CLINICAL STUDY PROTOCOL

Title: P R O - A C T : *Pr*evention of De N*o*vo HCV with *A*ntiviral H*C*V Therapy Post-Liver and Post-Kidney *T*ransplant

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REVISION HISTORY

Version 1.7, dated 18 January 2018:

1) HCV viremia is to be confirmed before sofosbuvir/velpatasvir (SOF/VEL) EPCLUSA therapy is initiated. Language to reflect this change has been updated in the Protocol Synopsis, Study Design (treatment regimen), Study Procedures (Clinical evaluations, recipient data in the post-transplant period, study visits), and Schedule of Assessments (Appendix 3).
2) In the event of virologic failure following treatment with SOF/VEL, subjects will be eligible for re-treatment with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) VOSEVI therapy in the Virologic Failure Substudy. These subjects must complete their Day 1 visit within 30 days of documentation of virologic failure. On-treatment visits will occur on Weeks 1, 4, 8 and 12. Post-treatment visits will occur at Weeks 4, 12 and 24 after last dose of SOF/VEL/VOX. SOF/VEL/VOX is not to be co-administered with cyclosporine. Language to reflect this change has been updated in the Protocol Synopsis, Background and Scientific Rationale (risk/benefit assessment), Study Design (description), Investigational Medicinal Products, Study Procedures, Responsibilities (informed consent process), and Schedule of Assessments (Appendix 3a).

PROTOCOL SYNOPSIS

Study Title:	Prevention of De Novo HCV with Antiviral HCV Therapy Post-Liver and Post-Kidney Transplant
Study Centers Planned:	6
Number of Subjects Planned:	30
Target Population:	HCV negative liver and/or kidney transplant recipients who receive an HCV nucleic acid test positive deceased donor organ
Duration of Treatment:	12 weeks
Duration of Study:	Up to 40 weeks (up to 1-4 week(s) between transplant and start of study medication, 12 weeks of treatment followed by 24 weeks of follow up). The duration for subjects in the Virologic Failure Substudy, will be up to an additional 36 weeks (12 weeks of treatment followed by 24 weeks of follow up).
Objectives:	1) To determine the efficacy of sofosbuvir/velpatasvir (SOF/VEL) EPCLUSA therapy in HCV negative liver and/or kidney transplant recipients with HCV nucleic acid test (NAT) positive donors. 2) To determine the safety of SOF/VEL therapy in HCV negative liver and/or kidney transplant recipients with HCV NAT positive donors. 3) To compare the observed waiting time for transplant for HCV negative liver and/or kidney transplant recipients with HCV NAT positive donors to the expected waiting time for transplant with HCV negative donors at participating centers.
Study Design:	An open label, multicenter, proof of concept, pilot study evaluating the safety and efficacy of SOF/VEL in HCV negative liver and/or kidney transplant recipients with HCV NAT positive donors

Key Inclusion Criteria:	1) HCV negative adults wait-listed for primary liver and/or kidney transplant without a suitable living donor; 2) Donor characteristics: serum HCV NAT positive and negative for hepatitis B surface antigen • For liver transplant: pre-donation liver biopsy with no fibrosis (F0) or minimal fibrosis (F1) • For kidney transplant: kidney donor profile index ≤ 85%; 3) HCV viremic after transplant
Key Exclusion Criteria:	1) Recipient or donor HIV infected or hepatitis B surface antigen positive; 2) Liver single organ recipients who received hemodialysis ≥ 7 days prior to transplant; 3) Kidney single organ recipients who have been on dialysis for > 5 years at time of screening, sensitized with panel reactive antibody > 80%, or with advanced liver fibrosis (Knodell stage 3) or cirrhosis;
Study Procedures/Frequency:	Potential subjects will complete a 3-step informed consent process: 1) at pre-screening, 2) Informed Consent Part 1 at screening before they are rendered eligible for HCV-viremic organ offers through the opt-in mechanism in the allocation system, and 3) Informed Consent Part 2 confirming their willingness to proceed with HCV viremic transplant when they are called in for transplant. Eligible subjects with documented HCV viremia will be started on SOF/VEL usually within one week (but up to 4 weeks per investigator discretion) after

	transplant. Prior to Day 1, laboratory assessment and assessment of severity of liver disease (if applicable) will be performed. Day 1 is defined as the day the study drug commences. There will be 7 on treatment study visits during which laboratory studies will be sent, concomitant medications will be reviewed and adverse events (AEs) will be assessed. There will be 5 on treatment laboratory only visits, which may also include a telephone call to verify concomitant medications. There will be 1 end of treatment visit during which laboratory studies will be sent, concomitant medications will be reviewed and AEs will be assessed. There will be 1 post-treatment study visit during which laboratory studies will be sent, concomitant medications will be reviewed and AEs will be assessed. There will be 2 post-treatment study visits during which laboratory studies will be sent and concomitant medications will be reviewed.
Virologic Failure Substudy	In the event of virologic failure following treatment with SOF/VEL, subjects will be eligible for re-treatment with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) VOSEVI therapy in the Virologic Failure Substudy. These subjects must complete their Virologic Failure Substudy Day 1 visit within 30 days of documentation of virologic failure. On-treatment visits will occur at Weeks 1, 4, 8 and 12. Post-treatment visits will occur at Weeks 4, 12 and 24 after last dose of VOSEVI.
Test Product:	SOF/VEL (sofosbuvir 400 mg/ velpatasvir 100 mg). For subjects in the Virologic Failure Substdy, SOF/VEL/VOX (sofosbuvir 400 mg/ velpatasvir 100 mg/ voxilaprevir 100 mg).
Dose and Mode of Administration:	One tablet SOF/VEL daily with or without food for 12 weeks. For subjects in the Virologic Failure Substudy, one tablet SOF/VEL/VOX daily with food for 12 weeks.

Criteria for Evaluation:

Efficacy:	The primary efficacy endpoint is the proportion of subjects who achieve a sustained virologic response (SVR12). Secondary endpoints include proportion of subjects who achieve SVR24, the proportion of subjects with viral relapse or viral breakthrough and patient and graft survival at Week 36 (24 weeks after starting study drug).
Safety:	Safety will be assessed through the reporting of adverse events and clinical laboratory tests When the first 10 subjects reach treatment week 4, the lead investigators and the independent data and safety monitor will conduct a Safety Review. When these same subjects reach follow up week 12 (24 weeks after starting study drug), the lead investigators and the independent data and safety monitor will conduct another Safety Review.
Statistical Methods:	Sample size was selected to provide safety and efficacy data. The small size of the pilot study does not permit hypothesis testing. Descriptive statistics on the number and types of AEs will be recorded and presented.
Safety Analysis:	Safety analysis will include summaries of AEs and laboratory evaluations

BACKGROUND AND SCIENTIFIC RATIONALE

In the Unites States, the number of patients listed for solid organ transplant dramatically exceeds the numbers of organs available and utilized for donation. For kidney transplant, mean waiting times are measured in years. There is a 4 % mortality on the kidney wait list, with much higher rates for diabetic and elderly candidates. On the liver wait list, the mortality rate is considerably higher, averaging about 20% at most centers. Numerous strategies are utilized to expand the standard donor pool for kidney or liver transplant, including using organs from deceased donors exposed to chronic viral infections (e.g. cytomegalovirus and hepatitis B virus), Public Health Services increased risk donors, older donors, donation after cardiac death, and livers with increased steatosis.

Deceased solid organ donors with hepatitis C virus (HCV) infection represent another potential source of expanding the organ donor pool. HCV affects about 1.6% of the general population in the United States. The prevalence of HCV was more than triple this number for American organ donors from 2004 - 2008 (Armstrong). Among high-risk donors, who represent up to 30% of all donors, the prevalence was as high as 18.2% (Ellingson, (Kucirka Am J Transplant 2009 PMID 20353475). Perhaps reflecting the ongoing opioid crises in the United States, in some organ procurement organization areas, nearly 15% of even the current general organ donor pool is HCV positive (personal communication, Alex Glazier, CEO, New England Organ Bank). As these donors are typically young, the organs may be higher quality than would be otherwise available from HCV negative donors.

Historically, organs from HCV-positive donors have been underutilized. Reese, et al. identified 3273 HCV-antibody positive deceased kidney donors from 2005-2014 for whom organ donation was authorized (Reese). Only 2402/6546 (37%) of the donated kidneys were transplanted; 91% of the recipients had documented HCV infection. The other kidneys were discarded. In addition, as many as one third of solid organs may not be procured from potential donors who were HCV-antibody positive (Seem), presumably due to concerns they would not be utilized by any transplant center.

In the past, this hesitancy to use HCV-positive organs reflected concerns about the negative liver and extrahepatic outcomes of refractory HCV infection in the setting of immunosuppression. Still, many centers in the United States have utilized hepatitis C-positive solid organs for hepatitis C-positive recipients. For liver transplant, most studies have shown equivalent survival for those HCV-positive recipients who receive carefully selected HCV-positive livers, particularly if older donors (>55 years) and donor livers with fibrosis are avoided (Vargas, Marroquin, Berenguer). For kidney transplant, in one study the median waiting time for patients who accepted HCV-positive kidneys was 469 days versus 856 days for patients who received HCV-negative organs (Kucirka 20353475). In the era before direct acting antiviral agents (DAAs), the reduced mortality on the kidney wait list may have been offset by some increase in adverse post-transplant outcomes (Morales, Kucirka Am J Kid, Gasink, Fabrizi).

The advent of safe and highly effective DAAs has revolutionized the treatment of HCV. In non-cirrhotic, immunocompetent patients, 12 weeks of treatment with the pan-genotypic regimen of sofosbuvir/velpatasvir (SOF/VEL) has demonstrated sustained virological response (SVR) rates above 94% for all HCV genotypes (Foster, Feld). In kidney transplant recipients with HCV, there are numerous publications showing excellent safety and near universal SVR using DAAs. In liver transplant recipients, including those with compensated cirrhosis, the SVR rates for all genotypes were 96-98% with sofosbuvir/ledipasvir with or without ribavirin. (Saab, Charlton, Manns) and at least 91% with sofosbuvir, daclatasvir and ribavirin (Poordad). In a recent study of 79 liver transplant recipients with chronic genotype 1-4 HCV infection treated with SOF/VEL, SVR rates were greater than 93% for all genotypes, including genotype 1 subtypes (Agarwal).

While there is ample precedent for using HCV-positive organs for HCV-positive recipients, utilizing an HCV-positive organ for an HCV-negative recipient has been done rarely and only in highly selected situations (Northup, Gasink, Gudmundsson). In an open-label pilot study, 10 HCV-negative kidney recipients received an HCV genotype-1 infected kidney (Goldberg). On day 3 after transplantation, all recipients had detectable HCV RNA. All 10 were cured with 12 weeks of the genotype-specific regimen of grazoprevir and elbasvir.

The need to study using HCV positive organs for HCV negative recipients was identified in a recent position paper from the American Society of Transplantation (Levitsky). In this current pilot study, we will utilize kidneys and livers from HCV NAT positive donors for HCV-negative recipients. Pan-genotypic HCV therapy with sofosbuvir and velpatasvir (SOF/VEL) will be started usually within the first week (but up to 4 weeks per investigator discretion) after transplant and continued for 12 weeks. Unlike the pilot study in kidney transplant recipients described above, we will not restrict donation to donors with genotype 1 or 4 HCV. The justification for using a pan-genotypic regimen is the imperative to start treating the HCV infection as soon as possible after transplant, potentially before commercial testing for HCV genotype would be available.

In summary, this study has the potential to demonstrate that organs from HCV NAT positive donors can be used safely and effectively in HCV negative patients. Given the established safety and efficacy of pan-genotypic regimens such as SOF/VEL, we hypothesize that the post-transplant *de novo* HCV infections will be successfully cured with a favorable safety profile. The importance of this study is that it may demonstrate an effective way to increase the organ donor pool and to shorten the waiting time for patients being transplanted who might otherwise not receive an organ.

Pharmacologic considerations. Velpatasvir is a substrate for Cytochrome p450 3A4 (CYP3A4), CYP2C8 and CYP2B6 and a weak (P-glycoprotein, organic anion-transporting polypeptide) to moderate (breast cancer resistance protein) transport inhibitor. It is moderately affected by potent inhibitors and to a greater extent, potent

inducers of enzyme/drug transporter systems (Mogalian). Based on this profile, which is similar to ledipasvir, clinically significant drug-drug interactions would not be expected for co-administration of SOF/VEL with tacrolimus, cyclosporine, corticosteroids and/or mycophenolate mofetil.

One potential concern for using SOF/VEL in the early post-transplant setting may be the development of post-transplant acute kidney insufficiency. The labelling information states that the safety and efficacy of SOF/VEL have not been established in patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) or ESRD requiring hemodialysis. However, post marketing data have characterized the safety of sofosbuvir-based therapy in patients with severe renal failure or on hemodialysis (Desnoyer, Dumortier) and specifically in the post-kidney (Beinhardt) and post-liver transplantation setting (Saab J Clin Gastro). Moreover, the principal investigators in this trial will use their discretion as to the exact timing of the initiation of DAA therapy and the subjects will be intensely monitored during the treatment and follow-up periods.

Risk/Benefit Assessment. This study will provide information regarding the safety of efficacy of SOF/VEL in HCV negative liver and/or kidney transplant recipients with HCV NAT positive donors. The potential benefits of utilizing HCV NAT-positive organs are reduced morbidity and mortality compared to what would be expected from remaining on the transplant waiting lists until a suitable HCV negative organ would become available. Potential risks of this study include those related to unsuccessfully treated HCV infection. To mitigate these potential risks, antiviral therapy will be started usually within the first week (but up to 4 weeks per investigator discretion) after transplant and there will be close monitoring of laboratory values as well as AEs. In addition, in the event of virologic failure following treatment with SOF/VEL, subjects will be eligible for re-treatment with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) VOSEVI therapy in the Virologic Failure Substudy There will also be two Safety Reviews conducted by the independent data and safety monitor in conjunction with the lead investigators. While the potential benefits and risks must be confirmed in this pilot study, the data from the THINKER trial, the endorsement of such a study from the American Society of Transplantation, and the favorable safety profile of SOF/VEL provide strong rationale for a positive benefit/risk ratio in support of this study.

Compliance. This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

OBJECTIVES

Objective #1: To determine the efficacy of sofosbuvir/velpatasvir (SOF/VEL) therapy among HCV negative liver and/or kidney transplant recipients with HCV NAT positive donors.

Hypothesis: SOF/VEL therapy initiated in the early post-transplant period provides a high rate of sustained virological response in HCV negative liver and/or kidney transplant recipients transplanted with HCV NAT positive donors.

Objective #2: To determine the safety and tolerability of SOF/VEL therapy among HCV negative liver and/or kidney transplant recipients with HCV NAT positive donors.

Hypothesis: SOF/VEL therapy initiated in the early post-transplant period is safe and well tolerated in HCV negative liver and/or kidney transplant recipients transplanted with HCV NAT positive donors.

Objective #3: To compare the observed waiting time for transplant for HCV negative liver and/or kidney transplant recipients with HCV nucleic acid test (NAT) positive donors to the expected waiting time for transplant with HCV negative donors in participating regions.

Hypothesis: Receiving a NAT positive liver and/or kidney substantially shortens the wait time for liver and/or kidney transplant.

STUDY DESIGN

Description

This is a prospective multicenter, open-label, proof of concept study being conducted at up to 6 American sites (See Appendix 2). The study aims to enroll up to 30 study subjects undergoing liver and/or kidney transplantation, at least 10 of them undergoing liver transplant and at least 10 undergoing kidney transplant.

Potential study candidates will be identified through the active wait-list for liver of kidney transplant at each participating institution. The informed consent process for this trial is comprised of three steps:

1) Pre-screening: As part of pre-transplant evaluation, treating nephrologists and hepatologists will have a detailed discussion with their patients regarding high-risk donors, including those who are HCV NAT-positive. For HCV negative patients who express interest in receiving an HCV NAT-positive donor, their treating hepatologist or nephrologist will refer them to the principal investigator or co-investigator for this study.

2. Informed consent: the principal investigator, or co-investigator, will review the potential risks and benefits of participating in this trial, including a discussion regarding HCV treatment and complications of unsuccessfully treated post-transplantation HCV, including graft loss, fibrosing cholestatic hepatitis, cirrhosis and death. The discussion will also describe that organ donors in the trial might be classified as Public Health Service elevated risk for window infection with HIV. This step of the informed consent process will include documentation that each of these elements has been reviewed with the patient who understands and has ample opportunity to have all of their questions and concerns addressed. Participants who are deemed eligible and sign consent will be rendered eligible for HCV-viremic kidney or liver offers through an opt-in mechanism in the allocation system administered by the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS).

3. Confirmation of Informed Consent: eligibility and subject's willingness to proceed with an HCV-positive donor will be re-confirmed by the subject signing the confirmation of consent block on the original consent form. This will be documented by study staff within 24 hours before the planned liver or kidney transplant (the "Pre-Transplant day") with a review of the potential risks and benefits of participating in this trial, including a discussion regarding HCV treatment and complications of unsuccessfully treated post-transplantation HCV, complications including graft loss, fibrosing cholestatic hepatitis, cirrhosis and death. This step of the informed consent process will include documentation that each of these elements has been reviewed with the patient who understands and has ample opportunity to have all of their questions and concerns addressed.

On the Pre-Transplant Day, after it has been confirmed that both the recipient and the

donor meet the eligibility criteria, the recipient will proceed with transplant surgery.

Treatment Regimen. Study medication will be initiated usually within the first week post-transplant (but up to 4 weeks post-transplant per investigator discretion). HCV viremia will be confirmed before study treatment is started. Day 1 is defined as the day that the study drug commences. Subjects will be administered SOF/VEL (Sofosbuvir 400 mg/Velpatasir 100 mg fixed-dose combination) once daily with or without food for 12 weeks.

Administration of study medication may be permanently discontinued at any time during the treatment period due to a clinical or laboratory event at the discretion of the investigator. There is no option for SOF/VEL dose reduction. If subjects miss a dose (or doses) of study drug, they will still complete the full 84 days of study drug.

Subjects who meet any of the following criteria must stop all study medications:

- Any medical condition, in the opinion of the investigator, where the risks of continuing the study medications outweighs the benefits;
- Any Grade 4 adverse event assessed as related to SOF/VEL.

Immunosuppressant therapy will be per the individual center's usual treatment protocol. Immunosuppressant levels will be done and immunosuppressant dosages will be recorded on treatment days 3 and 7; weekly during the treatment period; at the end of treatment; and 4, 12 and 24 weeks after discontinuation of therapy. Unscheduled therapeutic drug levels may be obtained more frequently at the discretion of the investigator. Modifications in immunosuppression regimen will be at the discretion of the investigator.

Efficacy. Serial quantitative HCV RNA testing will be performed by day 7 after transplant if study medication has not been started, Day 1, on treatment weeks 1 and 4; end of treatment; and weeks 4, 12 and 24 after discontinuation of therapy.

Safety. Adverse events (AEs) will be recorded for all patients who receive a NAT-positive HCV organ through 4 weeks after the last dose of study drug. Serious adverse events (SAEs) will be reported to the lead investigators and the independent data and safety monitor within 24 hours of recognition by study staff. SAEs will be collected for the entire duration of the study. After the 10th study subject has reached treatment week 4, the lead investigators and the independent data and safety monitor will conduct a safety and efficacy review of all safety and efficacy data to date. When these same subjects reach follow up week 12 (corresponding to 24 weeks after starting study drug), the lead investigators and the independent data and safety monitor will conduct another safety and efficacy review.

Virologic Failure Substudy. In the event of virologic failure following treatment with SOF/VEL, subjects will be eligible for re-treatment with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) VOSEVI therapy in the Virologic

Failure Substudy. These subjects must complete their Day 1 visit within 30 days of documentation of virologic failure. Day 1 is defined as the day that the SOF/VEL/VOX commences. Subjects will be administered SOF/VEL/VOX (Sofosbuvir 400 mg/Velpatasvir 100 mg/Voxilaprevir 100 mg fixed-dose combination) once daily with food for 12 weeks. SOF/VEL/VOX is not to be co-administered with cyclosporine. On-treatment visits will occur on Weeks 1, 4, 8 and 12. Post-treatment visits will occur at Weeks 4, 12 and 24 after last dose of SOF/VEL/VOX. There is no option for SOF/VEL/VOX dose reduction. If subjects miss a dose (or doses) of study drug, they will still complete the full 84 days of study drug.

SUBJECT POPULATION

This study will enroll approximately 30 HCV negative subjects

Inclusion criteria:

1. Adult (≥ 18 year-old), wait-listed for primary kidney or liver transplant without a potential suitable living donor or for simultaneous liver kidney transplant;
2. HCV non-infected at the time of transplant. Subjects who were previously HCV infected but who have had documented SVR12 are eligible to participate;
3. Able to provide informed consent;
4. Agree to use two methods of birth control during the study;
5. Donor characteristics: serum HCV NAT-positive and negative for hepatitis B surface antigen. Subjects who receive an organ from hepatitis B core antibody positive donors may be included, but will need to remain on nucleos(t)ide analogues for at least the study treatment period and follow-up period;
    - For liver transplant: pre-donation liver biopsy with no fibrosis (F0) or minimal fibrosis (F1);
    - For kidney transplant: kidney donor profile index < 85%.

Exclusion criteria:

1. Donor and/or recipient HIV infection
2. Subject pregnant or nursing
3. Donor and/or recipient Hepatitis B surface antigen positive
4. Kidney-pancreas transplant
5. Single organ liver recipients who received hemodialysis for more than 7 days prior to liver transplantation
6. Kidney recipients:
    - on dialysis for > 5 years at time of Screening
    - subjects sensitized with panel reactive antibody > 80%
    - for single organ kidney transplant, subjects with advanced liver fibrosis (Knodell stage 3) or cirrhosis
7. Individuals being treated with and needing to continue rifabutin, rifampin, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, St. John's wort (Hypericum perforatum), medium- or high-dose rosuvastatin or atorvastatin, or high-dose proton pump inhibitors (See Concomitant Medications).
8. Individuals treated with amiodarone within 42 days of organ transplant.

INESTIGATIONAL MEDICINAL PRODUCTS

Study drugs to be distributed to centers will be labeled to meet applicable requirements of the United States Food and Drug Administration. Study drug should be stored at controlled room temperature of 25˚C (77˚F); excursions are permitted between 15˚C and 30˚C (59˚F and 86˚F). Until dispensed to study subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied.

SOF/VEL will be provided by Gilead Sciences (Foster City, California). Subjects will take one tablet once daily at approximately the same time each day with or without food. If needed for virologic failure following treatment with SOF/VEL, re-treatment with, SOF/VEL/VOX (VOSEVI) will be provided by Gilead Sciences (Foster City, California) and administered at the discretion of the principal investigator in the Virologic Failure Substudy. VOSEVI is not to be co-administered with cyclosporine.

Prior and Concomitant Medications

Concomitant medications of interest will be recorded throughout the treatment period and will include immunosuppressants, proton pump inhibitors, H2 antagonists, and beta-blockers. Immunosuppressant doses will be recorded until follow up week 24. Concomitant medications, which are not recommended to be taken with the study drug, include, but are not limited to: rifabutin, rifampin, carbamazepine, phenytoin, phenobarbital, oxcarbazepine and St. John's wort (Hypericum perforatum). Amiodarone must be discontinued at least 6 weeks before study drug commences and is prohibited during the study treatment period. For subjects who must be treated with statins during the treatment period, low dose statins (such as pravastatin) may be used per package insert. H2-receptor antagonists (in doses not to exceed famotidine 40 mg bid) may be administered simultaneous with or 12 hours apart from SOF/VEL. If it is medically necessary to co-administer with proton pump inhibitors, SOF/VEL should be administered with food and taken 4 hours before the dose equivalent to 20 mg omeprazole daily.

For subjects in the Virologic Failure Substudy, concomitant medications of interest will be recorded throughout the treatment period and will include immunosuppressants, proton pump inhibitors, H2 antagonists, and beta-blockers. Immunosuppressant doses will be recorded until follow up week 24. Concomitant medications, which are not recommended to be taken with SOF/VEL/VOX, include, but are not limited to: rifabutin, carbamazepine, phenobarbital, oxcarbazepine, rosuvastatin, and St. John's wort (Hypericum perforatum). SOF/VEL/VOX is not to be co-administered with cyclosporine. Co-administration with rifampin is contraindicated. Amiodarone must be discontinued at least 6 weeks before SOF/VEL/VOX commences and is prohibited during the study treatment period. For subjects who must be treated with statins during the treatment period, low dose statins (such as pravastatin) may be used per package insert. H2-receptor antagonists (in doses not to exceed famotidine 40 mg bid) may be administered simultaneous with or 12 hours apart from SOF/VEL/VOX. If it is

medically necessary to co-administer with proton pump inhibitors, SOF/VEL/VOX can be administered simultaneous with 20 mg omeprazole daily.

Investigational Medicinal Product Accountability

The investigator or designee (e.g. pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug, dispensing records and returned or destroyed study drug. Dispensing records will document quantities received from Gilead Sciences and quantities dispensed to subjects, including the lot/kit number, date dispensed, subject identification number, and the initials of the person dispensing the medication. All unused study drug dispensed to subjects must be returned to the site.

Investigational Medicinal Product Return or Disposal

If a site has a standard operating procedure (SOP) for drug destruction, the site may destroy unused study drug in accordance with the site's SOP.

STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 3 and described in the text that follows.

Subject Enrollment

It is the responsibility of the site investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study. Documentation of the personally signed and dated the informed consent (ICF), using the study-specific ICF, is required before initiating the Screening process. After written informed consent is obtained and eligibility to participate established, investigative site personnel will obtain the subject's identification number.

Documentation of the personally signed and dated confirmation of consent section, using the subject's original signed consent, required before proceeding with HCV NAT-positive organ transplant. After confirmation of consent has been obtained and eligibility to participate confirmed, investigative site personnel will obtain the subject's study identification number (ST-ID).

Clinical Evaluations

Clinical data from the pre- and post-transplant assessment will be reviewed from the electronic medical record.

Recipient data Pre-Transplant Day:

- Age, sex, ethnicity, race, weight and body mass index;
- Type of transplant: liver, kidney, or simultaneous liver/kidney;
- Primary indication for transplant;
- Serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, serum or urine hCG for females of childbearing potential, HCV quantitative RNA, hepatitis B surface antigen and hepatitis B core antibody total;
- For liver transplant, presence or absence of hepatocellular carcinoma;
- For liver transplant, presence and severity of hepatic encephalopathy and ascites;
- For liver transplant, Lab MELD-Na, MELD exception score (if any) and Child-Pugh score (Appendix 4) at the time of transplant;
- For kidney transplant, panel reactive antibody.

Donor data Pre-Transplant Day:

- Age, sex, cause of death (brain or cardiac);
- UNOS region;
- For kidney transplant, kidney donor profile index;
- HCV RNA NAT testing, HCV genotype, hepatitis B core antibody;
- Sample for possible baseline resistance associated substitutions;
- Sample for serum banking;
- Liver biopsy: stage of fibrosis and estimated percentage of fat.

Transplant surgery data:

- For liver transplant, surgical technique: piggyback vs other;
- Cold and warm ischemia times (in hours);
- Time and date of transplant (time of reperfusion for liver transplant).

Recipient data in the post-transplant period:

- Time and date of first administration of study drug;
- Interval (in days) between time of transplant and time and date of first administration of study drug;
- HCV RNA on day 3 after transplant, If result is "HCV RNA not detected", HCV RNA to be repeated on day 7 after transplant and then weekly until HCV RNA is detected;
- Serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, and immunosuppressant level and dosage on treatment days 1, 3, and 7; weekly throughout the treatment period; at the end of treatment; and 4, 12, and 24 weeks after discontinuation of therapy;
- serum or urine serum hCG for females of childbearing potential at weeks 4 and 8 and at end of treatment;
- Serial quantitative HCV RNA testing will be done on Day 1, treatment weeks 1 and 4; end of treatment; and weeks 4, 12 and 24 after discontinuation of therapy;
- Testing for resistance associated substitutions if virologic failure;
- Length of index hospital stay (in days);
- Number, length and reason for subsequent post-transplant admissions (if any);
- Concomitant medications of interest;
- Interruptions of antiviral therapy > 72 hours.

Resistance Monitoring

Plasma samples will be collected for viral sequence analysis and possible phenotypic testing from the donor at baseline and from the recipient at treatment failure (if it occurs).

Subject identification number assignment

Subject Identification (ID) numbers will be assigned sequentially at each site to each subject who has signed informed consent (Part 1). A new subject ID number (indicated by the prefix "ST-" followed by the ID number previously assigned at the time of signing informed consent Part 1) will be assigned when eligibility has been confirmed, the subject has signed informed consent Part 2 and the subject undergoes transplant surgery. If a patient discontinues from the study, the Subject ID Number will not be reused.

Study Visits

1st visit: Screening Visit

This visit is anticipated to require 1 hour of the subject's time. During this visit, the following will take place:

- Review of eligibility criteria;
- Informed consent;
- Assignment of subject ID number.

2nd visit: Pre-Transplant Day

Screening/baseline visit is anticipated to require 1 hour of the subject's time. During this visit, the following will take place:

- Confirmation of consent signed and documentation of subject's willingness to proceed with HCV positive donor;
- Review of eligibility criteria;
- Laboratory tests including Quantitative HCV RNA, hepatitis B surface antigen, Serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, serum or urine hCG for females of childbearing potential;
- Assessment of presence and severity of ascites and hepatic encephalopathy;
- Assignment of subject ST-ID number.

3rd visit: Day 3 after transplant

- Quantitative HCV RNA. (if "HCV RNA not detected", repeat day 7 after transplant. If result is "HCV RNA not detected", HCV RNA to be repeated weekly after transplant until detected)

Day 1 (The day study drug commences)

- Confirm recipient still meets eligibility criteria;
- First administration of study drug;
- Laboratory tests including serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, immunosuppressant level, and quantitative HCV RNA.;
- Concomitant medications of interest including immunosuppressant;

On HCV treatment visits

These 7 visits will occur in the hospital or at the outpatient clinic per the schedule of assessments on Day 3, Week 1, Week 2, Week 3, Week 4, Week 6 and Week 8. It is anticipated that each of these visits will require 30 minutes of the subject's time. The following events will take place:

- Clinical examination;
- Laboratory tests including s erum blood urea nitrogen, creatinine, estimated glomerular filtration rate, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, INR, and immunosuppressant level;
- Serum or urine hCG for females of childbearing potential at weeks 4 and 8;
- Quantitative HCV RNA on weeks 1 and 4;
- Hepatitis B surface antigen on week 4;
- Concomitant medications of interest including immunosuppressant;
- Assessment for AEs.

Laboratory only visits

These 5 visits will occur at either the transplant center laboratory or a local laboratory per the schedule of assessments on Weeks 5, 7, 9, 10, and 11. These visits may also include a telephone call to confirm the dose of the immunosuppressant medication. It is anticipated that each of these visits will require 15 minutes of the subject's time.

End of HCV treatment visit

This visit will occur at the end of antiviral treatment at the outpatient clinic. It is anticipated to require 30 minutes of the subject's time. The following events will take place:

- Clinical examination;
- Laboratory tests including serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, and immunosuppressant level;
- Serum or urine hCG for females of childbearing potential;
- Quantitative HCV RNA;
- Concomitant medications of interest including immunosuppressant;
- Assessment for AEs.

Post-HCV treatment Follow Up visits

These three visits will occur at 4, 12, and 24 weeks after discontinuation of antiviral treatment. Follow Up visits 4 and 12 will take place in the outpatient clinic while Follow Up Week 24 will occur either in the transplant clinic or local laboratory and may also include a telephone call to confirm the dose of the immunosuppressant medications. Each visit is anticipated to require 15-30 minutes of the subject's time. The following

events will take place:

- Clinical examination (Follow Up visits 4 and 12 only;)
- Laboratory tests including serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, INR, and immunosuppressant level;
- Serum or urine hCG for females of childbearing potential at Follow Up Week 4;
- Hepatitis B surface antigen at Follow Up Week 4;
- Quantitative HCV RNA;
- Concomitant medications of interest including immunosuppressant on follow up week 4;
- Immunosuppressant dose;
- Assessment for AEs on Follow Up Week 4.

Early End of Treatment or Treatment Failure visit

This unscheduled visit will occur if the subject discontinues study drug prior to planned end of treatment for any reason OR the subject has been determined to have viral breakthrough or relapse. This visit must occur within 2 weeks of stopping treatment or recognition of viral breakthrough or relapse. Each visit is anticipated to require 30 minutes of the subject's time. The following events will take place:

- Clinical examination;
- Laboratory tests including serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, and immunosuppressant level;
- Quantitative HCV RNA and HCV genotype;
- Testing for HCV resistance associated substitutions;
- Concomitant medications of interest including immunosuppressant;
- Assessment for AEs.

Visit Windows

The study visit windows are +/- 2 days for the day 3 visit, +/- 4 days for the weekly on treatment visits and end of treatment visit, and +/- 10 days for the follow up visits

End of Study Definition

End of study is considered to be completion of the Follow Up Week 24 Visit. Subjects who enter the Virologic Failure Substudy will also follow an additional

Schedule of Assessments for the Virologic Failure Substudy (See Appendix 3a).

Sample Storage

Residual biological samples will be frozen and stored at the individual study sites. No

human genetic testing will be performed without express consent of the study subjects. At the conclusion of this study, these samples may be retained in storage per individual institution policy.

Study Visits for Virologic Failure Substudy

Study visits for the Virologic Failure Substudy may coincide with visits for the main study. When this occurs, laboratory assessments for the main study may also be used for the Virologic Failure Substudy.

Day 1 (The day SOF/VEL/VOX commences)

- First administration of study drug;
- Laboratory tests including serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, immunosuppressant level, and quantitative HCV RNA.
- Concomitant medications of interest including immunosuppressant;

On HCV treatment visits

These 3 visits will occur in the outpatient clinic per the schedule of assessments on Week 1, Week 4, and Week 8. It is anticipated that each of these visits will require 30 minutes of the subject's time. The following events will take place:

- Clinical examination;
- Laboratory tests including s erum blood urea nitrogen, creatinine, estimated glomerular filtration rate, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, INR, and immunosuppressant level;
- Serum or urine hCG for females of childbearing potential at weeks 4 and 8;
- Quantitative HCV RNA on weeks 1 and 4;
- Hepatitis B surface antigen on week 4;
- Concomitant medications of interest including immunosuppressant;
- Assessment for AEs.

End of HCV treatment visit

This visit will occur at the end of antiviral treatment at the outpatient clinic. It is anticipated to require 30 minutes of the subject's time. The following events will take place:

- Clinical examination;
- Laboratory tests including serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, and immunosuppressant level;
- Serum or urine hCG for females of childbearing potential;

- Quantitative HCV RNA;
- Concomitant medications of interest including immunosuppressant;
- Assessment for AEs.

Post-HCV treatment Follow Up visits

These three visits will occur at 4, 12, and 24 weeks after discontinuation of antiviral treatment. Follow Up visits 4 and 12 will take place in the outpatient clinic while Follow Up Week 24 will occur either in the transplant clinic or local laboratory and may also include a telephone call to confirm the dose of the immunosuppressant medications. Each visit is anticipated to require 15-30 minutes of the subject's time. The following events will take place:

- Clinical examination (Follow Up visits 4 and 12 only;)
- Laboratory tests including serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, INR, and immunosuppressant level;
- Serum or urine hCG for females of childbearing potential at Follow Up Week 4;
- Hepatitis B surface antigen at Follow Up Week 4;
- Quantitative HCV RNA;
- Concomitant medications of interest including immunosuppressant on follow up week 4;
- Immunosuppressant dose;
- Assessment for AEs on Follow Up Week 4.

Early End of Treatment or Treatment Failure visit

This unscheduled visit will occur if the subject discontinues study drug prior to planned end of treatment for any reason OR the subject has been determined to have viral breakthrough or relapse. This visit must occur within 2 weeks of stopping treatment or recognition of viral breakthrough or relapse. Each visit is anticipated to require 30 minutes of the subject's time. The following events will take place:

- Clinical examination;
- Laboratory tests including serum blood urea nitrogen, creatinine, estimated glomerular filtration rate, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, and immunosuppressant level;
- Quantitative HCV RNA and HCV genotype;
- Testing for HCV resistance associated substitutions;
- Concomitant medications of interest including immunosuppressant;
- Assessment for AEs.

Visit Windows

The study visit windows are +/- 2 days for the day 3 visit, +/- 4 days for the weekly on treatment visits and end of treatment visit, and +/- 10 days for the follow up visits

End of Study Definition
End of the Virologic Failure Substudy study is considered to be completion of the Follow Up Week 24 Visit.

Sample Storage
Residual biological samples will be frozen and stored at the individual study sites. No human genetic testing will be performed without express consent of the study subjects. At the conclusion of this study, these samples may be retained in storage per individual institution policy.

ADVERSE EVENTS AND TOXICICTY MANAGEMENT

Definitions

An adverse event (AE) is any untoward medical occurrence in a study subject administered a medicinal product. It does not necessarily have a causal relationship with the treatment. Preexisting events that increase in severity or change in nature during participation in a clinical study are considered AEs.

A serious adverse event (SAE) is defined as an event that results in the following:

- Death;
- Life threatening event in which the subject was at risk of death at the time of the event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- A medically important event or reaction that may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs.

Safety monitoring

Safety data will be collected for all subjects who sign their confirmation of consent at the end of the consent form and undergo a NAT-positive transplant through 4 weeks after the last dose of study drug. The Principal Investigators will continuously monitor the study for safety. An independent data and safety monitor will act in an advisory capacity to monitor participant safety and data quality, as well as to evaluate the progress of the study.

The lead investigators will be responsible for holding periodic meetings to update the study group regarding enrollment, study conduct, and potential safety issues that may affect subjects' decisions about enrolling or continuing study drug throughout the study, including, but not limited to: AEs, SAEs, and new treatments that come available.

Clinical Laboratory Abnormalities. Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well an SAE, if applicable. In addition, laboratory assessments that are associated with signs and/or symptoms must be recorded as an AE, or SAE, if applicable. If the laboratory abnormality is part of a syndrome, record the diagnosis (i.e. anemia), not the laboratory abnormality (i.e. decreased hemoglobin).

Adverse Events. The investigator, or sub-investigator, is responsible for assessing AEs and SAEs for causality and severity. AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. This grading scale can be found at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

For AEs associated with laboratory abnormalities, the event should be graded on the clinical severity in the context of the underlying conditions. All AEs, regardless of cause or relationship, must be collected and reported in the eCRF database as instructed.

SAEs will be collected for the duration of the study. SAEs related to study drug, graft loss, or death will be reported to the lead investigators and the independent data and safety monitor within 24 hours of recognition by study staff. Stable chronic conditions that are present prior to the Pre-Transplant Day and do not worsen during the treatment period and safety follow up period are not considered adverse events.

Safety Review. When the first 10 study subjects reach treatment week 4, the lead investigators and the independent data and safety monitor will conduct a safety and efficacy review. When these subjects reach follow up week 12 (24 weeks after starting study drug), the lead investigators and the independent data and safety monitor will conduct another safety and efficacy review.

Early termination: Participants may withdraw their consent to participate in this study at any time after they sign informed consent. Principal investigators can terminate participant(s) from the study for safety concerns. Subjects who take at least one dose of study drug and do not complete the planned 12 weeks of treatment will come for an early end of treatment visit.

STATISTICAL CONSIDERATIONS

Analysis Objectives

The primary objective of this study is to determine the efficacy of SOF/VEL in viral eradication among HCV negative liver and/or kidney transplant recipients with HCV NAT positive donors.

The secondary objective of this study is to determine the safety and tolerability of all SOF/VEL among HCV negative liver and/or kidney transplant recipients with HCV NAT positive donors.

The exploratory objective of this study is to compare the observed waiting time for transplant for HCV negative liver and/or kidney transplant recipients with HCV NAT positive donors to the expected waiting time for transplant with HCV negative donors at the participating centers.

Primary Efficacy Endpoint

The proportion of participants with SVR 12 defined as HCV RNA < lower limit of quantification 12 weeks after last dose of antiviral therapy.

Secondary Endpoints:

- Proportion of subjects with SVR24 defined as HCV RNA < lower limit of quantification 24 weeks after last dose of antiviral therapy;
- Proportion of subjects with viral relapse defined as HCV RNA <LLOQ at end of treatment with subsequent quantifiable HCV RNA;
- Proportion of participants with on-treatment virologic breakthrough defined as > 1 log increase in viral RNA after treatment week 1;
- Proportion of subjects who prematurely discontinue antiviral therapy before the planned end of treatment;
- Patient and graft survival at 6 months post-transplant.

Exploratory Endpoint

Change in wait time for kidney and/or liver transplant based on UNOS data for the participating regions.

Analysis Sets

The primary analysis set for safety and efficacy analyses includes all subjects who undergo liver and/or kidney transplant after signing Part 2 of the Informed Consent. Treatment-emergent data will be analyzed and defined as data collected from the first dose of study drug through the date of the last dose of study drug plus 30 days.

Data Handling Conventions

Missing data will not be imputed other than for quantitative HCV PCR. If a quantitative PCR is missing, the value will be imputed as LLOQ if the viral load before and after are both LLOQ.

Efficacy Analysis

Primary and Secondary Endpoints

No formal hypothesis testing will be performed, as this is an exploratory study. No inferential statistics or statistical comparisons are planned for efficacy endpoints. All subjects who undergo liver and/or kidney transplant with a nucleic acid test positive organ will be included in the analysis. We assume that none of the subjects will achieve SVR 12 without any antiviral therapy. The existing data for SOF/VEL have demonstrated a SVR rate above 94% in non-cirrhotic patients. We anticipate a similar SVR rate for our study. Along with the percentage of patients with SVR12, a two-sided 95% confidence interval (CI) is constructed by using the Clopper-Pearson method. With a sample size of 30 patients, if the SVR12 rate is 90%, the lower bound of the 95% CI would be 79% and the upper bound of the 95% CI would be 100%.

Exploratory Endpoint

Shorter wait time from listing to transplant is a potential benefit of accepting a HCV positive organ. To characterize wait time among HCV positive organ recipients, mean wait time in log10 days will be calculated separately for liver and kidney transplant recipients. With a sample size of 10, 15, or 20 patients per HCV positive organ type and a standard deviation of 1 log10 days of wait time, we have 80% power to obtain a two-sided 95% CI half-width of 8, 5, and 4 days, respectively (CI half-width of 0.9, 0.7, and 0.6 log10 days).

To explore wait time by acceptance of HCV positive versus negative organs, wait time would be collected for the HCV positive organ recipient and the next HCV negative organ recipient at the transplant center, matched on blood type, gender, and transplant MELD (+/-5) for liver recipients and KDPI (+/- 0.25) for kidney recipients. Mean wait time in log10 days for a HCV positive versus negative organ would be compared separately among liver and kidney recipients. We anticipate obtaining wait time on 60 transplant recipients (at least 20 liver and 20 kidney recipients). For a two-sided paired t-test assuming an alpha level of 0.05, we estimate having 80% power to detect a mean difference in wait time of 20, 10, and 8 days for sample sizes of 20, 30, and 40 patients, respectively.

Safety Analysis

Safety will be assessed during the study through the reporting of AEs and by clinical laboratory tests at various time points during the study. Concomitant medication usage will also be assessed throughout the study. Descriptive statistics on the number and types of AEs will be recorded and presented in a tabular format. Treatment-emergent AEs (TEAEs) will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of the study drug will be summarized and listed. Liver or kidney grade 3 or 4 laboratory abnormalities will be described in the narrative.

Independent Data and Safety Monitor (IDSM)

An IDSM with relevant clinical expertise will be chosen who has no financial, scientific,

or other conflict of interest with the trial. The IDSM will review the progress of the study, perform interim review of safety data, and provide recommendations whether the nature, frequency, and severity of AEs associated with the study warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The IDSM will also consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial. When the first 10 study subjects reach treatment week 4, the lead investigators and the IDSM will conduct an open safety and efficacy review. When these same subjects reach follow up week 12 (24 weeks after starting study drug), the lead investigators and the IDSM will conduct another open safety and efficacy review. The IDSM will make recommendations to the lead investigators, and, if required, to the Food and Drug Administration concerning continuation, termination, or other modifications of the trials based on the observed beneficial or adverse effects of the treatment under study.

RESPONSIBILITIES

Investigator Responsibilities

The Principal Investigators will be responsible for recruiting study personnel, obtaining REB/IRB approval, ensuring clinic staffs are informed about the study, and supervising study activities. The study personnel will be responsible for: identifying participants, obtaining informed consent, confirming eligibility, monitoring compliance, conducting study visits, ensuring subjects have regular follow-up, encouraging attendance at visits, and collecting subject data.

Study-wide coordination

The Lead Investigators will be responsible for:

1. Holding periodic meetings to update the study group regarding enrollment, study conduct, and potential safety issues that may affects the patient's decisions about enrolling or continuing study drug throughout the study;
2. Conducting safety reviews with the IDSM after the first 10 subjects reach treatment week 4, and after the first 10 subjects reach Follow Up week 12;
3. Distributing the recommendations from the safety reviews to all co-investigators and IRBs associated with the study;
4. Supervising data management and analysis.

Quality Control and Assurance

It is the responsibility of the Principal Investigators to ensure the quality of computerized data for this study. Information documents will be specifically developed and the data will be collected securely. For each subject consented, an electronic case report form (eCRF) will be completed by an authorized study staff member. eCRFs should be completed on the day of the subject visit. The eligibility criteria eCRF should be completed only after all data related to eligibility have been received. Investigators will ensure that entries accurately reflect the information in the source documents. The site coordinator is responsible for responding to queries in a timely manner and providing reasons for updates, as needed. All records will be kept in a secure location and will only be available only to the study investigators and assigned research staff. Center specific research ethics approval will be obtained before initiating the study at that center.

Ethical Considerations

ICH Guidance E6: Good Clinical Practice: Consolidating Guideline/ Declaration of Helsinki

The conduct of this study will conform to the International Conference for Harmonization and Good Clinical Practice (ICH-GCP) regulations and guidelines and the current revision of the Declaration of Helsinki and reflected in *a priori* approval by

all the study centers' institutional review boards.

Research Ethics Board/ Institutional Review Board

A copy of the protocol (including protocol amendments), all versions of the informed consents, other information to be completed by subjects such as questionnaires, and any proposed advertising/ recruitment materials will be reviewed and approved by the center's REB/IRB prior to implementation of the study. The investigator will notify the REB/IRB of violations from the protocol and serious adverse events.

Informed Consent Process

The informed consent process for this trial is comprised of three steps:

1) Pre-screening: As part of pre-transplant evaluation, treating nephrologists and hepatologists will have a detailed discussion with their HCV negative patients regarding high-risk donors, including those who are HCV NAT-positive. For patients who express interest in receiving an HCV NAT-positive donor, their treating hepatologist or nephrologist will refer them to the principal investigator or co-principal investigator for this study.

2) Informed Consent: The principal investigator or co-principal investigator will review the potential risks and benefits of participating in this trial, including a discussion regarding HCV treatment and complications of unsuccessfully treated post-transplantation HCV, including graft loss, fibrosing cholestatic hepatitis, cirrhosis and death. The discussion will also describe that organ donors in the trial might be classified as Public Health Service elevated risk for window infection with HIV. This step of the informed consent process will include documentation that each of these elements has been reviewed with the patient who understands and has ample opportunity to have all of their questions and concerns addressed. Part 1 of the informed consent, describing in detail the study procedures, anticipated benefits and potential risks, will be given to each participant and written documentation of informed consent is required prior to starting the study. Subjects must voluntarily sign and date Part 1 of the informed consent document that has been approved by a participating center's REB/IRB prior to any procedures being done specifically for the trial. Each subject should have sufficient opportunity to discuss the study and consider the information in the consent process prior to agreeing to participate. Subjects may withdraw consent at any time during the course of the trial. The informed consent will be signed and dated by the subject, the person who conducted the informed consent discussion and the investigator. The original signed informed consent form will be retained in the subject's study files and a copy will be provided to the subject. Participants who are deemed eligible and sign consent will be rendered eligible for HCV-viremic kidney or liver offers through an opt-in mechanism in the allocation system administered by the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS).

3. Confirmation of Consent: Eligibility and subject's willingness to proceed with an HCV-positive donor will be re-confirmed and documented by study staff within 24 hours of the planned liver or kidney transplant (the "Pre-Transplant day") with a review of the potential risks and benefits of participating in this trial, including a discussion regarding HCV treatment and complications of unsuccessfully treated post-transplantation HCV, including graft loss, fibrosing cholestatic hepatitis, cirrhosis and death. This step of the informed consent process will include documentation that each of these elements has been reviewed with the patient who understands and has ample opportunity to have all of their questions and concerns addressed. Part 2 The consent the patient originally signed will be presented to the patient to review and sign the Confirmation of Consent section at the bottom of the informed consent and written documentation of informed consent is required prior to proceeding with the study. Subjects must voluntarily sign and date the Confirmation of Consent section of the informed consent document that has been approved by a participating center's REB/IRB prior to proceeding with the trial. Each subject should have sufficient opportunity to discuss the study and consider the information in the consent process prior to agreeing to participate. Subjects may withdraw consent at any time during the course of the trial. The informed consent will be signed and dated by the subject, the person who conducted the informed consent discussion and the investigator. The original signed informed consent form will be retained in the subject's study files and a copy will be provided to the subject.

Virologic Failure Substudy. In the event of virologic failure following treatment with SOF/VEL, subjects will be eligible for re-treatment with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) VOSEVI therapy in the Virologic Failure Substudy. The principal investigator or co-principal investigator will review the potential risks and benefits of participating in this Substudy, Subjects will sign a separate consent form for the Virologic Failure Substudy. These subjects must complete their Day 1 visit in the Virologic Failure Substudy within 30 days of documentation of virologic failure in the main study.

Participant Confidentiality

All subject related information including the consent, laboratory samples, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject, and a subject letter code. All computerized databases will identify subjects by numeric codes only, and will be password protected. Upon request, clinical information may be reviewed by or released to auditors or regulatory agencies.

Record Retention

Data and study documents at all sites will be stored securely for at least 2 years after completion of the study per FDA requirements (with the specific length of time according to the site's specific requirements), after which they will be destroyed in keeping with

the privacy and confidentiality regulations and guidelines. Samples collected will be retained for at least 2 years after completion of the study (with the specific length of time according to the site's specific requirements), after which they will be destroyed.

Protocol violations and deviations

Protocol violations or deviations will be reported to the Principal Investigator and Lead Investigators. Protocol exemptions, violations, and deviations will be logged.

REFERENCES

Agarwal, K, Castells L, Mullhaupt B, Rosenberg WMC, McNabb B, Areterburn S, Camus G, McNally J, Brainard DM, Subramnian, Gonsalkorala, Londono M, Dufour J0F, Forns X. Sofosbuvir/Velpatasvir for 12 weeks in genotype 1-4 HCV-infected liver transplant recipients. Hepatology 2017; 66 (Suppl);571A.

Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144(10):705-14. [PMID: 17404354]

Beinhardt S, Al Zoairy R, Ferenci P, Kozbial K, Freissmuth C, Stern R, Stattermayer AF, Stauber R, Strasser M, Zoller H, Watschinger B, Schmidt A, Trauner M, Hofer H, Maieron A. DAA-based antiviral treatment of patients with chronic hepatitis C in the pre-and post-kidney transplantation setting. Transpl Int 2016;29:999-1007 [PMID: 27203857]

Berenguer M, Schuppan D. Progression of liver fibrosis in post-transplant hepatitis C: mechanisms, assessment and treatment. J Hepatol. 2013;58(5):1028-41. [PMID: 23262248]

Carbone M, Mutimer D, Neuberger J. Hepatitis C virus and nonliver solid organ transplantation. Transplantation. 2013;95(6):779-86. [PMID: 23172130]

Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, Fried MW, Terrault NA, O'Leary JG, Vargas HE, Kuo A, Schiff E, Sulkowski MS, Gilroy R, Watt KD, Brown K, Kwo P, Pungapong S, Korenblat KM, Muir A, Teperman L, Fontana RJ, Denning J, Arterburn S, Dvory-Sobol H, Brandt-Sarif T, Pang PS, McHutchison JG, Reddy KR, Afdhal N, SOLAR-1 Investigators. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649-59. [PMID: 25985734]

Desnoyer A, Pospai D, Le MP, Gervais A, Heurgue-Berlot A, Laradi A, Harent S, Pinto A, Salmon D, Hillaire S, Fontaine H, Zucman D, Simonpoli AM, Muret P, Larrouy L, Bernard Chabert B, Descamps D, Yazdanpanah Y, Peytavin G. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. J Hepatol 2016;65:40-47 [PMID: 26952005]

Dumortier J, Bailly F, Pageaux GP, Vallet-Pichard A, Radenne S, Habersetzer F, Gagnieu MC, Grange JD, Minello A, Guillaud O, Kamar N, Alric L, Leroy V. Sofosbuvir-based antiviral therapy in hepatitis C patients with severe renal failure. Nephrol Dial Transplant 2016 Oct 19 pii: gfw348 [Epub ahead of print] [PMID: 27760839]

Ellingson K, Seem D, Nowicki M, Strong DM, Kuehnert MJ, Organ Procurement Organization Nucleic Acid Testing Yield Project T. Estimated risk of human immunodeficiency virus and hepatitis C virus infection among potential organ donors from 17 organ procurement organizations in the United States. Am J Transplant.

2011;11(6):1201-8. [PMID: 21645253]

Fabrizi F, Martin P, Dixit V, Messa P. Meta-analysis of observational studies: hepatitis C and survival after renal transplant. J Viral Hepat. 2014;21(5):314-24. [PMID: 24716634]

Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1,2,4,5, and 6 Infection. N Engl J Med 2015;373:2599-607. [PMID: 26571066]

Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med 2015;373:2608-17. [PMID: 27119242]

Gasink LB, Blumberg EA, Localio AR, Desai SS, Israni AK, Lautenbach E. Hepatitis C virus seropositivity in organ donors and survival in heart transplant recipients. JAMA. 2006;296(15):1843-50. [PMID: 17047214]

Goldberg DS, Abt PL, Blkumberg EA, Van Deerlin VM, Levine M, Reddy KR, Bloom RD, Nazarian SM, Sawinski D, Porrett P, Naji A. Trial of transplantation of HCV-infected kidneys into uninfected recipients. N Engl J Med 2017;376:2394-2395. [PMID: 28902585]

Gudmundsson GS, Malinowska K, Robinson JA, Pisani BA, Mendez JC, Foy BK, Mullen GM. Five-year follow-up of hepatitis C-naïve heart transplant recipients who received hepatitis C-positive donor hearts. Transplant Proc 1003;35:1536-8. [PMID:12826214]

Kucirka LM, Alexander C, Namuyinga R, Hanrahan C, Montgomery RA, Segev DL. Viral nucleic acid testing (NAT) and OPO-level disposition of high-risk donor organs. Am J Transplant. 2009;9(3):620-8. [PMID: 19191766]

Kucirka LM, Singer AL, Ros RL, Montgomery RA, Dagher NN, Segev DL. Underutilization of hepatitis C- positive kidneys for hepatitis-C positive recipients. Am J Transplant 2010;10:1238-46. [PMID: 20353475]

Kucirka LM, Peters TG, Segev DL. Impact of donor hepatitis C virus infection status on death and need for liver transplant in hepatitis C-positive kidney transplant recipients. Am J Kidney Dis 2012;60:112-20. [PMID: 22560841]

Levitsky J, Formica RN, Bloom RD, Charlton M, Curry M, Friedewald J, Friedman J, Goldberg D, Hall S, Ison M, Kaiser T, Klassen D, Klintmalm G, Kobashigawa J, Liapakis A, O'Conner K, Reese P, Stewart D, Terrault N, Theodoropoulos N, Trotter J, Verna E, Volk M. The American Society of Transplantation consensus conference in the use of hepatitis C viremic donors in solid organ transplantation. Am J Transplant 2017;17:2790-2802. [PMID: 28556422]

Manns M, Samuel D, Gane E, Mutimer D, McCaughan G, Buti M, Prieto M, Calleja JL, Peck-Radosavljevic M, Mullhaupt B, Agarwal K, Angus P, Yoshida EM, Colombo M, Rizzetto M, Dvory-Sobol H, Denning J, Arterburn S, Pang PS, Brainard D, McHutchison JG, Dufour JF, Van Vlieberghe H, van Hoek B, Forns X, SOLAR-2 Investigators. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicenter, open-label, randomized, phase 2 trial. Lancet Infect Dis 2016;16:685-697. [PMID: 26907736]

Marroquin CE, Marino G, Kuo PC, Plotkin JS, Rustgi VK, Lu AD, Edwards E, Taranto S, Johnson LB. Transplantation of hepatitis C-positive livers in hepatitis C-positive patients is equivalent to transplanting hepatitis C-negative livers. Liver Transpl 20017:762-8. [PMID: 11552208]

Mogalian E, German P, Kearney BP, Yang CY, Brainard D, McNally J, Moorehead L, Mathias A. Use of multiple probes to assess transporter-and cytochrome p450-mediated drug-drug interaction potential of the pangenotypic HCV NS5A inhibitor velpatasvir. Clin Pharmacokinet 2016;55:605-13. [PMID: 26519191]

Morales JM, Campistol JM, Dominguez-Gil B, Andres A, Esforzado N, Oppenheimer F, Castellano G, Fuertes A, Bruguera M, Praga M. Long-term experience with kidney transplantation from hepatitis C-positive donors into hepatitis C –positive recipients. Am J Transpl 2010;10:2453-62. [PMID: 20977636]

Northup PG, Argo CK, Nguyen DT, McBride MA, Kumer SC, Schmitt TM, et al. Liver allografts from hepatitis C positive donors can offer good outcomes in hepatitis C positive recipients: a US National Transplant Registry analysis. Transpl Int. 2010;23(10):1038-44. [PMID: 20444239]

Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, McPhee F et al. Daclatsavir with Sofosbuvir and Ribavirin for Hepatitis C Virus Infection with Advanced Cirrhosis or Post-Liver Transplantation Recurrence. Hepatology 2016;63(5): 1493-505. [PMID: 26574432]

Reese PP, Abt PL, Blumberg EA, Goldberg DS. Transplanting hepatitis C-positive kidneys. N Engl J Med 2015;373: 303-5. [PMID: 26200976]

Saab S, A Jimenez M, N Bau S, Choi D, Durazo FA, El-Kabany M, Han SB, Busuttil RW. Use of sofosbuvir-based treatment of chronic hepatitis C in liver transplant recipients on hemodialysis. J Clin Gastro 2017;51:167-173 [PMID: 27548734]

Saab S, Rheem J, Jimenez MA, Fong TM, Mai MH, Kachadoorian CA, Esmailzadeh NL, Bau SN, Kang S, Ramirez SD, Grotts J, Choi G, Durazo FA, El-Kabany MM, Han SB, Busuttil RW. Effectiveness of Ledipasvir/sofosbuvir with/without ribavirin in liver transplant recipients with hepatitis C. J Clin Transl Hepatol 2017;28:101-8. [PMID:28660147]

Seem DL, Lee I, Umscheid CA, Kuehnert MJ, United States Public Health S. PHS guideline

for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. Public Health Rep2013;128(4):247-343. [PMID: 23814319]

Vargas HE, Laskus T, Wang LF, Lee R, Radkowski M, Dodson F, Fung JJ, Rakela J. Outcome of liver transplantation in hepatitis C virus-infected patients who received hepatitis C virus-infected grafts. Gastroenterology 1999;117:149-53. [PMID: 10381921]

APPENDIX 1
Investigator Signature Page

S T U D Y A C K N O W L E D G E M E N T

P R O - A C T : *Pr*evention of De N*o*vo HCV with *A*ntiviral H*C*V Therapy Post-Liver and Post-Kidney *T*ransplant

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol. I will discuss this material with them to ensure they are fully informed about the drugs and the study.

_____	_____
Principal Investigator Name (Printed)	Signature
_____	_____
Date	Site Number

APPENDIX 2
Investigators (Principal Investigators for each site in bold)

Investigator	Specialty*	Site
Norah Terrault, MD, MPH Claus Niemann, MD Chris Freise, MD Shiang-Cheng Kung, MD	H A S N	01-University of California, San Francisco
Raymond A. Rubin, MD Harrison Pollinger, DO Christina Klein, MD	H S N	02-Piedmont Transplant Institute (Atlanta)
James Trotter, MD **Johanna Bayer, MD** Bernard Fischbach, MD	H S N	03-Baylor Health Care (Dallas)
David Victor, MD **R. Mark Ghobrial, MD, PhD** Hassan Ibrahim, MD	H S N	04-Methodist Houston
James R. Burton, MD James Pompeselli MD Alexander Wiseman MD	H S N	05-University of Colorado
Elizabeth Verna, MD Lloyd Ratner MD, MPH: Jean Emond, MD Sumit Rohan MD, MPH	H S N	06-Columbia University

*H=Hepatology, A=Anesthesiology, S=Surgery, N=Nephrology

APPENDIX 3
Schedule of Assessments

			TREATMENT PERIOD													FOLLOW UP PERIOD			
	Screen	**Pre-Transplant Day**	**Day 1***	**Day 3**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**End of Rx**	**FU 4**	**FU 12**	**FU 24**	**Early end of Rx or Rx fail**
Visit Window (d)		**1**	**N.A.**	**2**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**10**	**10**	**10**	**14**
Informed consent	● #1	●# 2																		
Baseline recipient clinical data [a]		●																		
Donor assessment [b]		●																		
Study drug			●	●	●	●	●	●	●	●	●	●	●	●	●					
Study visit [c]			●	●	●	●	●	● [d]		●		●				●	● [d]	●		● [e]
Lab visit only [c]									●		●		●	●	●				●	
hCG if childbearing potential		●						●				●				●	●			
HCV RNA*			● [f]		●			●								●	●	●	●	●
AE assessment			●	●	●	●	●	●		●		●				●	●			
Concomitant medications of interest [g]			●	●	●	●	●	●		●		●				●				

*HCV RNA will be checked day 3 after transplant. If HCV RNA is positive, may proceed with Day 1. If , If result is "HCV RNA not detected", HCV RNA to be repeated on day 7 after transplant and then weekly until HCV RNA is detected. HCV RNA must be positive before starting study drug.

[a] Age, sex, ethnicity, race, weight, BMI, type of transplant (liver or kidney), indication for transplant, BUN, creatinine, GFR, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, presence of HCC (liver), CP score (liver), lab MELD (liver), exception MELD (liver), panel reactive antibody (kidney), quantitative HCV RNA,HBV surface antigen, HBV core antibody

[b] Age, sex, cause of death, UNOS region, kidney donor profile index (kidney), HCV nucleic acid test, HCV genotype, HBV core antibody, sample for baseline resistance associated substitution (RAS), sample for serum banking, liver biopsy fibrosis stage and fat percentage

[c] BUN, creatinine, GFR, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, and immunosuppressant level and dosage.

[d] hepatitis B surface antigen added to other evaluations

[e] BUN, creatinine, GFR, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, HCV genotype, sample for RAS, and immunosuppressant level and dosage.

[f] if subject has not started study drug within 7 days after transplant, a quantitative HCV RNA will also be obtained day 7 after transplant

[g] proton pump inhibitors, H2 antagonists, and beta blockers**APPENDIX 3a**

Schedule of Assessments for Virologic Failure Substudy

	Day 1[a]	Wk 1	Wk 4	Wk 8	End of Rx	FU 4	FU 12	FU 24	Early end of Rx or Rx fail
Visit Window (d)	**N.A.**	**4**	**4**	**4**	**4**	**10**	**10**	**10**	**14**
Informed consent	●								
Study drug	●	●	●	●					
Study visit [b]	●	●	●[c]	●	●	●[c]	●		●[d]
Lab visit only [a]								●	
hCG if childbearing potential			●	●	●	●			
HCV RNA	●	●	●		●	●	●	●	●
AE assessment	●	●	●	●	●	●			
Concomitant medications of interest [e]	●	●	●	●	●				

[a] Day 1 must occur within 30 days of documentation of virologic failure
[b]BUN, creatinine, GFR, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, and immunosuppressant level and dosage.
[c] hepatitis B surface antigen added to other evaluations
[d]BUN, creatinine, GFR, INR, sodium, potassium, bicarbonate, ALT, AST, alkaline phosphatase, total bilirubin, albumin, hemoglobin, HCV genotype, sample for RAS, and immunosuppressant level and dosage.
[e] proton pump inhibitors, H2 antagonists, and beta blockers

APPENDIX 4- CHILD-PUGH CLASSIFICATION OF THE SEVERITY OF CIRRHOSIS

	1	2	3
Hepatic Encephalopathy (HE)	**None** No encephalopathy and not on any treatment for hepatic encephalopathy	**Medication-Controlled** Subject is lethargic, may have moderate confusion Subject is receiving medical therapy for HE	**Medication-Refractory** Marked confusion/incoherent, rousable but sleeping or comatose
Ascites	**None** No ascites and not on treatment for ascites	**Mild/Moderate** Cross sectional imaging showing ascites Abdominal distension Medication for ascites	**Severe (diuretic-refractory)** Visible clinically
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3

Child-Pugh class:
A= 5-6 points
B= 7-9 points
C= 10-15 points