Transplantation of livers of hepatitis C (HCV) seropositive donors to HCV seronegative recipients with subsequent therapy with sofosbuvir/velpatasvir (Epclusa®)

NCT03819322

Document date: 05/22/2018

Study Objectives:

This study is being conducted to assess the safety and virologic outcomes of transplantation of livers from HCV seropositive non-viremic (HCV Ab+/NAT-) and HCV seropositive viremic (HCV Ab+/NAT+) donors to HCV seronegative recipients on the liver transplant waitlist, in the era of direct-acting antivirals (DAAs), using a transmission-triggered approach for the first scenario (HCV Ab+/NAT- donors, arm 1) and a prophylaxis approach for the later scenario (HCV Ab+/NAT+ donors, arm 2). Therapy with sofosbuvir/velpatasvir (Epclusa®) will be given if HCV transmission occurs in arm 1 and as the prophylactic agent in arm 2.

Study Background:

The demand for organ donors greatly exceeds the supply. Currently, 115,931 people need a lifesaving organ transplant in the United States and, on average, 20 people die each day while waiting for a transplant[1]. Different approaches have been implemented to safely expand the donor pool, including living donation, donation after circulatory death, the use of Public Health Service (PHS) increased risk donors, and the use of older donors. These approaches have had only a modest effect on organ availability. The number of deceased organ donors in the United States increased 27% since 2007[2].

There is currently a growing opioid crisis in the United States. In 2016, more than 64,000 Americans died from drug overdoses. Recent data from CDC shows that the number of HCV infections has significantly increased since 2011. Increases are being observed in all age groups, except for those aged ≥ 60 years, with the largest increase in persons 20-29 years. This has led to a decrease in the median deceased donor age for donors reported as HCV positive from 47 in 2012 to 35 in 2016, whereas median age did not change for those reported as HCV negative in this same time period[3].

Organs from hepatitis C seropositive (HCV Ab+) donors have almost exclusively been transplanted to HCV Ab+ recipients or in extreme life-saving situations, but with generally good outcomes. Historically, transmission of HCV has been a dreaded outcome owing to its impact on patient and graft survival and difficulty in treating HCV in the post-transplant setting. As a consequence, organs from young, HCV Ab+ donors are being discarded daily. With the advent of DAAs that are safe and can cure nearly all HCV infections, a new focus should be placed on HCV Ab+ donors. DAAs have the potential to expand the donor pool by eradicating HCV in organ donors and by permitting prophylaxis or curative treatment of recipients from HCV Ab+ donors.

Furthermore, since 2015, organ procurement organizations (OPOs) are required to perform HCV NAT for all organ donors. This has allowed for clarification of HCV status, creating two distinct types of HCV positive donors, those who are serologically positive but without viremia (HCV Ab+/NAT-) and those who are serologically positive and with NAT confirmed viremia (HCV Ab+/NAT+). The risk of HCV transmission from an HCVAb+/NAT- donor is unknown, but expected to be <1% for non-hepatic organs. The risk is potentially higher in liver recipients due to concern for persistence of HCV in the liver[4], and it was reported to be 16% in a recent study[5]. The risk of HCV transmission from an HCVAb+/NAT+ donor should be expected to be near 100%.

Rationale for current study:

Transplantation of organs from HCV positive donors to HCV negative recipients could save lives by increasing the donor pool. Transmission of HCV is likely to be either cured or prevented with the use of DAA, without detrimental effects to the allograft or the recipient. A systematic study of liver transplantation from HCV positive donors into HCV negative recipients in needed, however, to change the standard of care. The current study is designed to accomplish that goal.

Primary aims:

- To assess the safety of liver transplantation from HCVAb+/NAT- donors to HCV seronegative (HCV Ab-) recipients
- To assess the safety of liver transplantation from HCVAb+/NAT+ donors to HCV Ab- recipients

Secondary aims:

- To determine the rate of transmission of HCV from HCVAb+/NAT- liver donors to HCVAb-negative recipients
- To assess the rate of HCVAb- recipients of HCVAb+/NAT- donors who are free of HCV at 1 year following transplantation
- To assess the efficacy, safety and tolerability of sofosbuvir/velpatasvir (Epclusa®) in the treatment of donor-derived HCV infection after liver transplantation from a HCV Ab+/NAT-donor
- To assess the efficacy, safety and tolerability of sofosbuvir/velpatasvir (Epclusa®) in the prophylaxis of donor-derived HCV infection after liver transplantation from a HCV Ab+/NAT+ donors
- To assess the frequency of acute cellular rejection episodes following liver transplantation from HCVAb+/NAT- and HCVAb+/NAT+ liver donors to HCVAb- recipients
- To assess graft survival at weeks 1, 2, 3, 4, 8, 12; and months 6, 7, 8, 9, 10, 11, and 12; and years 2, 3, 4, and 5 after transplantation
- To assess patient survival at weeks 1, 2, 3, 4, 8, 12, and months 6 and 12, and years 2, 3, 4 and 5 after transplantation
- To assess the impact of utilization of HCVAb+/NAT- and HCVAb+/NAT+ donors on transplant waitlist time

Primary outcome measure:

The primary outcome measure is transmission of HCV by 12 months post-transplant.

Secondary outcome measures:

The secondary outcome measures are:

- Incidence of allograft rejection
- Incidence of graft loss
- All-cause mortality

Study design:

This is a prospective, single center, pilot, open-label study of transplantation of livers of HCVAb+ donors to HCVAb- recipients with subsequent therapy with sofosbuvir/velpatasvir (Epclusa®). Recipients of a liver from HCVAb+/NAT- donors will be in arm 1 or the transmission-triggered arm of the study. In this arm, the study will monitor transmission of HCV by measuring HCV RNA in liver transplant recipients. If HCV RNA is detected, indicating transmission of HCV, recipients will be treated with sofosbuvir/velpatasvir (Epclusa®) for 12 weeks. Virological response will be assessed at 4 weeks, end of treatment and 12 weeks after completion of therapy.

Recipients of a liver from HCVAb+/NAT+ donors will be in arm 2 of the prophylaxis arm of the study. In this arm, patients will be started on a 12-week course of sofosbuvir/velpatasvir (Epclusa®) immediately post-operatively and will undergo close monitoring of HCV RNA for evidence of transmission.

To be eligible for the study, subjects need to be listed for liver transplantation and agreeable to accepting a Public Health Service increased risk donor[1], be not infected with HCV, HBV or HIV, and sign informed consent.

Rationale for choice of sofosbuvir/velpatasvir (Epclusa®)

Sofosbuvir/velpatasvir (Epclusa®) is a fixed-dose combination of a nucleotide analogue HCV NS5B polymerase inhibitor (sofosbuvir) and a NS5A inhibitor (velpatasvir). It is approved by the FDA for the treatment of all HCV genotypes, with a 12-week oral course. It doesn't require performance of baseline resistance testing. It is associated with a 98% cure rate. The most common adverse events are headache and fatigue. There is no interaction between sofosbuvir/velpatasvir (Epclusa®) and tacrolimus or cyclosporine. There are no significant interactions expected with concomitant use of sofosbuvir/velpatasvir (Epclusa®) and azoles. The concomitant use of sofosbuvir/velpatasvir (Epclusa®) and amiodarone carries a risk of symptomatic bradycardia. There is currently no safety and efficacy data in patients with CrCl <30 ml/min or on renal replacement therapy, although use in this situations has been reported and thought to be feasible[6-8].

The pangenotypic HCV activity of sofosbuvir/velpatasvir (Epclusa®) allows for transplantation without prior determination of HCV genotype in the donor. This offers two advantages: 1) safe transplantation of organs from donors who are NAT negative or non-viremic - determination of HCV genotype is not possible in this setting; and 2) avoidance of delays while waiting for HCV genotype results from donors who are NAT positive or viremic – genotyping cannot be obtained in a timely fashion. The favorable toxicity profile of sofosbuvir/velpatasvir, the lack of significant drug-drug interactions with immunosuppressants and

azole antifungals make this the ideal drug for a study such as this. The management of patients with impaired renal function post-transplant is discussed in this protocol. Although sofosbuvir/velpatasvir (Epclusa®) has not been approved for the treatment of HCV after transplantation, response rates are expected to be similar than in the non-transplant population.

Estimated time to complete enrollment: approximately 1 year

Number of subjects: 20, 10 recipients of HCVAb+/NAT- donors and 10 recipients of HCVAb+/NAT+ donors

Site: UPMC Presbyterian

Study period (planned): 7 years, including follow-up

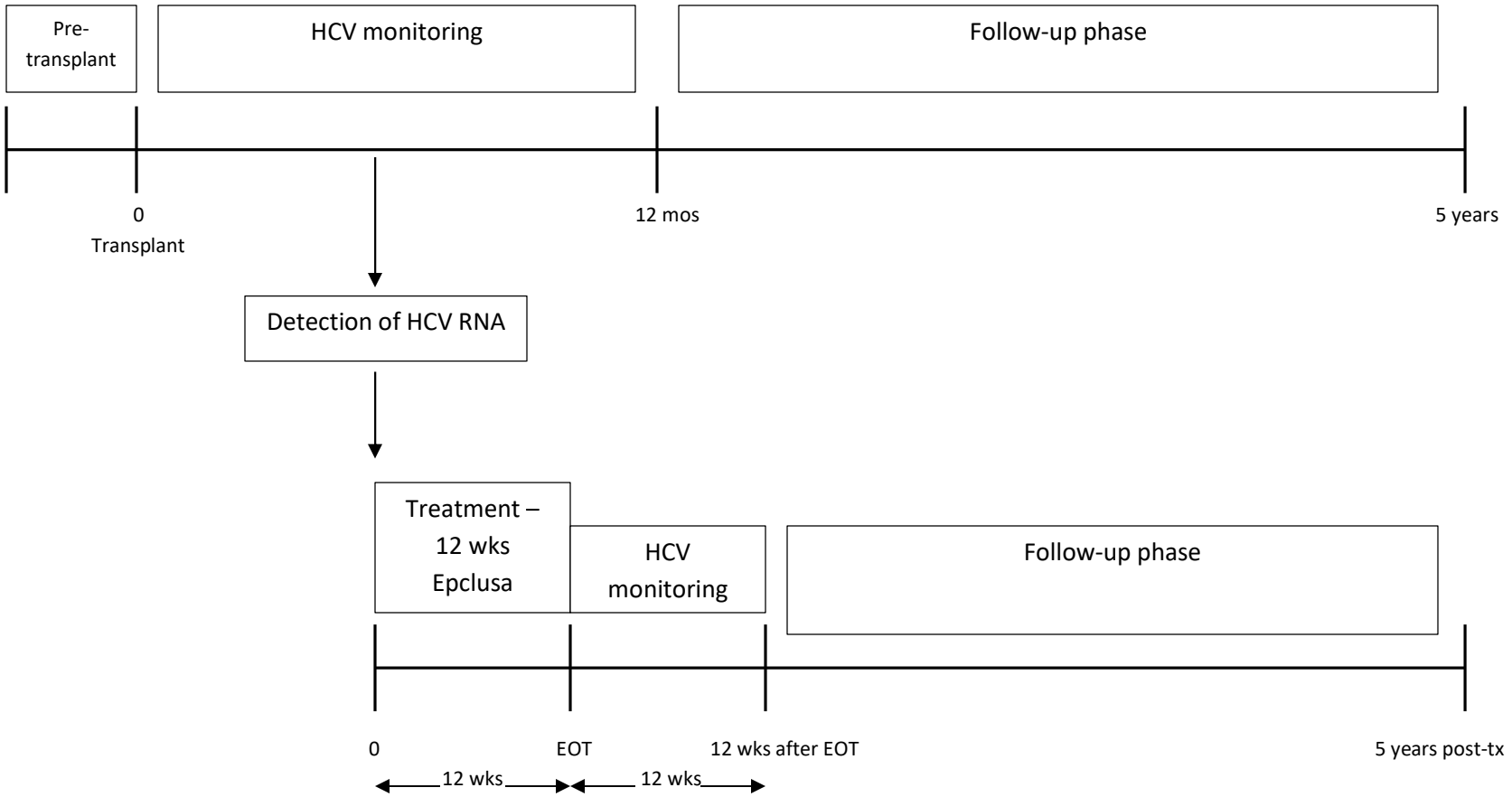
Source of funding: UPMC. Twelve courses of Epclusa will be donated by Gilead. These courses will be enough to treat up to 20% of patients in arm 1 or the transmission-triggered arm and give prophylaxis to all patients in arm 2 or the prophylaxis arm. Gilead will also donate 2 courses of sofosbuvir/velpatasvir/voxilaprevir (Vosevi®), to be used in cases of failure to Epclusa.

1. Study flow chart and study population

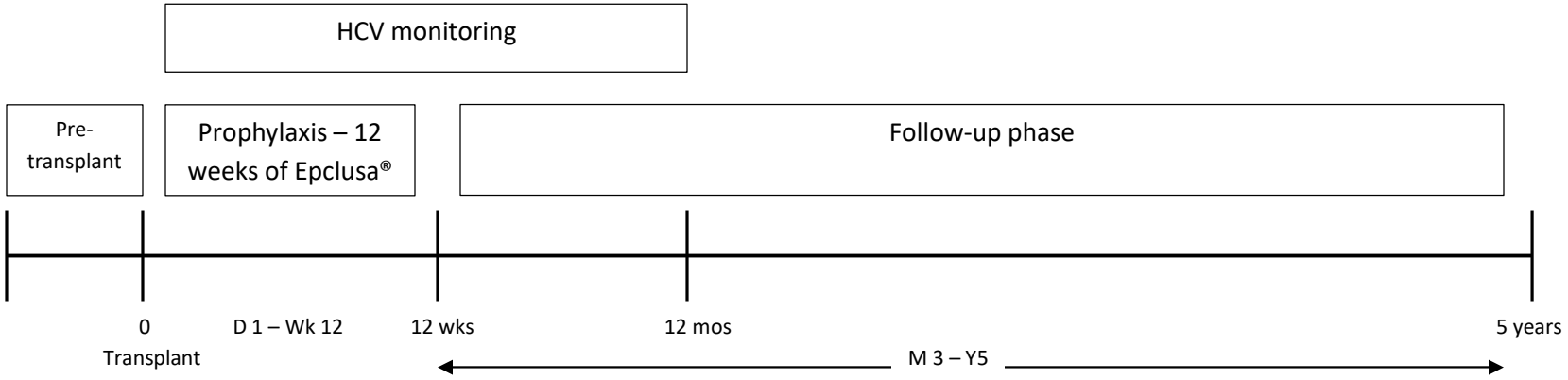
1.1. Study flow chart:

Figure: Study design flow chart

Arm 1 – HCVAb+/NAT- donors, transmission-triggered approach:



Arm 2 – HCVAb+/NAT+ donors, prophylaxis:



1.2. Study population:

Patients with end-stage liver disease listed for liver transplantation at UPMC.

1.3. Inclusion criteria (recipients):

1.3.1. Age ≥ 18

1.3.2. No available living liver donor

1.3.3. Listed for an isolated liver transplant at UPMC

1.3.4. Have panel reactive antibody level of <98%

1.3.5. Able to travel to UPMC for routine post-transplant visits and study visits for a minimum of 12 months after transplantation

1.3.6. Able to provide informed consent

1.3.7. Be willing to use a contraceptive method for a year after transplant

1.4. Exclusion criteria (recipients):

1.4.1. HIV positive

1.4.2. HCVAb or HCV RNA positive

1.4.3. Presence of behavioral risk factors for contracting HCV

1.4.4. Hepatitis B surface antigen positive

1.4.5. History of atrial fibrillation requiring the use of amiodarone over the past 12m

1.4.6. Receipt of prior organ transplant

1.4.7. Waitlisted for a multi-organ transplant

1.4.8. Pregnant women

1.4.9. Known allergy to sofosbuvir/velpatasvir

1.4.10. Any condition, psychiatric or physical, 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

1.5. Inclusion criteria (donors):

1.5.1. HCV antibody positive

1.5.2. HCV NAT negative or positive

1.6. Exclusion criteria (donors):

1.6.1. Confirmed HIV positive (positive HIV-1 antibody, positive HIV-2 antibody, positive p24 antigen and/or positive HIV NAT)

1.6.2. Confirmed HBV positive (positive hepatitis B surface antigen and/or HBV NAT)

1.6.3. Known ongoing therapy for HCV

2. Study procedures:

2.1. Study schedule:

Tables 1 and 2 show the study procedures for patients in arm 1 or transmission-triggered arm of the study. Table 1 shows the study procedures at screening, pre-transplant period, time of transplant, HCV monitoring phase and follow-up phase. Table 2 shows the study procedures if there is HCV transmission, i.e., HCV RNA is detected, during the HCV monitoring phase shown in table 1 for study monitoring phase and table 2 for study procedures for transmission-triggered treatment phase.

Table 3 shows the study procedures for patients in arm 2 or prophylaxis arm of the study.

2.1.1. Arm 1 or transmission-triggered arm (donors HCV Ab+/NAT-):

Screening visit - pre-transplant period (anytime from listing to transplantation at UPMC until transplant)

As specified in table 1, the study procedures in the pre-transplant period will include:

- Informed consent
- Inclusion/exclusion criteria
- Medical history, including etiology of end-stage renal disease
- Current medications, therapies, and procedures
- Physical examination
- 12-lead EKG (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- HIV antigen/antibody test (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- HBV testing - HBc antibody total, HBs antigen (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- HCV antibody (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- Liver enzymes (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- Pregnancy test (serum) for all females of childbearing potential

Time of transplant (during admission for transplant, prior to organ implantation)

As specified in table 1, the study procedures at the time of transplant will include:

- Current medications, therapies, and procedures
- Physical examination
- 12-lead EKG (clinical test obtained pre-operatively within 24 hours prior to transplant is acceptable)
- HIV antigen/antibody test
- HBV test (HBc Ab total, HBsAg)
- HCV antibody
- Liver enzymes

- Pregnancy test (serum) for all females of childbearing potential

HCV monitoring phase

Permissible assessment windows during the monitoring phase are: study days 1 through 6 +/- 1 day, weeks 1 through 12 +/- 3 days; study months 4 through 12 +/- 2 weeks.

As specified in table 1, the study procedures in the monitoring phase will include:

- Liver enzymes on days 1, 2, 3, 4, 5, 6; weeks 1, 2, 3, 4, 8 and 12; months 6, 9 and 12
- HCV RNA on days 1, 2, 3, 4, 5, 6; weeks 1, 2, 3, 4, 8, and 12; months 6, 9, and 12. HCV RNA will be obtained and processed at UPMC
- Assessment of graft function on weeks 1, 2, 3, 4, 8, 12; months 4, 5, 6, 7, 8, 9, 10, 11, 12; and years 2, 3, 4, and 5
- Assessment of rejection history on weeks 1, 2, 3, 4, 8, 12; and months 4, 5, 6, 7, 8, 9, 10, 11, 12
- Medications, therapies and procedures on weeks 1, 2, 3, 4, 8, 12; and months 6 and 12
- Assessment of patient survival on weeks 1, 2, 3, 4, 8, 12; and months 6 and 12

Patients with HCV RNA detection at any time point during the monitoring phase will initiate the transmission-triggered treatment phase.

Transmission-triggered treatment phase

Permissible assessment windows during the transmission-triggered treatment phase are: study day 0 +7 days, weeks 1 through 12 +/- 2 days, weeks 6, 12, 23 and 48 after end of treatment (EOT) +/- 3 days.

As specified in table 2, the study procedures in the pre-transplant period will include:

- Physical examination on day 0
- 12-lead EKG on day 0
- Pregnancy test (serum) for all females of childbearing potential on day 0 and end of therapy (EOT) visit
- Concomitant medications on day 0 and weeks 1, 2, 3, 4, 8 and 12 (EOT)
- HCV genotype on day 0
- Comprehensive metabolic panel on days 0 and weeks 1, 4, 8, and 12 (EOT); and weeks 12 and 24 after EOT
- Dispensation of sofosbuvir/velpatasvir on day 0; and weeks 1, 4, and 8
- HCV RNA on day 0; and weeks 4 and 12; and at weeks 6, 12, 24, and 48 after EOT. In case HCV RNA on week 4 is detectable, HCV RNA is also obtained on week 6
- Assessment of rejection history on weeks 4, 8, and 12
- Medications, therapies and procedures on day 0 and weeks 1, 2, 3, 4, 8, and 12

- Assessment of graft function on day 0 and weeks 1, 4, 8, 12; and at weeks 12, 24, and 48 after EOT
- Compliance counseling on day 0 and weeks 1, 2, 3, 4, 8, and 12
- Compliance assessment on weeks 1, 2, 3, 4, 8, and 12
- Adverse event and serious adverse event monitoring on weeks 1, 2, 3, 4, 8, and 12 and 12 weeks after EOT

Follow-up phase

Permissible assessment windows during the follow-up phase are: study years 2, 3, 4 and 5 +/- 3 months.

As specified in table 1, the study procedures in the follow-up phase will include:

- Assessment of graft function on years 2, 3, 4, and 5
- Assessment of patient survival on years 2, 3, 4, and 5

2.1.2. Arm 2 or prophylaxis arm (donors HCV Ab+/NAT+):

Screening visit - pre-transplant period (anytime from listing to transplantation at UPMC until transplant)

As specified in table 3, the study procedures in the pre-transplant period will include:

- Informed consent
- Inclusion/exclusion criteria
- Medical history, including etiology of end-stage renal disease
- Current medications, therapies, and procedures
- Physical examination
- 12-lead EKG (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- HIV antigen/antibody test (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- HBV testing - HBc antibody total, HBs antigen (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- HCV antibody (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- Liver enzymes (clinical test obtained within 3 months prior to informed consent is acceptable; a test will be performed at screening if data is not available)
- Pregnancy test (serum) for all females of childbearing potential

Time of transplant (during admission for transplant, prior to organ implantation)

As specified in table 3, the study procedures at the time of transplant will include:

- Current medications, therapies and procedures
- Physical examination
- 12-lead EKG (clinical test obtained pre-operatively within 24 hours prior to transplant is acceptable)
- HIV antigen/antibody test
- HBV test (HBc Ab total, HBsAg)
- HCV RNA
- Liver enzymes
- Pregnancy test (serum) for all females of childbearing potential
- Review of medications, therapies and procedures
- Request of HCV genotype from donor

HCV prophylaxis phase

Permissible assessment windows during the prophylaxis phase are: study days through 7 +/1 1 day, weeks 1 through 12 (EOT) +/- 3 days.

As specified in table 3, the study procedures during the HCV prophylaxis phase will be:

- HIV antigen/antibody test on week 4 (clinical test obtained as per protocol for monitoring of increased risk donors is acceptable; a test will be performed at screening if data is not available)
- HBV testing - HBc antibody total, HBs antigen, HBV DNA on week 4 (clinical test obtained as per protocol for monitoring of increased risk donors is acceptable; a test will be performed at screening if data is not available)
- Liver enzymes on days 1, 2, 3, 4, 5, 6, and 7; and weeks 2, 3, 4, 8, and 12 (EOT)
- Dispensation of sofosbuvir/velpatasvir on days 1, 2, 3, 4, 5, 6; and weeks 1, 4, and 8
- HCV RNA on days 1, 2, 3, 4, 5, 6; and weeks 1, 2, 3, 4, 8, and 12 (EOT)
- Compliance counseling on weeks 1, 2, 3, 4, and 8
- Compliance assessment on weeks 1, 2, 3, 4, 8, and 12 (EOT)
- Assessment of graft function on weeks 1, 2, 3, 4, 8, and 12 (EOT)
- Assessment of rejection on weeks 1, 2, 3, 4, 8, and 12 (EOT)
- Adverse event and serious adverse event monitoring on weeks 1, 2, 3, 4, 8, and 12 (EOT)
- Medications, therapies and procedures on weeks 1, 2, 3, 4, 8, and 12 (EOT)
- Survival on weeks 1, 2, 3, 4, 8, and 12 (EOT)

Follow-up phase

Permissible assessment windows during the follow-up phase are: week 24 +/- 7 days, month 12 +/- 2 weeks, and study years 2, 3, 4, and 5 +/- 3 months.

As specified in table 3, the study procedures in the follow-up phase will include:

- HBV DNA on month 12 (clinical test obtained as per protocol for monitoring of increased risk donors is acceptable; a test will be performed at screening if data is not available)
- Liver enzymes on week 24 and month 12
- HCV RNA on week 24 (12 weeks after EOT) and month 12
- Assessment of graft function on week 24 (12 weeks after EOT); months 7, 8, 9, 10, 11, and 12; and years 2, 3, 4 and 5
- Assessment of patient survival on week 24 (12 weeks after EOT); month 12; and years 2, 3, 4, and 5

Management of patients with renal dysfunction or intolerant to sofosbuvir/velpatasvir

Renal clearance is the major elimination pathway for the major metabolite of sofosbuvir. Pharmacokinetic studies show higher drug sofosbuvir and metabolite concentrations in those with eGFR <30 ml/min. There is limited safety and efficacy data in patients with eGFR <30 ml/min or on renal replacement therapy. In the event that patients requiring sofosbuvir/velpatasvir (patients in arm 1 with detectable HCV RNA or patients in arm 2) experience poor renal function with eGFR <30 ml/min or need for renal replacement therapy, one of three approaches will be undertaken, under the discretion of one of the investigators and approval by the principal investigator:

- Continuation of treatment with sofosbuvir/velpatasvir. This approach will be chosen if the renal dysfunction is expected to be transient or if the patient is close to completion of his/her 12-week course of sofosbuvir/velpatasvir
- Delay in treatment/prophylaxis with sofosbuvir/velpatasvir
- Use of an alternative regimen, which will depend on HCV genotype and patient's insurance formulary

3. Adverse events and serious adverse events management:
   3.1. ICH E6 definition of adverse event:

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor. For this study, AEs are reportable only if study related or unexpected, please see definition of reportable events for this study 3.3.

   3.2. FDA definition of AE:

The FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Please note: for this study, AEs are reportable only if study related or unexpected, please see definition of reportable events for this study 3.3)

3.3. This study's definition of AE:

For this study, a reportable adverse event is defined as:

a. Any clinically important untoward medical occurrence in a subject receiving study drug that is different from what is expected in the clinical course of a patient with a liver transplant (see appendix A for events considered to be part of the expected course of liver transplant)

   OR

b. Any clinically important, untoward medical occurrence that is thought to be related to the study drug, regardless of the "expectedness" of the event for the course of a patient with a liver transplant. Expected events for liver transplant are untoward clinical occurrences that are deemed by the investigator to occur with reasonable frequency in the day-to-day care of patients with a liver transplant (see appendix A for events considered to be part of the expected course of liver transplant)

   OR

c. Delay in treatment/prophylaxis with sofosbuvir/velpatasvir or use of an alternative regimen due to occurrence of eGFR <30 ml/min or need for renal replacement therapy

3.4. Documentation of reportable AEs:

All reportable AEs should be captured in the case report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, and relationship to study product or procedure (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. Reportable AEs occurring while on study must be documented appropriately and will be followed to resolution or stabilization. AE events that are assessed as serious require additional reporting as described below. Any medical condition that is present at the time that the subject is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study and meets reportable criteria it should be recorded as an AE.

3.5. Assessment of adverse events:

The determination of seriousness, severity, and causality of an AE will be made by an investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants and nurse practitioners.

3.6. Serious adverse events (SAEs):

An adverse event is considered “serious” if, in the view of the either the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

3.6.1. Reportable SAEs for this study

Liver transplant recipients represent a critically-ill population in whom a high rate of untoward medical events are commonly seen during the routine post-transplant course as part of their underlying medical condition, transplant surgery or postoperative state. In an effort to document only clinically-relevant untoward medical events that have a greater likelihood of being study-related, rather than the normal course of liver transplantation, study endpoints (detection of HCV RNA, rejection, graft loss, mortality) and certain pre-specified expected events commonly seen in this population (see appendix A for list of expected events for liver transplant recipients) will not be reported as serious adverse events SAEs even if they meet the serious event criteria listed in 3.6. Reportable SAEs for this study will be adverse events that are serious and unexpected, i.e., not expected to occur with a reasonable frequency in the typical course of a patient following liver transplant (appendix A).

Death will be recorded in the CRF although it will not be a reportable SAE as it is an endpoint for this study unless it meets the study’s reportable criteria of related and/or unexpected (see appendix A for list of expected events for liver transplant recipients).

Reportable SAEs will be recorded on appropriate CRF, followed through resolution by a study clinician, reviewed and evaluated by a study clinician.

3.7. Assessment of severity:

Reportable AEs will be graded according to Common Terminology Criteria for Adverse Events (CTCAE). The severity of each event will be classified into one of five defined categories as follows:

- Grade 1 Mild
- Grade 2 Moderate
- Grade 3 Severe
- Grade 4 Life Threatening or Disabling
- Grade 5 Death

3.8. Assessment of relationship to study product or procedure

Relationship to study: the clinician's assessment of an AE's relationship to study product or study procedures is part of the documentation process and may determine what is or is not reported in the study. If there is any doubt as to whether a clinical observation is a reportable AE, the event should be reported. Reportable AEs must have their relationship to study product or procedure assessed using the terms related or not related.

- Related: there is a reasonable possibility that the study product or study procedure caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product or study procedure and the adverse event.
- Not related: there is not a reasonable possibility that the study product or study procedure caused the adverse event. The investigator must provide an assessment of relationship of AEs to the study product based on:
    - Temporal relationship of the event to the administration of study product or procedure
    - Whether an alternative etiology has been identified
    - Biological plausibility
    - Existing therapy, and/or concomitant medications.

4. Informed consent process:

The process of obtaining informed consent must be documented in the medical records, clinic chart, and/or research chart. The consent form must be signed and dated by the study participant or legal guardian before participation in the study. A copy of the signed consent form must be provided to the study participant or legal guardian. Signed consent forms must remain in each study participants study file and must be available for verification at any time.

Informed consent will be obtained by a physician, after transplant listing but prior to organ availability.

5. Data and safety monitoring plan:

The principal investigator will have oversight of the DSMP. The principal investigator, co-investigators, and primary research coordinator will meet monthly and will review the following elements:

5.1. Overall study progress, including recruitment and retention
5.2. Adverse events, unanticipated problems, and subject withdrawals. An assessment of any change to the anticipated benefit-to-risk ratio of study participation will be made and, based on that, it will be determined if the study should continue as originally designed, should be changed, or should be terminated.
5.3. Assessment of new pertinent scientific literature or therapeutic developments that may have an impact on the safety of study participants or the ethics of this research protocol

5.4. Breaches of confidentiality and procedures to protect the privacy of research subjects and confidentiality of research data

Any unanticipated events or reportable adverse events will be reported to University of Pittsburgh IRB as per its current policies. A summary of the DSMP meetings and its findings will be provided to the IRB yearly, at the time of study renewal.

Enrollment and transplantation of patients in arm 1 of the study will be halted if HCV transmission is equal or greater than 20%.

6. Tables:

Table 1- Schedule of study procedures: pre-transplant, transplant and monitoring phase for liver recipients of NAT negative donors, arm 1 or transmission-triggered approach

	Screening/Pre-transplant	**Time of transplant**	**HCV Monitoring phase**																				**Follow-up phase**			
Study week/month/year	**Any time prior to transplant**	**0**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 6**	**1 wk**	**2 wk**	**3 wk**	**4 wk**	**8 wk**	**12 wk**	**4m [d]**	**5m [d]**	**6 m**	**7m [d]**	**8m [d]**	**9m [d]**	**10 m[d]**	**11 m[d]**	**12 m**	**2 y [d]**	**3 y [d]**	**4 y [d]**	**5 y [d]**
Informed consent	X																									
Inclusion/exclusion criteria	X																									
Medical history	X																									
Current medications, therapies and procedures	X	X																								
Physical examination	X	X																								
12-lead EKG	*X[a]*	*X[b]*																								
HIV Ag/Ab test	*X[a]*	*X[b]*										*X[b]*														
HBV test (HBcAb, HBsAg)	*X[a]*	*X[b]*										*X[b]*														
HBV DNA												*X[b]*											*X[b]*			
HCV antibody	*X[a]*	*X[b]*																								
Liver enzymes	*X[a]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*			*X[b]*			*X[b]*			*X[b]*				

Pregnancy test	*X[a]*	*X[b]*																										
HCV RNA		X[b]	**X[c]**	**X[c]**	**X[c]**	**X[c]**	**X[c]**	**X[c]**	**X[c]**	**X[c]**	**X[c]**	**X[c]**	**X[c]**	**X[c]**			**X[c]**			**X[c]**			**X[c]**					
Graft function									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rejection history									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Medications, therapies and procedures		X							X	X	X	X	X	X			X							X				
Survival									X	X	X	X	X	X			X							X	X	X	X	X

a Clinical results obtained within 3 months prior to study enrollment can be utilized.

b Clinical testing result is acceptable

c If detectable HCV RNA, transmission-triggered treatment initiates

d Telephone visits or review of medical records

Italics: clinical results can be used

Bold: performed for study purposes only

HIV Ag/Ab test and HBV testing at 4 weeks and 12 months done as part of clinical protocol for monitoring of increased risk donors

Table 2- Schedule of study procedures: transmission-triggered treatment phase

Time from HCV RNA detection	**0 (+7d)[b]**	**1wk[b]**	**2wk[a]**	**3wk[a]**	**4wk[b]**	**6wk[b]**	**8wk[b]**	**12wk (EOT)[b]**	**6 wks after EOT[b]**	**12 wks after EOT[b]**	**24 wks after EOT[b]**	**48 wks after EOT[b]**
Physical examination	X				X		X	X				
12-lead EKG	**X**											
Pregnancy test	**X**											
Concomitant medications	X	X	X	X	X		X	X				
HCV genotype	**X**											
Comprehensive metabolic panel	*X*[c]	*X*[c]			*X*[c]		*X*[c]	*X*[c]		*X*[c]	*X*[c]	
Sofosbuvir/velpatasvir dispensed to patient (12 week treatment)	X	X			X		X					
HCV RNA	**X**				**X**	**X**[d]		**X**	**X**	**X**	**X**	**X**
Rejection history					X		X	X				
Medications, therapies, procedures	X	X	X	X	X		X	X				
Graft function	X	X			X		X	X		X	X	X
Compliance counseling	X	X	X	X	X		X	X				
Compliance assessment		X	X	X	X		X	X				
AE/SAE monitoring		X	X	X	X		X	X		X		

a Phone visits

b In person visits

c Clinical testing result is acceptable

d Only if HCV RNA detectable at 4 weeks

HCV RNA will also be done if there is elevation of transaminases
Italics: clinical results can be used
Bold: performed for study purposes only

Table 3 -Schedule of study procedures: any recipient of NAT positive donor, arm 2 or prophylaxis arm

	Screening/Pre-transplant	Time of transplant	Prophylaxis												Follow-up phase										
Study week/month/year	**Any time prior to transplant**	**0**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 6**	**1 wk**	**2 wk**	**3 wk**	**4 wk**	**8 wk**	**12 wk (EOT)**	**24 wk (12wk after EOT)**	**7m [c]**	**8m [c]**	**9m [c]**	**10 m[c]**	**11 m[c]**	**12 m**	**2 y [c]**	**3 y [c]**	**4 y [c]**	**5 y [c]**
Informed consent	X																								
Inclusion/exclusion criteria	X																								
Medical history	X																								
Current medications, therapies and procedures	X	X																							
Physical examination	X	X																							
12-lead EKG	*X[a]*	*X[b]*																							
HIV Ag/Ab test	*X[a]*	*X[b]*										*X[b]*													
HBV test (HBcAb, HBsAg)	*X[a]*	*X[b]*										*X[b]*													
HBV DNA												*X[b]*									*X[b]*				
HCV antibody	*X[a]*	*X[b]*																							
Liver enzymes	*X[a]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*	*X[b]*						*X[b]*				

Pregnancy test	*X*[a]	*X*[b]																							
Sofosbuvir/velpatasvir administration (12 week course)			X	X	X	X	X	X	X	X	X	X	X												
HCV RNA		X[b]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**							**X**				
Donor HCV genotype		X																							
Compliance counseling									X	X	X	X	X												
Compliance assessment									X	X	X	X	X	X											
Graft function									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rejection history									X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse events and serious adverse events									X	X	X	X	X	X											
Medications, therapies and procedures		X							X	X	X	X	X	X											
Survival									X	X	X	X	X	X	X							X	X	X	X	X

a Clinical results obtained within 3 months prior to study enrollment can be utilized.

b Clinical testing result is acceptable

c Telephone visits or review of medical records

Italics: clinical results can be used

Bold: performed for study purposes only

HIV Ag/Ab test and HBV testing at 4 weeks and 12 months done as part of clinical protocol for monitoring of increased risk donors

APPENDIX A: EXPECTED EVENTS FOR LIVER TRANSPLANT RECIPIENTS

The following events are expected to occur with a reasonable frequency in the typical/expected clinical course of a patient following liver transplant:

- Hepatobiliary: graft rejection, non-function of liver, delayed graft function, hepatic artery thrombosis, hepatic necrosis, liver abscess, biliary complications, biliary stricture or leak, biliary stenosis, cholecystitis, pancreatitis, liver failure
- Surgical: leaks (gastrointestinal, biliary or anastomotic), hemorrhage, tracheostomy, return to the operation room for surgery, retransplantation, vascular stenosis or thrombosis (inferior vena cava, portal vein), anastomotic problems, strictures, hernia, lymphocele, incision dehiscence, abdominal wall defect, wound infection, fluid collection, seroma, hematoma, hepatic artery thrombosis, hepatic artery stenosis
- Gastrointestinal: vomiting, diarrhea, dyspepsia, abdominal distention or bloating, abdominal pain, anorexia, perforation, ischemic bowel, reflux gastritis, ascites, ileus, bowel obstruction, GI bleed
- Neurologic: tremors, seizures, confusion, dizziness, hallucinations, delusion, psychosis, insomnia, somnolence, lethargy, depressed level of consciousness, agitation, amnesia, anxiety, emotional lability, vertigo, abnormal dreams, encephalopathy, posterior reversible encephalopathy syndrome, tacrolimus toxicity, neuropathy
- Neuromuscular and skeletal: incoordination, leg cramps, nerve compression
- Constitutional/systemic: fever, asthenia, failure to thrive, weight loss or weight gain, anasarca, embolism, multiorgan failure, malnutrition
- Infection: fever, hypothermia, rigors, chills, systemic inflammatory response syndrome, infection (documented or suspected), sepsis, multisystem organ failure
- Pulmonary: acute lung injury, respiratory distress syndrome, aspiration, asthma, atelectasis, mucus plugging, respiratory failure, dyspnea, hypoxia, pneumonia, pleural effusion, pneumothorax, pulmonary edema, sinusitis, need for mechanical ventilation, intubation or reintubation, chest tube insertion, tracheostomy insertion, embolism, pulmonary hypertension
- Electrolyte and metabolic: acidosis or alkalosis, low albumin, dehydration, gout, increase or decrease in the levels of sodium, potassium, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphate, uric acid, cholesterol, lipids, iron
- Hematologic: anemia, blood loss, prolonged PT or PTT, abnormalities in coagulation, hematoma, hemorrhage, bleeding, venous thrombosis, thrombocytopenia/thrombocytosis, leukopenia/leukocytosis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, pancytopenia
- Cardiac: arrhythmias, prolonged QT interval, QRS or ST segment abnormal, tachycardia, bradycardia, torsade de pointes, hypertension, hypotension, pulmonary hypertension, myocardial ischemia or infarction, syncope, postural hypotension, phlebitis, thrombosis
- Renal: acute renal failure, albuminuria, nephropathy, hematuria, proteinuria, acute tubular necrosis, interstitial nephritis, hemorraghic cystitis
- Genitourinary: bladder spasm, dysuria, nocturia, incontinence, urinary frequency, urinary retention
- Malignancies: lymphoproliferative disorder, skin neoplasm
- Dermatologic: edema at any body site, rash, ecchymosis, bruising, flushing, cellulitis, dermatitis, decubitus ulcer, photosensitivity, skin ulcer, impaired wound healing

References

1. Seem DL, Lee I, Umscheid CA, Kuehnert MJ. PHS guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. *Public Health Rep.* Jul 2013;128(4):247-343.

2. Lobo LJ, Noone PG. Respiratory infections in patients with cystic fibrosis undergoing lung transplantation. *Lancet Respir Med.* Jan 2014;2(1):73-82.

3. Levitsky J, Formica RN, Bloom RD, et al. The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. *Am J Transplant.* Nov 2017;17(11):2790-2802.

4. Maylin S, Martinot-Peignoux M, Moucari R, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. *Gastroenterology.* Sep 2008;135(3):821-829.

5. Bari K, Luckett K, Kaiser T, et al. Hepatitis C Transmission from Seropositive, Non-Viremic Donors to Non-Hepatitis C Liver Transplant Recipients. *Hepatology.* Dec 2 2017.

6. Saxena V, Koraishy FM, Sise ME, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int.* Jun 2016;36(6):807-816.

7. Desnoyer A, Pospai D, Le MP, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. *J Hepatol.* Jul 2016;65(1):40-47.

8. Singh T, Guirguis J, Anthony S, Rivas J, Hanouneh IA, Alkhouri N. Sofosbuvir-based treatment is safe and effective in patients with chronic hepatitis C infection and end stage renal disease: a case series. *Liver Int.* Jun 2016;36(6):802-806.