Zepatier™ and other similar drugs. This could limit treatment options for the patient in the future.

Risks Related to Study Procedures

Risk of Stored Samples

Storing research samples can potentially become a confidentiality risk. If future studies involve genetic testing, then there is a chance that this genetic information could get out.

Risks of Blood Draws

The patient may have a bruise (a black-and-blue mark) or pain where researchers take the blood samples. There is also a small risk of feeling lightheaded, fainting, or infection.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

Because the effect, if any, of Zepatier™ on an embryo or fetus is not known, the patient may not participate in this study if they are pregnant, breastfeeding, or planning to become pregnant. The patient must agree not to get pregnant during the study and for 6 months after the completion of the study.

VIII. Potential Benefits

Participants may receive a high quality kidney transplant because they are enrolled in this study. They may wait for a much shorter period of time than they otherwise would have if they had not been a part of the research study. It is possible that patients will not get an HCV infection even though the kidney donor was known to have an HCV infection.

A kidney that would have gone to waste would be used to prolong the life of an individual. This procedure could also eliminate costs of dialysis for a recipient and the healthcare system. The study overall could serve as a proof of concept that would end up greatly reducing healthcare costs due to extended wait-times and complications on dialysis. It could also increase the number of viable kidneys for transplant and greatly reduce the HCV-positive kidney discard rate.

IX. Monitoring and Quality Assurance

An independent data safety monitoring board (DSMB) will not be used in this study as it is an open label study, will have low enrollment (11 subjects total) and will only take place at 1 sites

Once a patient is enrolled, Dr. Williams, Dr. Chung, Dr. Sise, Dr. Wojiechowski, and Dr. Elias will meet in person every three months to review any safety concerns. More frequent meetings will occur if needed. Dr. Chung and Dr. Sise will be regularly monitoring the study documents for accuracy and meeting with study staff to review the status of the study. Dr. Chung will ultimately be responsible for protecting the rights, safety and welfare of all subjects enrolled in this study. In the case of Dr. Chung's absence, monitoring responsibilities will be delegated to one of the sub-investigators listed on the 1572 as well as the IRB protocol application.

Adverse events will be thoroughly assessed at each treatment visit. Adverse events will be reported to the HRC as per current guidelines. We plan to comply with the reporting of any IND safety reports or any other federal regulations. The study coordinator will work with the physician investigators to process the report of these events as they happen.

Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines.

Dr. Chung will ensure that all adverse events are reported according to the PHRC guidelines.

Dr. Chung and the study staff will meet monthly to review the accuracy and completeness of case report form entries, source documents, informed consent, and all regulatory documents.

X. References

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Appendix 1: Study Assessments (Schedule of Events)

	Screening		On treatment assessments												Post Treatment Assessments			
	Screening Visit 1	**Screening Visit 2**	**Baseline**	**Day 1**	**Day 3**	**Day 7**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 13**	**Week 16**	**PT + 4**	**PT+12**	**PT+24**	**PT+40 (1 year follow-up)**
Clinical Assessments																		
Informed consent	x																	
Determine Eligilibty	x																	
Medical History	x																	
Physical Exam	x		x															
Height	x																	
Weight	x														x			x
Vital Signs	x														x	x	x	x
Educational Session		x																
12-Lead EKG	x			x	x	x		x				x		x				
AE's				x	x	x	x	x	x	x	x	x	x	x	x			
Concomitant Medications	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study Drug Dispensing			x	x	x	x		x		x		x						
Quality of Life Questionnaires	x									x						x		x
Phone Check in Prior to Transplant		x																
Laboratory Assessments																		
Hematology (with differential)	x		**x**	**x**	x	**x**	x	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	x	x
Complete Metabolic Panel (inc. LFTs)	x		**x**	**x**	x	**x**	x	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	x	x
Coagulation (PT/INR, PTT)	x		x					x		x		x			x	x	x	x
HCV Ab	x																	
HCV RNA			**x**	**x**	x	**x**	x	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	x	x
HCV Genotyping																		
HIV Ab	x																	
Urine Pregnancy*	x							x		x		x		x	x	x	x	
Urinalysis	x		x															
Tacrolimus level													x					
Kidney Function tests													x					
Archive Plasma* (10ml)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Archive Serum* (10ml)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

** Post transplant archive serum and plasma will only be collected if patients HBg is >9.5*