1.0 Title Page

Clinical Study Protocol

A Multi-Center, Open-Label Study of Glecaprevir/Pibrentasvir to Treat Recipients of Transplanted Kidneys from Deceased Donors with Hepatitis C Virus

(MYTHIC: Multi-center studY to Transplant Hepatitis-C InfeCted kidneys)

AbbVie Investigational Product:	Glecaprevir, Pibrentasvir	
Date:	Feb 13, 2019	
Development Phase:	4	
Study Design:	This is an open-label, multi-center study.	
Investigators:	Investigator information is on file with Massachusetts General Hospital, Harvard University	
Sponsor:	Massachusetts General Hospital	
Sponsor/Emergency Contact:	Raymond Chung, MD Address: Gastrointestinal Unit, Massachusetts General Hospital 55 Fruit Street Boston, MA 02114 E-mail: chung.raymond@mgh.harvard.edu	Phone: 617-643-2257 Mobile: 617-529-3942

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Synopsis

Sponsor: Massachusetts General Hospital	**Protocol Number**: B17-166
Name of Study Drug: Glecaprevir (ABT-493), Pibrentasvir (ABT-530)	**Phase of Development**: 4
Name of Active Ingredient: ABT-493, ABT-530	**Date of Protocol Synopsis**: October 09, 2018
Protocol Title: A Multi-Center, Open-Label Study of glecaprevir/pibrentasvir to Treat Recipients of Transplanted Kidneys from Deceased Donors with Hepatitis C Virus (MYTHIC: Multi-center studY to Transplant Hepatitis-C InfeCted kidneys)	

Objectives:

The primary objective of this study is to demonstrate the safety and efficacy (sustained viral response 12 weeks post treatment [SVR12]) of an 8-week treatment with glecaprevir/pibrentasvir (G/P) in Hepatitis C Virus (HCV)-negative recipients who received study eligible HCV RNA-positive kidneys in Arm 1.

The secondary objectives are:

1) Among all subjects enrolled in the study, to describe time to kidney transplant and cumulative incidence of each type of transplant: a study-eligible HCV RNA-positive kidney (Arm 1), a study-eligible HCV RNA-negative/HCV antibody-positive kidney (Arm 2A), or a kidney transplant performed as part of standard of care treatment (Arm 2B).

2) To describe clinical outcomes while on the waitlist after consent (Serious Adverse Event [SAEs], delisting from waitlist, death) between those who receive a study-eligible HCV RNA-positive kidney (Arm 1) and in subjects consented for this study who do not receive a study-eligible kidney transplant from an HCV RNA-positive donor (all Arm 2 subjects) overall and with breakdown by the 3 categories of Arm 2 as below:

   A: subjects who receive a kidney from a study-eligible HCV RNA-

negative/HCV Ab-positive donor

B: subjects who receive a standard of care kidney transplant

C: subjects who were not transplanted within 1 year of consent

Hereafter, these categories will be referred to as Arms 2A, 2B and 2C.

A "standard of care" transplant will be defined as any of the following kidney transplants: a deceased donor HCV RNA-positive kidney transplant that did not meet donor criteria for Arm 1 or HCV RNA-positive kidney transplant that place after last transplant allowed for Arm 1 but met criteria for Arm 1 inclusion (2B1); a deceased donor HCV RNA-negative/HCV Ab-positive kidney transplant that either did not meet donor criteria or took place > 6 months after the last Arm 1 transplant (2B2); a deceased donor HCV RNA-negative/HCV Ab-negative transplant at a MYTHIC clinical site (2B3); any living donor kidney transplant at a MYTHIC clinical site (2B4); or any kidney transplant at a different center than the 7 clinical sites (2B5).

In addition, to compare the total number of inpatient hospital days while on the waitlist and after study consent in those who did receive a study-eligible HCV RNA-positive kidney (Arm 1) vs total inpatient hospital days in those who did not (Arm 2) overall and with breakdown by the 3 categories of Arm 2 (2A, 2B and 2C).

3) To describe clinical outcomes and data post-transplant (death, graft failure, acute allograft rejection, delayed graft function, estimated glomerular filtration rate [eGFR], proteinuria, ALT elevation > 5 times the upper limit of normal (ULN), SAEs) between those who receive an HCV RNA-positive kidney (Arm1) and in subjects who receive an HCV RNA-negative/HCV Ab-positive kidney allograft (Arm 2A) or a standard of care kidney transplant (from Arm 2B1 – 2B4) combined and separately. For subjects of Arm 1 and Arm 2A who become HCV infected, we will collect additional clinical outcomes of sclerosing cholestatic hepatitis and extrahepatic manifestations of HCV. In addition, the clinical

outcomes and data post-transplant will be compared between Arm 1 and Arm 2 where a) any study drug (G/P) related severe treatment emergent adverse events are included as a clinical outcome for Arm 1 and b) all events of treatment emergent Grade≥ 3 laboratory values and severe G/P-related treatment emergent adverse events are included as clinical outcomes for Arm 1. 4) To compare time to deceased donor kidney transplantation among all patients who enrolled in this MYTHIC trial to transplant candidates from the Organ Procurement and Transplantation Network (OPTN) database; MYTHIC participants will be matched 1:3 to OPTN patients on demographics and characteristics known to influence waiting time including waiting list priority, blood group, geographic region, and sensitization.
Investigators: Multi-center, names on file with sponsor
Study Sites: Up to 7 sites
Study Population: HCV-negative subjects wait-listed for a kidney transplant
Number of Subjects to be Enrolled: Up to 90, including a target number of 30 kidney transplantation events from study eligible HCV RNA-positive kidney donors.
Methodology: This is an open-label, multi-center, two-arm study to evaluate the efficacy and safety of fixed-dose combination tablets of glecaprevir/pibrentasvir (G/P) in HCV-negative subjects who consent to receive a kidney transplant from an HCV RNA-positive deceased kidney donor. 90 subjects will be consented for trial participation, out of whom 30 subjects at up to 7 sites are planned to receive an HCV RNA-positive kidney meeting study criteria and will be enrolled into a post-transplant treatment arm (Arm 1) receiving open-label G/P for 8 weeks post-transplant. The remaining enrolled subjects including those who do not receive a kidney meeting study criteria from an HCV RNA-positive donor will be followed in Arm 2 for the minimum duration of 1 year post-enrollment. Arm 2 includes subjects who do not receive a kidney at one of the study sites or who receive a standard of care kidney transplant (Arm 2B5 patients will be censored at the time of transplant at a non-study site). For subjects enrolled in Arm 1 of the study, the

first dose of G/P will be given as early as 3 days post-transplant. Patients must be out of the ICU, able to eat and drink, and take oral medications, so that G/P treatment can be safely initiated orally as judged by the site investigator.

Subjects who are transplanted with kidneys from HCV RNA-positive donors in Arm 1 will be followed for 1 year after the date of transplantation to evaluate safety, graft survival, mortality, allograft rejection, and potential hepatic and extrahepatic manifestations of HCV infection. All recipients of Arm 1 HCV RNA-positive kidneys will be assessed for SVR-12 after G/P treatment. Scheduled visits for subjects who accept an organ from HCV RNA-positive donors in Arm 1 and receive G/P treatment will consist of screening, day of transplant, day 1 of G/P treatment, week 1, week 2, week 4, week 6 and week 8 of treatment (planned end of treatment visit) after starting G/P. Additional scheduled visits will take place at weeks 4, 12 and 24 following completion of the G/P treatment and week 52 (1 year) after transplant. Subjects treated with G/P who experience virological failure will be evaluated for the emergence/persistence of direct-acting antiviral agent (DAA)-resistant viral variants, and suitable retreatment will be offered to study participants.

All subjects in study arm 2 will be followed for a minimum of 1 year from enrollment. In addition, subjects in study arm 2A who received a kidney from an HCV RNA-negative/HCV Ab-positive donor will be followed for a minimum of 24 weeks after the date of transplantation or 1-year post enrollment, whichever is longer, to evaluate safety, graft survival, mortality, and allograft rejection, and potential development of HCV viremia. Study visits for patients receiving a HCV RNA-negative/HCV Ab-positive kidney transplant in Arm 2A will take place at weeks 1, 4, 8, 12, and 24 weeks after transplantation. If a recipient of an HCV RNA-negative/HCV antibody-positive kidney in Arm 2A develops HCV infection within the first 24 weeks of follow-up after transplantation, that recipient will be offered treatment with G/P for 8 weeks. G/P treatment will be administered and subject will be followed as per local transplant center

standard-of-care and study-objective pertinent data from the G/P treatment period and post treatment period will be collected. This includes SAEs, treatment-emergent Grade 3 or greater laboratory abnormalities, and HCV RNA 12 weeks post G/P treatment completion.

Other subjects in Arm 2 who remain on the transplant waiting list, receive a standard of care kidney transplant at a study site (Arms 2B1 - 2B4) will be followed as per transplant center standard of care for at least 12 months post-enrollment with study-objective pertinent collection of data during waitlist period and/or related to transplant events which may include transplant-related complications and graft function, SAEs, delisting from the transplant wait list and death.

Efficacy and safety data will be monitored throughout the study for all participants. However, the approach to surveillance for adverse events will be customized for patients on the waiting list and after transplantation.

Inclusion Criteria for Kidney Transplant Candidates at Enrollment

1. Age ≥21 and <65 years at the time of consent
2. Estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m^2 (calculated using the 4-variable Modification of Diet in Renal Disease [MDRD] equation) at the time of consent
3. Listed for an isolated kidney transplantation
4. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements, and must voluntarily sign and date an informed consent
5. No available medically acceptable, compatible living kidney donor
6. Subject must agree to use an effective method of birth control as outlined in Appendix D, and must have implemented the method by the day of transplant
7. Assent from the patient's primary transplant nephrologist that participation would be reasonable for the patient

8. Attended an educational session on use of HCV seropositive allografts

Exclusion Criteria for Kidney Transplant Candidates at Enrollment

1. History of severe, life-threatening or other significant sensitivity to immunosuppressants utilized in kidney transplant.
2. Female who is pregnant, breastfeeding, or is planning to become pregnant during the study
3. Human immunodeficiency virus (HIV) RNA-positive or HIV antibody-positive
4. HCV RNA-positive
5. Hepatitis B Virus (HBV) surface Ag-positive or detectable HBV DNA
6. Primary focal segmental glomerulosclerosis (FSGS) or disease process with increased risk of causing early graft failure as assessed by the transplant nephrologist and/or investigator team
7. Presence of clinically significant liver disease evident after review of history, labs and fibroscan imaging

a) Persistently elevated liver enzymes (Alanine aminotransferase [ALT] >2 times upper limit of normal) of unknown cause

b) Liver fibroscan result >8kPA, or >F2 on liver biopsy

8. Transplant candidate requiring antibody desensitization protocol for transplantation
9. Most recent calculated panel reactive antibody (cPRA) $\geq$80%. For this purpose, the cPRA assessed will be the cPRA most-recently reported to United Network of Organ Sharing (UNOS) at the time of wait listing.
10. Prior recipient of a non-renal solid organ transplant
11. Subject has any other medical condition that, in the opinion of the Investigator, would adversely affect the participant's participation in the study. Additionally, the investigator may exclude any patient with a pre-existing cancer that does not have a high probability of cure or control and as per local transplant center guidance.
12. Requirement for and inability to safely discontinue the medications or

supplements listed in Table 7 of the protocol at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug

13. Participation in another interventional study of any investigational agent or approved medication, or participation in another interventional study that the responsible investigator deemed to be an exclusion, from 6 months prior to screening to the last study visit.

Inclusion criteria for kidney donor and allograft*

1. Deceased donor organ with kidney donor profile index (KDPI) ≤0.85
2. HCV RNA-positive

Exclusion criteria for HCV RNA-positive kidney donor and allograft

1. Known prior HCV treatment with direct acting antiviral medication
2. HIV RNA-positive
3. HBV Surface antigen-positive or HBV DNA-positive

*Standard of care deceased or living donor kidney transplants are allowed to be accepted by enrolled subjects. For HCV RNA-negative/HCV antibody-positive donor offers in Arm 2A, all other donor inclusion and exclusion criteria above apply, except the donor is not HCV RNA-positive. For subjects who accept a standard of care transplant (Arm 2B), no study allograft criteria apply.

Investigational Product:	Glecaprevir/pibrentasvir 100 mg/40 mg Film-coated Tablet
Doses:	Glecaprevir Dose: 300 mg QD Pibrentasvir Dose: 120 mg QD Glecaprevir/pibrentasvir tablets: 300 mg/120 mg QD (3 tablets)
Mode of Administration:	Oral once daily with food
Reference Therapy:	N/A

Duration of Treatment: Treatment duration is 8 weeks
Criteria for Evaluation: **Efficacy**: Efficacy will be assessed by plasma HCV RNA levels after start of G/P treatment
DAA Resistance: The following resistance information will be analyzed for Arms 1 or 2A kidney transplant recipients receiving G/P who experienced virologic failure and who have a sample from time of failure with HCV RNA ≥1000 IU/mL after failure. The HCV NS3 and NS5A amino acid sequences from the sample closest in time after virologic failure or treatment discontinuation will be determined by population sequencing or next generation sequencing, and a listing by subject of all substitutions at GLE and PIB signature amino acid positions relative to the appropriate prototypic reference sequence of NS3 and NS5A will be provided.
Safety: Separate safety data will be collected for patients while on the waiting list and after transplantation. Because subjects are unlikely to suffer adverse events related to study participation while on the waiting list, adverse event ascertainment will take place every two months by phone as well as during an in-person evaluation every 6 months while on the waiting list. The following clinical outcomes will be collected from all subjects while on the waiting list: SAEs, hospital days, delisting from waitlist, death. For all transplanted subjects in Arm 1 or Arm 2, the following data will be collected and analyzed descriptively post-transplant: death, graft failure, acute allograft rejection, delayed graft function, eGFR, proteinuria, ALT elevations greater 5 times upper limit of normal, and SAEs. For transplanted subjects of Arm 1 and Arm 2A of the study who develop HCV viremia, the additional data of potential sclerosing cholestatic hepatitis and extrahepatic manifestations of HCV will be collected.

The analysis of adverse events after kidney transplantation will include categorization of the event as to whether the event was caused by transplantation or its treatment generally , or caused by HCV infection and/or HCV therapy as applicable. All subjects who receive at least one dose of G/P in Arm 1 will have additional safety data collected including treatment-emergent adverse events of all grades, physical examinations, clinical laboratory tests, and vital signs.
Statistical Methods **Efficacy:** The primary efficacy endpoint is sustained virologic response 12 weeks post dosing (SVR_{12}), defined as HCV RNA < LLOQ 12 weeks after the last actual dose of G/P. The SVR_{12} rate will be determined from all enrolled subjects who received an HCV RNA-positive kidney in Arm 1 and received at least one dose of G/P study drug along with a two-sided 95% confidence interval. The confidence interval for the SVR_{12} rate will be calculated using Wilson's score method.
The secondary efficacy endpoints for recipients of kidney transplants from HCV RNA-positive donors in Arm 1 are: 1. The percentage of subjects with on-treatment virologic failure; 2. The percentage of subjects with post-treatment virologic relapse. Additional efficacy analyses will be performed.
Clinical endpoints: Secondary endpoints for the secondary objectives are: 1. Among all subjects enrolled in the study who receive a kidney transplant, the time to kidney transplant and cumulative incidence of each type of transplant will be determined for: study-eligible HCV RNA-positive kidneys (Arm 1), study-eligible HCV RNA-negative/HCV Ab-positive kidneys (Arm 2A), and standard of care kidney transplants (Arm 2B). 2. The number and percentage of subjects with clinical outcomes while on the

waitlist (SAEs, delisting from waitlist, death) among subjects who receive an HCV RNA-positive kidney in Arm 1 and among those subjects who do not receive a study eligiblee HCV RNA-positive kidney (all Arm 2 subjects) overall and with breakdown by the category in Arm 2 (2A, 2B and 2C). In addition, the total number of inpatient hospital days while on waitlist in those who did receive a study eligible HCV RNA-positive kidney (Arm 1) and total inpatient hospital days in those who did not (Arm 2) overall and with breakdown by categories of Arm 2 will be summarized descriptively.

3. The number and percentage of subjects with the following clinical outcomes and data post-transplant as applicable: death, graft failure, acute allograft rejection, delayed graft function, ALT elevations > 5x ULN, and SAEs. The difference in the overall percentage of subjects with clinical outcomes and data post-transplant between Arm 1 and Arms (2A + 2B1 – 2B4) will be assessed by logistic regression with Arm as a factor and appropriate covariates to adjust for possible differences between Arms including waiting list priority, blood group, geographic region and sensitization as appropriate.

   For subjects of Arm 1 and Arm 2A who become HCV infected, we will collect additional clinical outcomes of sclerosing cholestatic hepatitis and extrahepatic manifestations of HCV.

   In additional analyses, G/P treatment-related severe adverse events, and G/P treatment-emergent Grade ≥ 3 laboratory values will be counted as clinical outcomes for subjects in Arm 1.
4. Additional allograft function outcomes for subjects post-transplant: mean eGFR over time and proteinuria.
5. Time to deceased donor kidney transplantation will be compared between all patients who enrolled in this MYTHIC trial and transplant candidates from the Organ Procurement and Transplantation Network (OPTN) database using a Cox

proportional hazards model; MYTHIC participants will be matched 1:3 to OPTN patients on demographics and characteristics known to influence waiting time including waiting list priority, blood group, geographic region, and sensitization.

6. In addition, for subjects in study Arm 2A receiving HCV RNA-negative/HCV Ab-positive kidneys, the rate of HCV transmission will be summarized.

1.2 List of Abbreviations, Definitions and Terms

Abbreviations

AASLD	American Association for the Study of Liver Diseases
Ab	Antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APRI	Aminotransferase/platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body Mass Index
BUN	Blood urea nitrogen
CBC	Complete blood count
CCC	Clinical Coordinating Center
CKD	Chronic kidney disease
CLIA	Clinical Laboratory Improvement Amendment
CMP	Comprehensive metabolic panel
CPK	Creatine phosphokinase
cPRA	Calculated panel reactive antibody
CR/CL	Creatinine clearance
CRF	Case report form
CT	Computed Tomography
DAA	Direct-acting antiviral agent
D/C	Discontinuation
DCC	Data Coordinating Center
DMS	Data management system
DNA	Deoxyribonucleic acid

DSMC	Data safety monitoring committee
EC	Ethics Committee
EDC	Electronic data capture
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EHR	Electronic health record
EMR	Electronic medical record
EOT	End of treatment
ESRD	End stage renal disease
EU	European Union
FSGS	Focal Segmental Glomerulosclerosis
FSH	Follicle stimulating hormone
GAM	Generalized additive method
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLE	Glecaprevir
G/P	Glecaprevir/Pibrentasvir fixed dose combination
GT	Genotype
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
Hemoglobin A1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent ethics committee

IFN	Interferon
IL28B	Interleukin 28B
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International units
IUD	Intrauterine device
KDPI	Kidney Donor Profile Index
KT	Kidney transplant
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
MGH	Massachusetts General Hospital
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NGS	Next generation sequencing
NONMEM	Non-linear mixed-effect modelling
NS3	Nonstructural viral protein 3
NS5A	Nonstructural viral protein 5A
OPTN	Organ Procurement and Transplantation Network
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase Chain Reaction
PE	Physical exam
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PegIFN/RBV	Combination of pegylated-interferon alfa-2a or alfa-2b and ribavirin
PI	Protease Inhibitor
PIB	Pibrentasvir

PK	Pharmacokinetic
POR	Proof of Receipt
PRA	Panel reactive antibody
PRS	IFN, pegIFN, RBV and/or sofosbuvir
PT	Post-Treatment
QD	Once daily
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase PCR
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class/Standard of Care
SOF	Sofosbuvir
SVR	Sustained virologic response
SVR_4	Sustained virologic response 4 weeks post dosing
SVR_{12}	Sustained virologic response 12 weeks post dosing
SVR_{24}	Sustained virologic response 24 weeks post dosing
TE	Treatment experienced
TN	Treatment naive
ULN	Upper limit of normal
UNOS	United Network of Organ Sharing
USPI	United States Prescribing Information
VS	Vital signs
WBC	White blood cells

Definition of Terms

Study Drug	Glecaprevir (GLE, ABT-493), pibrentasvir (PIB,ABT-530) fixed dose combination tablets (G/P)
G/P Day 1	First day of study drug (G/P) dosing
G/P Treatment Period	From G/P Day 1 through last dose of G/P (week 8) treatment
Post-Treatment Period	From Day after the last dose of G/P up to 1 year post transplant

2.0 Table of Contents

List of Tables

List of Figures

3.0 Introduction

Approximately 71 million people are chronically infected with HCV worldwide, including up to 4 million in the United States.[1,2] Without treatment, the majority of infected individuals will develop chronic hepatitis, which can lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[3] HCV is the leading cause of liver transplantation and HCC in most countries.[3] Recently, the development of oral, interferon-free, direct-acting antiviral therapy has been a major advance for the treatment of HCV with available combinations curing the majority of infected patients and leading to few adverse effects.[4,5]

Currently in the United States, approximately 95,000 patients are waiting for kidney transplantation and these numbers continue to rise.[6] There is a definite shortage of viable donated organs, and it is of paramount importance that available resources are handled efficiently. All transplantable organs must be recognized for their enormous value as scarce resources and utilized to their maximum potential for the maximum benefit (the principle of utility), while also promoting equity.[7] Transplantation of HCV-infected donor kidneys to HCV-infected recipients has been performed for over twenty years with increasing evidence of long-term safety and decreased mortality compared to remaining on the waitlist.[8] However, in a survey of kidney donations between 1995 and 2009, of the 93,825 HCV-positive deceased donors (potentially 187,650 kidneys), over 50% were discarded. An advantage of using HCV-infected organs is a decrease in wait time and waitlist mortality. In addition, as a result of the opioid epidemic currently plaguing the young demographic, the quality of HCV-infected donor organ may often be better, as compared to other extended criteria organs, as many derive from a young population, age 18 to 35 years, following drug overdoses.[9]

With pre-emptive HCV treatment shortly after transplantation, we hope to prevent significant viremia from ever occurring in the recipient and abrogate establishment of HCV infection in the liver. Glecaprevir/Pibrentasvir (G/P) is the first pan-genotypic regimen that is safe and effective in patients with renal impairment. G/P has potent in vitro antiviral

activity against genotypes 1 through 6 and a high genetic barrier to resistance, with no or little loss of potency against common resistant-associated substitutions. G/P is co-formulated Glecaprevir 100 mg and Pibrentasvir 40 mg as a fixed-dose combination tablet, which provides patients with a convenient treatment regimen of three tablets once daily to be taken with food.[10]

Expedition 4 was an international, open-label Phase 3 study of 12 weeks of G/P in 104 patients with eGFR < 30mL/min/1.73m^2 including 85 patients on dialysis and 19 with pre-dialysis chronic kidney disease (CKD). By intention to treat analysis 102/104 patients were cured and there were no virologic failures (1 treatment discontinuation due to diarrhea and 1 died of unrelated causes). Also, there were no treatment-related serious adverse events.[11]

G/P has multiple advantages in the solid organ transplantation context. G/P is the only DAA regimen that is appropriate to administer among dialysis patients or in the immediate post-kidney transplant period (where a substantial proportion of deceased donor transplant recipients have delayed graft function)[12] that is effective against all genotypes of HCV.[13] Furthermore, G/P 300mg/120mg once daily given for 12 weeks has also been studied in 100 patients with chronic HCV infection post liver (n=80) or kidney transplantation (n=20). The overall SVR12 rate was 98% (98/100) with 1 post liver transplant patient experiencing virologic relapse and one patient was lost to follow-up. The most common adverse events in >10% of patients included headache, fatigue, nausea, pruritus, and diarrhea. There were two serious AEs deemed related to G/P including sinusitis and abnormal hepatic function at post-treatment week 4. There was one AE, a cerebrovascular accident that led to study drug discontinuation at week 6 of treatment and the patient achieved SVR12. Subjects were on the following immunosuppressant medications Tacrolimus (n=68), Mycophenolate mofetil (n=30), Cyclosporine (n=13), Prednisone (n=13), Everolimus (n=8), Azathioprine (n=6), and Sirolimus (n=7)[14].

The results of the THINKER trial provided preliminary evidence that HCV-infected organs could be safely transplanted into recipients who do not have HCV infection, and the virus

could be eradicated shortly after kidney transplant. This open-label, single-arm trial performed by Goldberg and colleagues, transplanted ten patients without HCV with kidneys from HCV-infected deceased donors with active viremia. When the recipient developed viremia, which occurred in all patients within three days post kidney transplant, they immediately began treatment with elbasvir-grazoprevir for twelve weeks. Patients received kidneys only from deceased donors with genotype 1 infection, because elbasvir-grazoprevir is not effective at treating genotypes 2 or 3. All patients were cured of HCV, and elbasvir-grazoprevir was well tolerated in the immediate post-transplant period. Notably, one patient with biopsy-proven IgA nephropathy pre-transplant received an HCV-infected kidney and developed proteinuria subsequent to completing 12 weeks of elbasvir-grazoprevir. The patient underwent kidney biopsy which demonstrated focal segmental glomerulosclerosis. This event was considered possibly related to HCV or its therapy.[15]

To allow for more widespread use of this protocol, an ideal regimen to treat HCV infection in the post-kidney transplant (KT) recipient would need to be safe in patients with low eGFR so it could be used in patients with delayed graft function, should have few to no interactions with immunosuppressant medications, and ideally treat all genotypes of HCV infection, thus obviating the need for rapid genotyping of donors prior to transplantation. The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation has highlighted the urgent need for prospective research protocols that study the risk versus benefit of using organs from hepatitis C-infected donors.[16]

In light of these recent advances in DAA therapy, we hypothesize that G/P could prevent transmission of HCV or establishment of HCV infection in the liver that could occur after transplantation of an HCV RNA-positive kidney into an HCV uninfected recipient. Because it is a pan-genotypic regimen, it would eliminate the need to rapidly genotype deceased donors prior to transplantation. Other regimens that could be used in the post-transplant period require genotyping to be sure the agents are active against the particular genotype that the donor has or are not safe in patients with eGFR < 30 mL/min/1.73m^2. Genotyping

is a multi-step process that would require extra logistics during the time pressured process of organ allocation. Using a pan-genotypic regimen streamlines this process and ensures all HCV-infected organs are effectively utilized. If this approach proves successful, it could curtail the current high discard rates for HCV-infected kidneys and other organs. This new approach of using a pan-genotypic HCV regimen and avoiding donor genotyping has the potential to result in a large increase in the number of organs available in the kidney donor pool. Demonstration that pre-emptive treatment of HCV can prevent HCV transmission or establishment of HCV infection in the liver would greatly expand the viable kidney donor pool and could result in a substantial reduction in long-term healthcare costs for patients with end-stage renal disease.

While there are no data for G/P in acute HCV infection, we hypothesize that an 8-week duration of G/P will be highly effective when given shortly after transplant of an HCV RNA-positive kidney into an HCV RNA-negative recipients who is non-cirrhotic and before a chronic HCV infection is established. On the basis of the clinical studies referenced[17,18], an 8-week duration of G/P has been approved for the treatment of an established, chronic HCV infection with genotype 1-6 in treatment naive non-cirrhotic subjects.[10]

Because the focus of this study is about transplantation of kidneys from HCV-seropositive donors, we will also allow kidneys from patients who have a positive HCV antibody test (HCV Ab-positive) but have no detectable plasma HCV RNA. Prior to offering an organ, the Regional Organ Bank is aware of both the status of the HCV antibody and HCV RNA testing. In most parts of the country, the current organ allocation schema, categorizes organ donors who are HCV RNA-negative/HCV Ab-positive as similar to HCV RNA-positive despite the important difference of absence of HCV viremia in donors who are only HCV Ab- positive. Kidneys from HCV-positive donors (including HCV RNA-negative/HCV Ab-positive and HCV RNA-positive) are still being discarded despite the fact that kidneys from HCV RNA-negative/HCV Ab-positive donors are unlikely to transmit HCV. If HCV

transmission occurs from a study-eligible HCV RNA-negative/HCV Ab-positive kidney in Arm 2A of this study, which is anticipated to be a rare event, we would provide "reactive" G/P treatment. Patients would be treated with G/P as per transplant center standard of care. Limited data from the "reactive" G/P treatment and HCV outcome will be collected from these subjects. The following data will be obtained from these subjects: Plasma HCV RNA prior to HCV treatment initiation with G/P, SAEs that occurred during the G/P treatment period, HCV RNA results at post treatment week 12, early discontinuation of G/P treatment, and reasons for not achieving SVR12, as applicable.

3.1 Glecaprevir/Pibrentasvir (G/P)

Overview of G/P Registration Program and Supportive Studies

The G/P registration program included a broad subject population including subjects with compensated liver disease and subjects with severe renal insufficiency across all 6 major genotypes using a single dose of 300 mg/120 mg QD. Supportive Phase 2 studies used the Phase 2 formulation of separate GLE and PIB tablets, with each tablet containing 100 mg and 40 mg, respectively. Treatment arms from these supportive Phase 2 studies using the regimen selected for registration studies (GLE 300 mg plus PIB 120 mg) were pooled with arms from the registration studies for analyses of efficacy and safety. Treatment-naïve (TN) and treatment experienced (TE) subjects to any combination of pegylated IFN (pegIFN), RBV, sofosbuvir (SOF), NS5A inhibitors, or PIs were allowed in the program. In addition, the program included subjects with human immunodeficiency virus (HIV) coinfection (Study M13-590), subjects with chronic kidney disease [CKD] Stages 4 – 5, including those on hemodialysis (Study M15-462), subjects with compensated cirrhosis (Studies M14-172, M15-462, and M14-868), and subjects with or without cirrhosis who failed a previous regimen containing an NS5A inhibitor and/or an NS3/4A PI (Study M15-410).

A total of 2,376 subjects were randomized or enrolled in the registration studies or supportive Phase 2 studies to receive G/P 300 mg QD/120 mg QD. Of these, 2,369 subjects received at least 1 dose of G/P 300 mg QD/120 mg QD (Table 1).

Table 1. Overview of Registrational and Supportive Phase 2 Clinical Studies by Subject Population

Genotype	Clinical Study	Summary of Study Design
TN and TE Subjects Without Cirrhosis		
GT1	M13-590	G/P 300 mg/120 mg QD for 8 (n = 351) or 12 weeks (n = 352)
	M14-867	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 34)
GT2	M15-464	G/P 300 mg/120 mg QD (n = 202) or placebo (n = 100) for 12 weeks
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 199) or 12 weeks (n = 25)
GT3	M13-594	G/P 300 mg/120 mg QD for 8 (n = 157) or 12 weeks (n = 233) or SOF 400 mg + DCV 60 mg QD for 12 weeks (n = 115) (all subjects in study were TN)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 29; TN only), 12 weeks (n = 76), or 16 weeks (n = 22; TE only)
GT4, 5, 6	M13-583	G/P 300 mg/120 mg QD for 12 weeks (n = 121)
	M14-867	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 32)
	M14-868	GLE/PIB 300 mg/120 mg QD for 8 weeks (n = 58)
TN and TE Subjects with compensated Cirrhosis		
GT1, 2, 4, 5, 6	M14-172	G/P 300 mg/120 mg QD for 12 weeks (n = 146)
GT3	M14-868	GLE/PIB 300 mg/120 mg QD for 12 weeks (n = 64; TN only) or 16 weeks (n = 51; TE only)
Subjects with CKD Stages 4 – 5 With or Without compensated Cirrhosis		
GT1 – 6	M15-462	G/P 300 mg/120 mg QD for 12 weeks (n = 104)
NS5A Inhibitor and/or PI-Experienced Subjects With or Without compensated Cirrhosis		
GT1, 4	M15-410	G/P 300 mg/120 mg QD for 12 (n = 66) or 16 weeks (n = 47)

CKD = chronic kidney disease; DCV = daclatasvir; GLE = glecaprevir; GT = genotype; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PIB = pibrentasvir; QD = once daily; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naïve

3.1.1 Efficacy

In TN or IFN, pegIFN, RBV, and/or SOF treatment-experienced (TE-PRS) subjects, the pooled overall SVR_{12} rates with G/P were > 97% across GT1, 2, 4, 5 and 6 regardless of treatment experience, treatment duration, including any degree of renal impairment, presence of cirrhosis, or HIV-1 coinfection (Table 2).

Among subjects with GT3 infection, the pooled SVR_{12} rates across durations were 95.2% among all subjects, 96.6% among cirrhotic subjects, and 100% among subjects with CKD

Stages 4 – 5. The SVR_{12} rates among subjects previously treated with a PI and/or NS5A inhibitor were ≥ 89.0% for GT1 and GT4.

Table 2. SVR_{12} Rates by Treatment Experience and HCV Genotype – GT1 – 6 (ITT Population, Phase 2 and 3 Analysis Set)

Genotype	TN n/N (%) 95% CI[a]	TE-PRS n/N (%) 95% CI[a]	TN + TE-PRS			TE-NS5A and/or PIs n/N (%) 95% CI[a]	Overall n/N (%) 95% CI[a]
			All[a]	Cirrhotic n/N (%) 95% CI[b]	CKD 4 – 5 n/N (%) 95% CI[b]		
Phase 2 and 3 Analysis Set	1604/1640 (**97.8**) 97.1, 98.5	602/616 (**97.7**) 96.6, 98.9	2206/2256 (**97.8**) 97.2, 98.4	274/281 (**97.5**) 95.7, 99.3	102/104 (**98.1**) 95.4, 100.0	101/113 (**89.4**) 83.7, 95.1	2307/2369 (**97.4**) 96.7, 98.0
GT1	555/561 (**98.9**) 98.1, 99.8	326/328 (**99.4**) 98.5, 100.0	881/889 (**99.1**) 98.5, 99.7	98/101 (**97.0**) 93.7, 100.0	53/55 (**96.4**) 91.4, 100.0	97/109 (**89.0**) 83.1, 94.9	978/998[c] (**98.0**) 97.1, 98.8
GT2	365/369 (**98.9**) 97.9, 100.0	95/97 (**97.9**) 95.1, 100.0	460/466 (**98.7**) 97.7, 99.7	35/35 (**100**) 100.0, 100.0	16/16 (**100**) 100.0, 100.0	N/A	460/466 (**98.7**) 97.7, 99.7
GT3	499/521 (**95.8**) 94.0, 97.5	113/122 (**92.6**) 88.0, 97.3	612/643 (**95.2**) 93.5, 96.8	112/116 (**96.6**) 93.2, 99.9	11/11 (**100**) 100.0, 100.0	N/A	612/643 (**95.2**) 93.5, 96.8
GT4	119/122 (**97.5**) 94.8, 100.0	55/56 (**98.2**) 94.7, 100.0	174/178 (**97.8**) 95.6, 99.9	20/20 (**100**) 100.0, 100.0	20/20 (**100**) 100.0, 100.0	4/4 (**100**) 100.0, 100.0	178/182 (**97.8**) 95.7, 99.9
GT5	26/26 (**100**) 100.0, 100.0	6/6 (**100**) 100.0, 100.0	32/32 (**100**) 100.0, 100.0	2/2 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	32/32 (**100**) 100.0, 100.0
GT6	40/41 (**97.6**) 92.8, 100.0	7/7 (**100**) 100.0, 100.0	47/48 (**97.9**) 93.8, 100.0	7/7 (**100**) 100.0, 100.0	1/1 (**100**) 100.0, 100.0	N/A	47/48 (**97.9**) 93.8, 100.0

CI = confidence interval; CKD = chronic kidney disease; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; N/A = not applicable; NS5A = nonstructural viral protein 5A; PI = protease inhibitor; PRS = regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir; SVR_{12} = sustained virologic response 12 weeks post dosing; TE = treatment-experienced; TN = treatment-naïve; TE-NS5A and/or PI = TE with NS5A inhibitor and/or PI

1. CI was calculated using a stratum-weighted proportion and variance.
2. CI was calculated using the normal approximation to the binomial distribution.
3. Eleven subjects were classified by the central laboratory and treated as GT2 but included here as GT1 due to being identified as such by phylogenetic analysis; all 11 subjects achieved SVR_{12}
4. Cross reference: AbbVie, data on file.

3.1.2 Impact of Baseline Polymorphisms on Treatment Outcome

The association between baseline polymorphisms and treatment outcome in TN and TE-PRS subjects who received G/P 300 mg/120 mg QD in the registration or supportive Phase 2 studies was evaluated by conducting an integrated analysis of baseline sequence data. Next-generation sequencing (NGS) was conducted on all baseline samples at 15% detection threshold at key amino acid positions 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A.

In subjects who were TN or TE-PRS, baseline polymorphisms in NS3 were detected in 1.1% (9/845), 0.8% (3/398), 1.6% (10/613), 1.2% (2/164), 41.9% (13/31), and 2.9% (1/34) of subjects with HCV genotype 1, 2, 3, 4, 5 and 6 infection, respectively. Baseline polymorphisms in NS5A were detected in 26.8% (225/841), 79.8% (331/415), 22.1% (136/615), 49.7% (80/161), 12.9% (4/31), and 54.1% (20/37) of subjects with HCV genotype 1, 2, 3, 4, 5, and 6 infection, respectively.

The presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR_{12} rates for GT1-, 2-, 4-, 5-, or 6-infected subjects.
Within GT3-infected subjects, baseline polymorphisms in NS3 and the NS5A polymorphisms at positions 24, 28, 31, 58, 92, or 93 did not have an impact on treatment outcome.

3.1.3 Amino Acid Substitutions in Subject Experiencing Virologic Failure

Among TN and TE-PRS subjects with or without cirrhosis treated for 8, 12, or 16 weeks, 23 subjects experienced virologic failure (2 with GT1, 2 with GT2, and 19 with GT3). One GT3-infected subject experiencing virologic failure was determined to have been re-infected with GT3a virus distinct from the one present at baseline. Therefore, baseline polymorphisms and treatment-emergent substitutions were analyzed for 22 subjects experiencing virologic failure.

Among the 2 GT1-infected subjects, 1 had treatment-emergent substitutions A156V in NS3 and Q30R/L31M/H58D in NS5A, and 1 had treatment-emergent Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A.
Among the 2 GT2-infected subjects, no treatment-emergent substitutions were observed in NS3 or NS5A; the prevalent M31 polymorphism in NS5A was present at baseline and post-treatment in both subjects.

Among the 18 GT3-infected subjects, the majority of subjects had treatment-emergent variants at the time of failure in NS3 (61.1%, 11/18) and NS5A (88.9%, 16/18). Treatment-emergent NS3 substitutions Y56H/N, Q80K/R, A156G, and Q168L/R were observed in 11 subjects, and A166S or Q168R was present at both baseline and post-treatment in 5 subjects. Treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H were observed in 16 subjects, and 13 subjects had A30K (n = 9) or Y93H (n = 5) at both baseline and post-treatment.

3.1.4 Integrated Safety Results

A summary of treatment-emergent adverse events (AEs) from pooled analyses of the registration studies and supportive Phase 2 studies are presented in Table 3. The severity of the underlying renal disease and its associated comorbidities in patients with CKD Stages 4 and 5, the frequency and severity of the AEs in subjects enrolled Study M15-462 were expected to be higher than in subjects enrolled in the other registration studies. Therefore, the summary of adverse events reported in Table 3 does not include the results of Study M15-462.

As shown in Table 3, the AEs occurring with a frequency ≥ 5% are headache, fatigue, nausea and diarrhea. The majority of subjects experienced an AE, which were mostly considered to be mild in severity by the investigator (Grade 1). Rates of AEs that were serious, led to premature study drug discontinuation or had a severity Grade ≥ 3 were low. Including data from Study M15-462, there were 7 deaths, none of which were related to study drug, and the majority occurred several months after the last dose of study drug.

Table 3. Adverse Events Reported for ≥ 5.0% of Subjects (Phase 2 and 3 Analysis Set)

	Phase 2 and 3 Analysis Set[a] (N = 2,265) n (%)	
	All Adverse Events	**DAA-Related Adverse Events[b]**
Any AE	1,529 (67.5)	929 (41.0)
An AE Grade ≥ 3	65 (2.9)	4 (0.2)
Any SAE	48 (2.1)	1 (< 0.1)
Discontinuation of study drug due to any AE	8 (0.4)	3 (0.1)
All deaths[c]	6 (0.3)	0
Preferred Term[d]		
Headache	410 (18.1)	298 (13.2)
Fatigue	330 (14.6)	259 (11.4)
Nausea	208 (9.2)	172 (7.6)
Diarrhea	146 (6.4)	86 (3.8)

AE = adverse event; DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event

a. Excludes Study M15-462.

b. DAAs = GLE, PIB, or GLE/PIB.

c. Includes non-treatment-emergent deaths. One additional death occurred in Study M15-462.

d. DAA-related AEs reported for ≥ 5.0% of subjects in the Phase 2 and 3 Analysis Set.

Cross reference: AbbVie, data on file.

Adverse events in subjects without cirrhosis (n = 1,977) were similar in type, frequency, and severity compared with subjects with cirrhosis (n = 288). The safety profile in subjects with HCV/HIV-1 co-infection (n = 33) was similar to that in HCV mono-infected subjects. Overall, the safety profile of G/P in the elderly population (≥ 65 years old, n = 328) was comparable to the safety profile in the non-elderly population (n = 2,041).

The frequency and severity of hepatic-related AEs as well as liver chemistry abnormalities evaluating potential hepatotoxicity were low across the Phase 2 and 3 studies. Liver-related safety results indicated that:

- Four subjects had post-nadir Grade 3 ALT abnormalities or Grade 2 ALT with total bilirubin ≥ 2 × ULN. None of these subjects prematurely discontinued study drug due to an ALT or bilirubin increase.

- ALT abnormalities in 3 of these 4 subjects were not clinically significant
- One subject experienced concurrent ALT > 3 × ULN (increased from nadir grade) and total bilirubin ≥ 2 × ULN in the context of multiple gallstones and was not considered to have drug-induced liver injury
- Based on exposure-response analyses, no exposure-dependent ALT increases were observed in subjects with ALT abnormalities
- Grade 3 increases in bilirubin were infrequent (0.4%) and without bilirubin-related AEs; none were associated with liver disease progression
- No subjects experienced drug-related hepatic decompensation. One subject with cirrhosis (Study M14-172) who had known esophageal varices experienced an episode of esophageal varices hemorrhage that was considered not related to study drug. Treatment was continued without clinical or laboratory signs of liver disease progression.
- A total of 6 (0.3%) subjects experienced a de novo event of HCC. In all 6 subjects, the events were considered related to subject's medical history of underlying liver disease and not to G/P.

In summary, G/P demonstrated a favorable safety profile similar across durations of 8, 12, and 16 weeks. The regimen was well tolerated across a broad and diverse population of subjects, including subjects with cirrhosis, HIV co-infection, and CKD Stage 4 or 5. Based on the combined Phase 2 and 3 Analysis Set common study drug-related AEs occurring in ≥ 5% of subjects were headache, fatigue, nausea (Table 3) and were mostly Grade 1 (mild) in severity. Serious AEs and AEs leading to premature study drug discontinuation were rare. There were no hematological or blood chemistry findings of concern or considered likely related to treatment. Unlike other protease inhibitors, no liver-related toxicities and no cases consistent with drug-induced liver injury were identified.

3.2 Study Rationale

DAA therapy has made is possible to effectively and safely treat HCV before or after kidney transplant. However, most waitlisted end-stage renal disease patients are predicted to live longer with transplant than on dialysis;[19-21] this benefit extends to HCV-infected patients. Approximately 500 kidneys from HCV-infected donors are discarded annually in the United States. Strategies to increase utilization of HCV-infected kidneys to shorten wait time for patients on dialysis are desperately needed.[22] The purpose of this study is to determine if G/P treatment when initiated early after kidney transplant (e.g., as early as 3 days post-transplant) can prevent significant HCV viremia and prevent establishment of HCV infection in the liver and associated complications. G/P's registration program has demonstrated high efficacy with an overall SVR12 rate of 98% for the label-recommended regimen/duration, good safety and tolerability. These data suggest that G/P may achieve similar high SVR12 rates and safety results in HCV negative recipients of HCV viremic kidneys when G/P treatment is started early post-transplant.

3.3 Benefits and Risks

Potential benefits of early post-transplant treatment with G/P in the setting of high unmet need subjects on the kidney transplant wait list include:

1. Potential for high SVR rate in a population with long and/or additional waiting times on the kidney transplant list and substantial risk for health complications before a good-quality HCV-negative kidney becomes available for transplantation.
2. The approved dose of G/P e.g., 300mg/120mg (=3 tablets) once daily can be used in subjects with or without any level of renal impairment and for all HCV genotypes 1-6.
3. The safety profile and high efficacy (98% SVR12 with no virologic failure) of G/P in subjects with end-stage renal disease has been established.
4. G/P demonstrated good tolerability, safety and high efficacy in patients treated for chronic HCV infection post kidney transplantation.
5. The benefit of a short 8 week therapy and no Ribavarin (RBV) needed as part of the treatment regimen

6. The benefit of early treatment initiation of G/P after transplant of an HCV RNA-positive allograft greatly reduces the risks of sequelae of acute HCV infection.

The safety of G/P has been established in a diverse population of patients with and without compensated cirrhosis in Phase II and III clinical trials (Section 3.1.4). The most common AEs in greater than 10% of subjects include headache, and fatigue. Additional Safety data for G/P are detailed in the Mavyret USPI.[10] In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures.

Risks associated with acute HCV infection,[15,23] the treatment with G/P, including the risks of medication toxicity, virologic failure, and development of resistance-associated substitutions (Section 3.1.3), appear to be limited and manageable based upon the available data. A subject experiencing G/P treatment failure in this study will be offered retreatment with a regimen deemed suitable. Given the potential for high rates of SVR in this population with limited current treatment options, the risk-benefit assessment is favourable.

4.0 Study Objectives

4.1 Primary Objective

The primary objective of this study is to demonstrate the safety and efficacy (SVR12) of an 8-week treatment with G/P in HCV-negative recipients who received a study eligible HCV RNA-positive kidneys in Arm 1

4.2 Secondary Objectives

The secondary objectives are:

1) Among all subjects enrolled in the study, to describe time to kidney transplant and cumulative incidence of each type of transplant: a study-eligible HCV RNA-positive kidney (Arm 1), a study-eligible HCV RNA-negative/HCV antibody-positive kidney (Arm 2A), or a kidney transplant performed as part of standard of care treatment (Arm 2B).

2) To describe clinical outcomes while on the waitlist after consent (Serious Adverse events [SAEs], delisting from waitlist, death) between those who receive a study-eligible HCV RNA-positive kidney (Arm 1) and in subjects consented for this study who do not receive a study-eligible kidney transplant from an HCV RNA-positive donor (all Arm 2 subjects) overall and with breakdown by the 3 categories of Arm 2 as below:

A: subjects who receive a kidney from a study-eligible HCV RNA-negative/HCV Ab-positive donor

B: subjects who receive a standard of care kidney transplant

C: subjects who were not transplanted within 1 year of consent

Hereafter, these categories will be referred to as Arms 2A, 2B and 2C.

A "standard of care" transplant will be defined as any of the following kidney transplants: a deceased donor HCV RNA-positive kidney transplant that did not meet donor criteria for Arm 1 or HCV RNA-positive kidney transplant that place after last transplant allowed for Arm 1 but met criteria for Arm 1 inclusion (2B1); a deceased donor HCV RNA-negative/HCV Ab-positive kidney transplant that either did not meet donor criteria or took place > 6 months after the last Arm 1 transplant (2B2); a deceased donor HCV RNA-negative/HCV Ab-negative transplant at a MYTHIC clinical site (2B3); any living donor kidney transplant at a MYTHIC clinical site (2B4); or any kidney transplant at a different center than the 7 clinical sites (2B5).

In addition, to compare the total number of inpatient hospital days while on the waitlist and after study consent in those who did receive a study eligible HCV RNA-positive kidney (Arm 1) vs total inpatient hospital days in those who did not (Arm 2) overall and with breakdown by the 3 categories of Arm 2 (2A, 2B and 2C).

3) To describe clinical outcomes and data post-transplant (death, graft failure, acute allograft rejection, delayed graft function, estimated glomerular filtration rate [eGFR], proteinuria, ALT elevation > 5 times the upper limit of normal (ULN), SAEs)

between those who receive an HCV RNA-positive kidney (Arm1) and in subjects who receive an HCV RNA-negative/HCV Ab-positive kidney allograft (Arm 2A) or a standard of care kidney transplant (from Arm 2B1 – 2B4) combined and separately. For subjects of Arm 1 and Arm 2A who become HCV infected, we will collect additional clinical outcomes of sclerosing cholestatic hepatitis and extrahepatic manifestations of HCV. In addition, the clinical outcomes and data post-transplant will be compared between Arm 1 and Arm 2 where a) any study drug (G/P) related severe treatment emergent adverse events are included as a clinical outcome for Arm 1 and b) all events of treatment emergent Grade≥ 3 laboratory values and severe G/P-related treatment emergent adverse events are included as clinical outcomes for Arm 1.

4) To compare time to deceased donor kidney transplantation among all patients who enrolled in this MYTHIC trial to transplant candidates from the Organ Procurement and Transplantation Network (OPTN) database; MYTHIC participants will be matched 1:3 to OPTN patients on demographics and characteristics known to influence waiting time including waiting list priority, blood group, geographic region, and sensitization.

5.0 Investigational Plan

5.1 Overall Study Design, Rationale and Plan: Description

This is a Phase 4, open-label, multi-center, 2-arm study with the primary objective of evaluating the efficacy (SVR12) and safety of the fixed-dose combination tablets of glecaprevir/pibrentasvir (G/P) in HCV-negative subjects who receive a kidney transplant from an HCV RNA-positive deceased kidney donor. Among 90 subjects consented for trial participation, 30 subjects at up to 7 sites are planned to receive an HCV RNA-positive kidney and will be enrolled into a post-transplant treatment arm (Arm 1) receiving open-label G/P for 8 weeks post-transplant. The remaining consented patients who do not receive a study eligible kidney from an HCV RNA-positive donor will be followed in Arm 2 for the minimum duration of 1 year post-enrollment (Arm 2B and 2C), or 24 weeks post-transplant, whichever is longer (Arm 2A). These Arm 2 subjects include patients who do

not receive a kidney transplant (Arm 2C) or who receive a study eligible kidney from an HCV RNA-negative/HCV Ab-positive donor (Arm2A), or from a standard of care donor (Arm 2B). Follow-up for study participants who receive a kidney transplant at a non-study site (Arm 2B5) will be censored at transplantation.
For subjects of Arm 1 of the study, the first dose of G/P will be given as early as 3 days post-transplant. Patients must be out of the ICU, able to eat and drink, take oral medications, and G/P treatment can be safely initiated orally as judged by the site investigator.

Enrolled subjects will be activated in the United Network for Organ Sharing (UNOS) allocation system as eligible for kidney allograft offers from deceased donors that are HCV RNA-positive, HCV Ab-positive, or both.

Subjects who are transplanted with kidneys from HCV RNA-positive donors in Arm 1 will be followed for 1 year after the date of transplantation to evaluate SVR12, SVR24, safety, death, graft failure, acute allograft rejection, delayed graft function, ALT elevation >5 times the upper limit of normal, eGFR and proteinuria. Specifically, scheduled in-person visits for subjects who received organs from HCV RNA-positive donors in Arm 1 and receive G/P treatment will consist of day of transplant, Day 1 of G/P treatment, weeks 1, 2, 4, and 8 (planned end of treatment visit) after starting G/P. Additional scheduled visits will take place at Post Treatment Week 4, Post Treatment Week 12, Post Treatment Week 24 (e.g., post G/P treatment visits) to evaluate SVR4, SVR12 and SVR24 and 1 year post transplant. The post-transplant study visit schedule for MYTHIC has been designed such that these visits should take place on the same days as standard of care clinical visits. For subjects in Arm 1 study-objective pertinent data will be collected while awaiting a transplant (ie, SAEs, hospitalizations, delisting from waitlist, death), and post-transplant (ie, death, graft failure, acute allograft rejection, delayed graft function, eGFR, proteinuria, ALT elevation >5 times the upper limit of normal, and SAEs). Subjects who experience virologic failure in

Arm 1 will be evaluated for the emergence/persistence of DAA-resistant viral variants, and suitable retreatment will be offered.

Study visits in Arm 2A will take place at weeks 1, 4, 8, 12, and 24 weeks after transplantation. Safety, graft survival, mortality, allograft rejection, and results of HCV RNA testing will be captured for a period of 24 weeks post-transplant. Study-objective pertinent data will be collected while awaiting a transplant (i.e., SAEs, delisting from waitlist, death), and post-transplant (i.e., death, graft failure, acute allograft rejection, delayed graft function, eGFR, proteinuria, ALT elevation >5 times the upper limit of normal, and SAEs. For subjects of Arm 1 and Arm 2A who become HCV infected, we will collect additional clinical outcomes of sclerosing cholestatic hepatitis and extrahepatic manifestations of HCV.

If any recipients of a study-eligible HCV RNA-negative/HCV antibody-positive kidney develops HCV infection within 24 weeks after transplantation, that recipient will be offered treatment with G/P for 8 weeks. G/P treatment will be administered and subject will be followed as per local transplant center standard of care not reimbursed by the study but G/P will be supplied by the study. Limited data of this "reactive" G/P treatment and HCV outcome will be collected from these subjects. The following data will be obtained: plasma HCV RNA prior to HCV treatment initiation with G/P, SAEs that occurred during the G/P treatment period, any early discontinuation of G/P treatment, HCV RNA results at post treatment week 12, , and reasons for not achieving SVR12, as applicable. In the case of active HCV viremia, a sample of plasma and PBMCs will be sent to MGH as early as possible after viremia is detected.

Other subjects in Arm 2 who remain on the transplant waiting list, or receive a standard of care kidney transplant will be followed as per transplant center standard of care for at least 12 months post enrollment with study-objective pertinent collection of data while awaiting a transplant (e.g., SAEs, delisting from waitlist, death), and post-transplant events as

applicable (death, graft failure, acute allograft rejection, delayed graft function, eGFR, proteinuria, ALT elevation >5 times the upper limit of normal, and SAEs). However, for Arm 2B5 recipients, no further data will be collected after transplantation.

During the first 6 months after the trial commences, each study site will be assured of the ability to perform at least one kidney transplantation from an HCV RNA-positive donor and G/P therapy provided through the trial. The period of "the first 6 months after the trial commences" will start on the date that the first clinical site has institutional review board approval to start enrolling patients into the trial until 183 days later. The other kidney transplants from HCV RNA-positive donors will take place competitively, such that any site may perform kidney transplants up to a maximum of 10 transplants from HCV-RNA-positive donors with recipients receiving study drug and being analyzed in Arm 1.

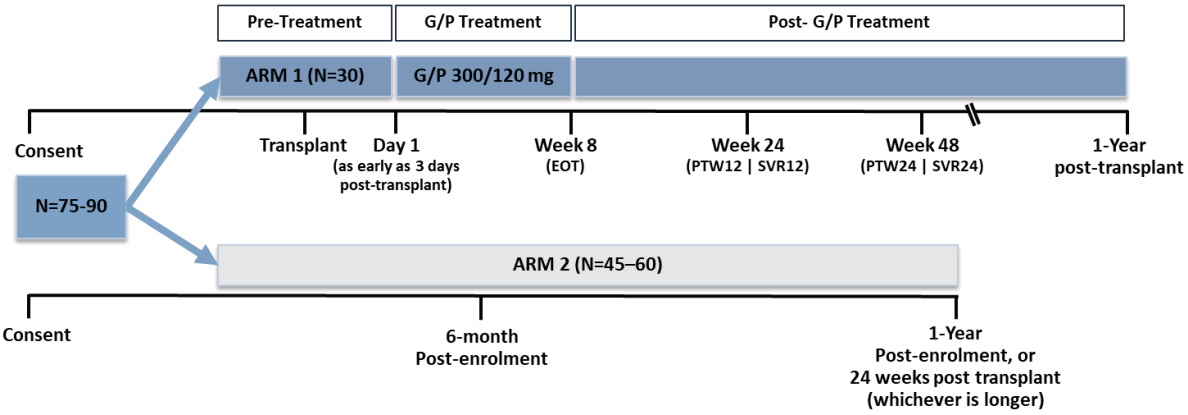
Treatment Period for recipients of HCV RNA-positive kidneys in Arm 1:
Eligible subjects will initiate G/P 300 mg/120 mg QD for 8 weeks early after kidney transplantation. Day 3 post-transplant is targeted for the start of G/P treatment for HCV RNA-positive kidney recipients, with the conditions met that the subject should be out of the ICU, able to eat and drink and take medications orally, and in the judgement of the investigator, starting oral G/P treatment is safe for the subject.

A delay in commencing G/P after day 3 should only take place because the responsible site investigator and/or responsible clinicians believe that G/P cannot be safely administered or because of a high probability that G/P will subsequently need to be discontinued or held for prolonged period because the patient is likely to experience clinical deterioration. In the case of any patient who has not started G/P by day 3 after transplantation, the site investigator will discuss that case with the Principal Investigator Ray Chung, MD, or delegate, and develop and document a plan to start G/P at a later time.

Post Treatment (PT) Period for recipients of HCV RNA-positive kidneys in Arm 1 :

Subjects who complete or prematurely discontinue G/P treatment will be followed for 24 weeks after their last dose of study drug to evaluate efficacy and to monitor HCV RNA and the emergence and persistence of viral substitutions in the NS3 and NS5A, and subjects will be followed up at 1 year post the date of kidney transplant to assess graft function and survival and anti-HCV antibody serology.

Figure 1A: Overall Study Schematic



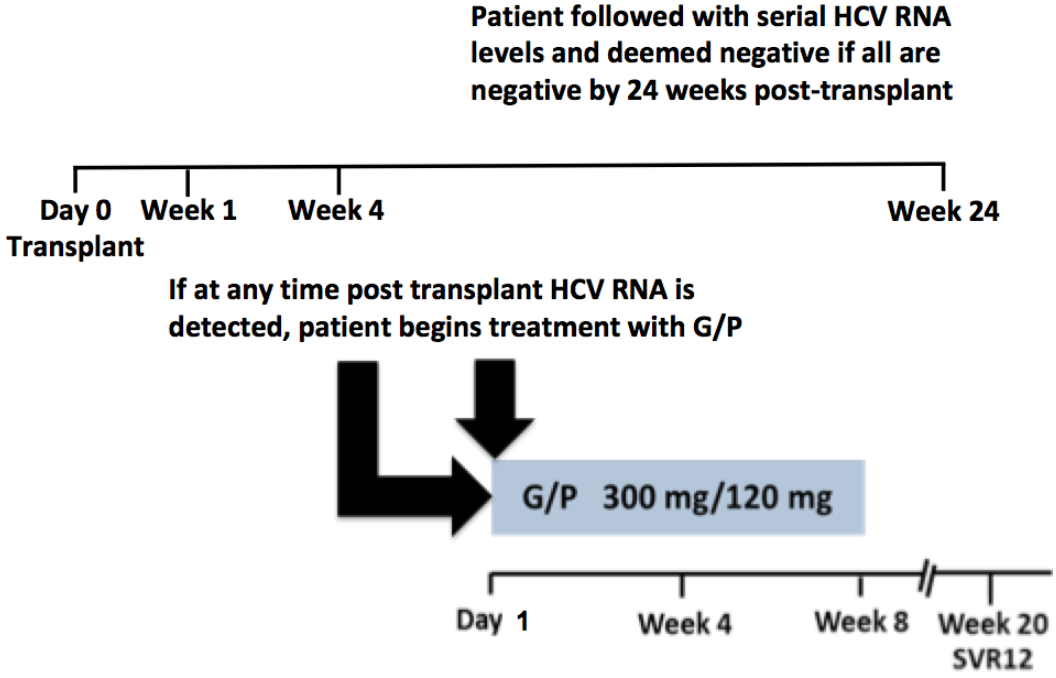
Treatment and PT Period for Study Arm 2A recipients of HCV RNA-negative/HCV antibody-positive kidneys:

Eligible subjects will be followed for 24 weeks after transplantation or 12 months after enrollment, whichever is longer, with surveillance for HCV infection using HCV RNA testing on week 1, week 4 (usual care), and week 24 (Figure 1B) after transplantation. A maximum number of up to n=20 subjects who are enrolled into the study can accept a study-eligible kidney from an HCV RNA-negative/HCV antibody-positive donor and be assigned to Arm 2A and will be followed in the study for 24 weeks post-transplant. The last study-eligible kidney transplant from an HCV RNA-negative/HCV antibody-positive donor in Arm 2A must occur no later than 24 weeks after the date of the 30th kidney transplant from and HCV RNA-positive donor in Arm 1 (see also section 5.1.5).

Any subject in Arm 2A who develops HCV infection by 24 weeks after transplantation will be offered open-label G/P 300 mg/120 mg QD for 8 weeks. G/P will be provided by AbbVie, and while all patients will receive an 8-week course, the patient treatment visit schedule

and follow-up will be guided by the transplant center standard of care and AASLD/IDSA Guidelines for HCV treatment[26], and as described in section 5.1.1, 5.1.2 and Table 6. Outcome data, including SAEs, treatment emergent Grade 3 or greater laboratory abnormalities, sclerosing cholestatic hepatitis and extra-hepatic manifestations, and post-treatment week-12 HCV RNA will be collected from the subject medical record and entered into the study eCRFs. For kidneys from HCV RNA-negative/HCV Ab-positive donors in Arm 2A, the inclusion/exclusion criteria for donors are identical to donor inclusion/exclusion criteria as outlined in section 5.2.1 and 5.2.2, except that donor must be HCV RNA-negative.

Figure 1B: Schematic for patients undergoing transplantation with HCV RNA-negative/HCV antibody-positive kidney in Arm 2A



Observation period for other Study Arm 2 subjects

Enrolled Arm 2 subjects who were not transplanted will be followed for 1 year post enrollment and Arm 2 subjects who received an standard of care kidney (Arm 2B) will be

followed for a minimum of 1 year post-enrollment, or 24 weeks post transplantation whichever is longer, unless they are transplanted at a non-study site (Arm 2B5), in which case no further data will be collected after transplant.

5.1.1 Standard of Care Assessments for all patients – (patient managed clinically and billed per standard medical practice)

1. Subject assessment for kidney transplant candidacy, kidney transplantation, and follow-up care after transplant; prior HCV treatment history; medical history; co-morbid conditions; for-cause kidney biopsy or for cause liver biopsy, due to new or worsening symptoms of pre-transplant kidney or liver disease; or post-transplant delayed or decreasing kidney graft function with suspicion for FSGS, graft rejection, or suspicion for post-transplant fibrosing cholestatic hepatitis, or other new liver disease.
2. Donor kidney assessment and organ procurement, and including HCV RNA
3. Assessment of recipient and donor-organ match
4. G/P treatment regimen monitoring that takes place as part of SOC visits
5. Clinical factors (physical examinations, vital signs)
6. Adverse events and related safety management
7. Concomitant medications
8. Assessments during waitlist period
9. Clinical Chemistry and Hematology labs
10. Pregnancy tests post-transplant, except as noted below for research purposes
11. Drug level monitoring of tacrolimus or other immunosuppressants post-transplant

5.1.2 Protocol Required Assessments

1. All outside standard of care, study-required safety and efficacy labs, G/P treatment monitoring during study visits, including baseline liver fibrosis assessment by Fibroscan as specified in Tables 4, 5, and 6.

2. NS3- and NS5A sequencing at evidence of failure of HCV treatment with G/P in Arm 1 or 2A
3. Determination of HCV genotype from blood sample of HCV RNA-positive donor
4. Archive plasma samples

5.1.2.1 Protocol Optional Assessments

1. Archive peripheral blood mononuclear cell (PBMC) samples

5.1.3 Screening

Potential subjects will first be contacted by the investigator, research coordinator and/or research staff to determine interest and provide basic information about the study. Potential subjects will be invited to attend an **educational session** on HCV infection and transplantation. There should be at least 3 days between the initial contact and the educational session. During this educational session, study investigators and research staff will teach participants about HCV, how it is spread, and the human disease it causes. They will explain the study and its risks and benefits. The potential subject will be encouraged to attend the educational session with at least one other family member or friend. The educational session may be attended by one or multiple potential subjects (and people the subjects invite) at a time. After completion of the educational session, the subject will be eligible for a screening visit. The **Appendix A** contains an educational handout for participants that will be reviewed in the educational session.

If the patient is interested in participating in the study, the patient will undergo a **screening visit**. There should be at least 24 hours between the educational session and the screening visit. However, in specific cases, the site PI can allow the education session and screening visit at which the subject consent is obtained to happen on the same day: The subject wishes to proceed with the screening visit on the same day, and there are extenuating circumstances that make it very beneficial to the subject. One such circumstance may be that a subject is travelling a long distance to the study site for a one-day evaluation and it

would pose a financial or logistical burden to the subject to come back another day. After patient education and signed written and dated informed consent to participate in the study is obtained, subject eligibility will be verified based the protocol inclusion and exclusion criteria. Each subject will receive a unique subject number assigned sequentially by the study site. Enrolled subjects will keep their screening number as their subject number throughout the study.

The investigator/clinician designee will evaluate whether the subject meets all of the eligibility criteria for the organ recipient specified in Section 5.2.1 and Section 5.2.2 and will record the results of this assessment and the details of the informed consent process in the subject's medical records and enter required subject data into the electronic case report form (eCRF) for this study. Enrolled patients will then enter the "waiting list phase." Transplants will occur as deceased donor kidneys become available for consented patients and the study aims for accrual of 30 study-eligible kidney transplants from HCV-RNA positive donors. However, subjects who received a study-eligible HCV RNA-positive kidney offer and scheduled to be transplanted within 24 hours after the 30th HCV-RNA-positive kidney transplant will be allowed into Arm 1 of the study. Subjects who provided consent but do not receive an HCV RNA-positive organ offer will be actively followed in study Arm 2 for at least 1year post enrollment, or 24 weeks post-transplantation, whichever is longer , unless they are transplanted at a non-study site (Arm 2B5), in which case no further data will be collected after transplant.

Medical records to support the medical history will be entered into the study electronic case report forms (eCRFs) developed by the Data Coordinating Center (DCC). Pre-specified information entered will include data from clinic visits, telephone contacts, relevant local laboratory testing and diagnostic/disease screening results (e.g. laboratory studies) collected as part of the standard medical care of the subject and relevant to their kidney transplant candidacy. The up-to-date data should also include sufficient medical history medications

to determine study candidacy. Older records (greater than 24 months) to document key medical history such as kidney disease and HCV treatment history may also be submitted.

Laboratory testing to determine eligibility for the study is part of standard of care assessments supplemented by protocol required laboratory testing outside standard of care and will include the testing specified in Table 4. Additional, protocol-required laboratory tests will be performed by the central laboratory at MGH. All clinical laboratory tests which are standard of care will be performed by the local study site lab. For screening lab results without specific entry criteria that are **abnormal and noted as clinically significant** by the study investigator, the study investigator or designee will consult with the study Medical Monitor from Massachusetts General Hospital (MGH) for approval to enroll the patient in the study.

This phase will also include identification of any medications used by the subject that are contraindicated or not recommended with the concomitant use of G/P (listed in Table 7, and see recipient exclusion criteria 5.2.2). Patients who cannot switch to alternative allowed co-medications or cannot stop contraindicated or not recommended medications at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of G/P treatment are not eligible to participate in the trial. Contraindicated or not recommended medications include: atorvastatin, lovastatin, simvastatin, carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin, astemizole, cisapride, terfenadine, ethinyl estradiol, St John's Wort, and Red yeast rice (monacolin K).

- Subject eligibility for study participation has to be verified by the CCC at MGH, Boston, MA. In addition to study eligibility criteria, the subject's UNOS status as being changed to receive offers from HCV RNA-positive and/or HCV Ab-positive donors should be documented. Once a subject is identified as an eligible study subject by the local clinical site, the local clinical site will submit the subject's

screening/historical medical record information according to the CCC to be verified for meeting enrollment eligibility criteria for organ recipient.

During this phase prior to transplantation, the study staff will contact the study subjects by phone every two months and in-person every six months. The two goals of these interactions will be to a) ascertain adverse events and b) ensure that the subject still meets study eligibility criteria for organ recipient.

Table 4: Screening visit procedures

	Research Visit Activities				Standard of care data to review, and data obtained at screening visit[1]								Research labs
Screening visit	**Informed Consent**	**Current Medications**	**Liver fibrosis assessment[2]**	**Review cause of ESRD**	**HBV: Surface antigen, core antibody, HBV DNA**	**HCV Antibody**	**HCV RNA**	**HIV antibody**	**Hematology labs**	**Clinical Chemistry labs**	**Vitals and Physical Exam**	**pregnancy test**	**Archive plasma sample, PBMC[3]sample**
	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

1 Acceptable screening data: HBV serologies/reflex HBV DNA if HBV core antibody positive, HIV antibody, HCV antibody, liver fibroscan or liver biopsy all obtained <18 months before or at date of screening date. Vital Signs & Physical Exam, HCV RNA, Clinical Chemistry, Hematology, serum pregnancy test (only for women of childbearing potential) obtained ≤60 days before or at date of screening. Research Labs are obtained at screening.
2 If no fibroscan was obtained <18 month before screening visit, a fibroscan will be obtained.
3 PBMC sample is optional and restricted to sites with collection capability.

5.1.3.1 Rescreening

Subjects may be retested or rescreened only once. These subjects must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary. Subjects may be rescreened only in the event that they failed initial screening for the following reasons:

1) Exclusionary laboratory parameter in which the primary investigator believes initial results were not accurate or indeterminate or in the case of cPRA, the investigator

confirms that the cPRA is now <80%. The cPRA of record shall be the cPRA reported to UNOS for organ allocation.

2) Subject had a potential living kidney donor initially, but no longer has a potential living donor
3) ALT > 2x the upper limit of normal
4) Investigator initially deemed participant not an acceptable candidate for the trial

For subjects who rescreen or subjects that do not meet the study eligibility criteria upon retest/rescreen, the site personnel must contact the sponsor and identify the subject as a screen failure.

5.1.4 Waiting List and Transplantation Phases

5.1.4.1 Waiting List Phase

The waiting list phase will commence when the CCC at MGH authorizes the clinical site to render the participant eligible for kidney allograft offers that are seropositive for HCV using the United Network for Organ Sharing allocation system.

Subsequently, during the waiting list phase, the study staff will contact the study subjects by phone every two months and in-person every six months. The two goals of these interactions will be to a) ascertain adverse events and b) ensure that the subject still meets study eligibility criteria.

5.1.4.2 Maintenance of Enrollment status

For enrolled subjects who did not receive a kidney transplant at 6 months post-enrollment, the following data are acceptable to verify continued study eligibility at 6 months post enrollment: vital signs and physical exam, liver function test panel (see footnote C, Table 8), serum or urine pregnancy test as appropriate (obtained <60 days or at date of 6 month post enrollment visit), review of co-medications, medical history, AEs and hospitalizations, and transplant waitlist status.

5.1.4.3 Transplantation Phase

At the end of any organ offer from a deceased donor, per usual transplant center practice, the investigator will discuss with the subject characteristics of the allograft and risks and benefits presented by transplantation using that allograft, and the subject can accept or reject that allograft.

A kidney transplantation event will prompt a shift to the "transplantation phase." The elements of the transplantation phase will depend on the type of kidney transplant. Subjects who undergo transplantation with a study-eligible HCV RNA-negative/HCV Ab-positive in Arm 2A will be followed as per standard of care, and with surveillance of HCV RNA as per Figure 1b, and outcomes of G/P treatment collected up to 1 year post transplant if applicable and according to Table 6 and Section 5.1.5.2.

5.1.4.4 Peri-Transplant and Post-Kidney Transplant Visits and Laboratory Evaluations for Recipients of Kidneys from HCV RNA-positive donors in Arm 1

Starting around the time of organ offer and transplantation, patients are followed closely by both the surgical and nephrology team. As a part of standard of care visits, the following procedures activities will be performed:

- Phlebotomy
- Vital signs
- Physical exam

The study staff will follow procedures and activities closely along with transplant team and this information (vital signs, physical exam, and phlebotomy results) will be collected as a part of data collection. In addition to these standard of care procedures and activities, the study team will also perform specific research related activities at specific time points.

5.1.4.5 Post-Kidney Transplant Research Phlebotomy in Arms 1

Research laboratory blood draws will take place along with standard of care blood draws. The study staff will call the research subject to coordinate research blood draws appropriately. In addition, study staff will assess for adverse events/side effects and obtain

current medication data. Additional laboratory testing will be performed if the PIs feel it is necessary for patient safety.

5.1.5 Treatment Period with G/P for patients treated for HCV infection in Arm 1 and Arm 2A

Subjects who undergo transplantation with a study-eligible HCV RNA-positive kidney in Arm 1 will initiate G/P 300 mg/120 mg QD for 8 weeks early after kidney transplantation. Day 3 post-transplant is targeted for the start of G/P treatment. The subject should be out of the ICU, able to eat and drink and take medications orally, and by judgement of the investigator it is safe to start G/P treatment orally. These subjects will be followed according to Table 5 schedule. Subjects who undergo transplantation with a study-eligible HCV RNA-negative/HCV-Ab-positive kidney in Arm 2A will undergo surveillance for HCV RNA for 24 weeks post-transplant and be treated with G/P if necessary and according to transplant center standard of care in the event of HCV infection (Figure 1B).

Efficacy and safety outcomes assessments recorded in the medical record as part of the subject's standard clinical management and follow up will be submitted using electronic CRFs where available in the medical record, except for protocol defined central laboratory assessment collection, drug dispensation and accountability, and required monthly medical record source record verification/submission. The central laboratory will be at MGH.

The schedule of procedures for the study regarding the treatment of HCV infection for recipients of HCV RNA-positive kidneys in Arm 1 (Table 5) is more intense but principally based on the AASLD guidelines[26] for the treatment of HCV, which recommends:

1) Baseline: hepatic fibrosis assessment, drug-drug interaction assessment, hepatitis B serologies (HBs Ag, anti-HBc, anti-HBs, reflex HBV DNA if anti-HBc-positive),

CBC/platelets, hepatic function panel, and estimated glomerular filtration rate (eGFR, done in this study using the MDRD equation);
2) On treatment monitoring: HCV RNA and routine CBC/platelets, hepatic panel and eGFR) are recommended at week 4 and as clinically indicated;
3) Post-treatment monitoring: HCV RNA and routine labs are recommended at 4 and 12 weeks post-treatment.

In Arm 1, G/P dosing in Arm 1, treatment/side effect management, and duration will be recorded in the study CRFs by the site PI and or clinical provider designee and managed according to the AASLD guidelines, center standard of care, with additional assessments required by the protocol according to the Study Activities table (Table 5).
The schedule of procedures regarding kidney transplantation activities is based on the local center's practice for kidney transplant care.

Relevant medical records include clinic visits and telephone contact as clinically indicated to ensure medication adherence and to monitor for adverse events. Original clinic notes, telephone notes, locally available safety labs/evaluations and/or diagnostic tests or health screenings collected during HCV treatment period will be abstracted on-site to identify adverse events and to record vital signs, physical examinations, concomitant medications, HCV RNA, HCV resistance, and clinical laboratory tests that were collected as part of standard of care practice. Sites will follow their standard of care practice as far as collection of vital sign data and clinical laboratory tests. Specifically, for example, it will not be considered a protocol violation if a site does not collect respiratory rate or temperature at every outpatient visit if such measurements are not always performed as standard of care practice.

During the post-transplantation period, study staff will also perform periodic verification for new clinical interactions that may have occurred. This involves reviewing records from the prior 4 weeks when the subject visits the site laboratory assessment collection

and drug dispensing/accountability.

Study visits and procedures during the post-transplantation period for Arm 1 and ARM 2A are detailed in Tables 5, and 6, respectively. Safety and tolerability will be assessed throughout the study per AASLD and center guidelines with additional assessments required by the protocol according to the Study Activities (Tables 5, 6). Central laboratory testing at MGH will include DAA resistance testing. All other laboratory testing will be performed by local laboratories, which must be CLIA certified and using laboratory test which are approved by FDA.

All Arm 1 and Arm 2A subjects will continue to return to the site on an inpatient/outpatient basis as outlined in Tables 5 and 6. Sites should ensure that subjects adhere to all the study visits for laboratory sample collection and drug dispensing/reconciliation. Subjects who cannot complete their study visit per the visit schedule should ensure that they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

Virologic stopping criteria will be evaluated and applied by the investigator as detailed in Section 5.4.1.1.

Subjects who prematurely discontinue treatment during the transplantation phase should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Tables 5 and 6.

In Arm 1, 30 candidates will undergo kidney transplantation with kidneys from HCV RNA-positive donors. After n=30 kidney transplantation events from HCV RNA-positive donors have occurred, no further subjects will be enrolled into the study. Already enrolled subjects who receive an HCV RNA-positive donor kidney offer that meets study criteria and are scheduled to be transplanted within 24 hours after the 30th kidney transplant from an HCV RNA-positive donor will also be allowed into treatment arm A of the study.

Patients enrolled in the trial will be notified by phone that the HCV RNA-positive arm of the trial has completed enrollment and remaining subjects (now in Arm 2) will have the ability to accept (i) a study-eligible kidney from an HCV RNA-negative/HCV Ab-positive donor up until 24 weeks after the last kidney transplant event from a study-eligible HCV RNA-positive donor, (ii) a standard of care kidney transplant, or remain on the waiting list for the duration of the study. G/P treatment, if needed, will be provided free of charge to a subject in Arm 2A who developed HCV viremia after up to 24 weeks post-transplant of a kidney from an HCV RNA-negative/HCV Ab-positive donor.

5.1.5.1 G/P treatment phase/Visits and laboratory evaluations after transplantation for subjects who receive a study eligible HCV RNA-positive kidney in Arm 1

Visit 1: Peri-transplant visit

The treating physician will evaluate the patient's overall condition and make a judgment on whether transplantation is safe. The following recipient-donor-kidney match results exclude transplantation in this protocol: a) Blood group incompatibility between donor and recipient; b) Cross match reactivity, or clinically meaningful donor specific antibody, or other immunological reactivity related to an allograft offer deemed a substantial risk for rejection by the responsible investigator.

The following research procedures and activities will be performed:

- Obtain medication data
- Donor blood sample (if available)
- Assessment of recipient and donor-kidney match for exclusion from transplantation in this protocol

Visit 2: Post-kidney transplant (Day 3 ± 1 day)

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

The following research procedures and activities will be performed:

- Assess for Adverse Events
- Obtain medication data
- Research Phlebotomy

This visit will be the target date to start G/P, as per judgement by the investigator.

Visit 3: (Day 1 of G/P treatment)

Visit 3 may be combined with visit 2, 3 days post-transplant, if G/P treatment can be safely initiated as per judgement by the investigator. The following research procedures and activities will be performed:

- Assess for Transplant-related, HCV-related and study drug related Adverse Events, including clinical outcomes and data (death, graft failure, acute allograft rejection, eGFR, delayed graft function ALT elevation > 5x ULN, SAEs, sclerosing cholestatic hepatitis, and extrahepatic manifestations of HCV)
- Obtain medication data
- Research Phlebotomy
- Pregnancy test, as indicated
- Start G/P treatment with food, and dispense 1 month supply of G/P
- Schedule appointments for follow-up visits

The study staff will reinforce instructions on bringing the subject's routine and study medications to each visit, and reinforce adherence with the study medication and protocol.

Visit 4: (1 week after start of G/P)

Visit 4 should occur one week (± 3 days) after starting G/P and should immediately follow the subject's regularly scheduled post-transplant follow-up visit. The subject will arrive at the study site outpatient clinic (or the hospital, if needed). The following research procedures and activities will be performed:

- Assess for Transplant-related, HCV-related and study drug related Adverse Events, including clinical outcomes (same as described in Visit 3)
- Obtain medication data
- Research Phlebotomy
- Pill count of G/P tablets
- Confirm follow-up visits
- Replenish study drug if necessary

Visit 5: Telephone encounter or in-person visit (2 weeks after start of G/P treatment)
Visit 5 should occur 2 weeks ± 3 days after starting G/P and should follow the subject's regularly scheduled post-transplant follow-up visit**.** The subject will arrive at the study site outpatient clinic (or the hospital, if needed). Alternatively, this can be a telephone encounter. The following research procedures and activities will be performed:

- Assess for Transplant-related, HCV related and study drug related Adverse Events, including clinical outcomes (same as described in Visit 3)
- Obtain medication data
- Pill count of G/P tablets
- Confirm follow-up visits

Visit 6: (4 weeks after start of G/P treatment)
Visit 6 should occur 4 weeks ± 3 days) after start of G/P. If possible, this visit should follow the subject's regularly scheduled post-transplant follow-up visit (or the hospital, if needed).

The following procedures and activities will be performed:

- Assess for Transplant-related, HCV-related, and study drug related Adverse Events, including clinical outcomes (same as described in Visit 3 plus eGFR and proteinuria)
- Obtain medication data
- Research Phlebotomy

- Pregnancy test, as indicated
- Pill count of G/P tablets
- Dispense G/P 4 week supply
- Confirm follow-up visits

Visit 7: Telephone encounter (6 weeks after start of G/P treatment)

This visit should occur at 6 weeks ±3 days after start of G/P treatment as a telephone encounter. Note that this visit can be performed as an in person visit to the study site, if there is a standard of care post-transplant visit on the same date.

The subject is called by authorized study staff who perform the following activities:

- Assess for Transplant-related, HCV-related, and study drug related Adverse Events, including clinical outcomes (same as described in Visit 3)
- Obtain medication data
- check on adherence with taking G/P
- confirm follow up visits

Visit 8: End of G/P treatment visit (8 weeks after start of G/P treatment)

Visit 8 should occur approximately 8 weeks ±7 days after start of G/P treatment. If possible, this visit should follow the subject's regularly scheduled post-transplant follow-up visit (or the hospital, if needed).

The following procedures and activities will be performed:

- Assess for Transplant-related, HCV-related, and study drug related Adverse Events, including clinical outcomes (same as described in Visit 3 plus eGFR and proteinuria)
- Obtain medication data
- Research Phlebotomy (including optional PBMC collection for sites with capability)
- Pregnancy test, as indicated
- Pill count of G/P tablets

- Confirm follow up visits

5.1.6 Post-Treatment Period for Arm 1

All subjects who received at least one dose of study drug will be monitored during the post-transplantation period for safety, HCV RNA, and the emergence and persistence of resistance-associated viral substitutions for an additional 12 and 24 weeks following the last dose of G/P. For recipients of HCV RNA-positive transplants in Arm 1, a 1-year post kidney transplant visit is included to assess for graft function and survival, eGFR and proteinuria, and donor specific antibody (abstracted from the center's medical records), as applicable per the center's standard of care.

Appropriate information from original clinic notes, telephone notes, locally available safety labs/evaluations and/or diagnostic tests, or health screenings collected during the post-HCV treatment period will be abstracted at the clinical sites to identify and report adverse events, vital signs, physical examinations, concomitant medications, HCV RNA, HCV resistance, and clinical laboratory tests that were collected as part of standard of care practice.

The Post-Treatment Period will begin the day following the last dose of study drug treatment.

Subjects who prematurely discontinue treatment should return to the site for a Post-Treatment Discontinuation Visit as outlined in Tables 5 and 7 and will be followed for all post-treatment safety, HCV RNA, and resistance-associated substitutions according to the post treatment period schedule.

5.1.6.1 Post-treatment visits for subjects who receive an HCV RNA-positive kidney in Arm 1

Visit 9: Telephone encounter or in person visit (4 week after end of G/P treatment)

Visit 9 should occur 4 weeks after end of G/P treatment ±7 days. Note that this visit can be performed as an in-person visit to the study site, if there is a standard of care post-transplant visit on the same date.

The following research procedures and activities will be performed

- Assess for Transplant-related, HCV-related, and study drug related Adverse Events, including clinical outcomes (same as described in Visit 3)
- Obtain medication data
- Confirm follow-up visits

Visit 10: (12 weeks after end of G/P treatment)

Visit 10 should occur 12 weeks after end of G/P treatment ± 14 days. If possible, it should immediately follow the subject's regularly scheduled post-transplant follow-up visit at the study site and will provide an opportunity to assess SVR12.

The following research procedures and activities will be performed:

- Assess for Transplant-related- and HCV-related Adverse Events, including clinical outcomes (same as described in Visit 3 plus eGFR and proteinuria)
- Obtain medication data
- Research Phlebotomy (including optional PBMC collection for sites with capability)
- Confirm follow up visits

Visit 11: (24 weeks after end of G/P treatment)

Visit 11 should occur 24 weeks ± 28 days after end of G/P treatment. If possible, the visit should follow the subject's regularly scheduled post-transplant follow-up visit and will provide an opportunity to assess SVR-24**.**

The following research procedures and activities will be performed:

- Assess for Transplant-related and HCV-related Adverse Events, including clinical outcomes (same as described in Visit 3 plus eGFR and proteinuria)

- Obtain medication data
- Research Phlebotomy
- Confirm follow up visit

Visit 12: (1 year post-transplant, end of study visit)

Visit 12 should occur 1 year ±28 days after the kidney transplant and is the end of study visit. If possible, the visit should immediately follow the subject's regularly scheduled post-transplant follow-up visit and provides an opportunity to perform an end of study assessment

The following research procedures and activities must be performed:

- Assess for Transplant-related and HCV-related Adverse Events, including clinical outcomes (same as described in Visit 3 plus eGFR and proteinuria)
    - Obtain medication data
    - Research Phlebotomy (including optional PBMC collection for sites with capability)
    - Obtain information on donor specific antibodies as applicable per center's standard of care

The Research Staff should fill out the **Study Closeout Form.** This form must be signed by the site investigator.

Table 5: Transplantation, G/P treatment and post-treatment Phase Study Procedures for Recipients of Kidneys from HCV RNA-Positive Donors in Arm 1

	Visit	Research Visit Activities			Research labs						G/P		Standard of Care					
Transplant, G/P treatment, & post treatment follow-up	**Visit[1]**	**Assess Adverse Events[12]**	**Current Medications**	**Confirm donor-recipient pair meet trial criteria[2]**	**G/P adherence**	**HCV Antibody**	**Urine Prot./Creat. Ratio**	**HCV RNA[3]**	**Archive blood samples[4]**	**DAA resistance**	**Donor blood sample[5]**	**Pregnancy test[6]**	**Study drugs dispensed**	**Vitals & PE[7]**	**Clinical Chemistry[8]**	**Hematology**	**HCV RNA[3]**	**Pregnancy test[6]**	**Tacrolimus level[9]**
Peri-transplant visit	V1	✓	✓	✓							✓			✓	✓	✓		As per transplant center standard of care	As per transplant center standard of care
Day 3[7] Post KT	V2	✓	✓			✓		✓	✓			✓		✓	✓	✓			
Day 1 of G/P treatment	V3	✓	✓									✓	✓	✓	✓	✓			
Treatment week 1±3 days	V4	✓	✓		✓			✓						✓	✓	✓			
Treatment week 2 ±3 days	V5 T5	✓	✓		✓														
Treatment week 4 ±3 days	V6	✓	✓		✓	✓	✓		✓			✓	✓	✓	✓	✓	✓		
Treatment week 6 ±3 days[10]	T7	✓	✓		✓														
Treatment week 8 ±7 days (EOT)	V8	✓	✓		✓		✓	✓	✓			✓		✓	✓	✓			
Post treatment week 4 ±7 days	V9 T9	✓	✓																
Post treatment week 12 ±14 days	V10	✓	✓				✓	✓	✓										
Post treatment week 24 ±28 days	V11	✓	✓				✓	✓	✓					✓	✓	✓			
1 year Post transplant ±28 days; End of study[11]	V12	✓	✓			✓	✓		✓					✓	✓	✓			
G/P treatment failure		✓						✓	✓	✓									
Premature discontinuation		✓					✓	✓	✓					✓	✓	✓			

1 Visit types: V - in person visit to site; L - Lab visit; T - Telephone encounter
2 Includes evaluation of blood type and HLA compatibility
3 HCV RNA testing at V2, V4, V8, and V10 and V11 are study paid labs. HCV RNA testing at visit 6 is billed as SOC. All HCV RNA testing is done at local laboratory by a CLIA certified laboratory and with an FDA approved test.
4 Archived plasma samples (required) and PBMC (optional at Visits 8, 10, and 12) samples are shipped to the clinical coordinating center at Massachusetts General Hospital, see section 5.3.1.1
5 Lack of availability of donor blood sample will not preclude donor eligibility or transplant. HCV genotype is determined from the donor blood sample at local laboratory; Another portion of the donor sample is frozen for storage and potential testing for DAA resistance as needed. See section

5.3.1.1
6 If visit 2 and visit 3 are on the same day or within 14 days of each other only 1 serum pregnancy test need to be obtained. Visit 6 and Visit 8 pregnancy tests can be urine tests. Additional pregnancy tests not billed to the study are obtained as per transplant center standard of care.
7 Vitals and physical exam will be conducted and documented as per standard of care at transplant center
8 Liver function tests (ALT, AST, Alk Phos., total bilirubin) will be ordered as a study lab if not standard of care as part of clinical chemistry labs at the local transplant center. See table 8 for clinical chemistry labs and hematology labs.
9 Includes Tacrolimus level and/or other utilized immunosuppressant that requires therapeutic drug monitoring as per transplant center standard of care;
10 Telephone call will be performed between clinic visits at treatment week 6 to assess subject adherence to G/P treatment.
11 Obtain information on donor specific antibodies as applicable per center's standard of care from subject medical record.
12. Assess for clinical outcomes, including fibrosing cholestatic hepatitis, and extrahepatic manifestations of HCV at Visits 4-11.

5.1.7. Peri-Transplant and Post-Kidney Transplant Visits and Laboratory Evaluations for Recipients of Kidneys from HCV RNA-negative/HCV Antibody-Positive donors in Arm 2A

Starting around the time of organ offer and transplantation, patients are followed closely by both the surgical and nephrology team. As a part of standard of care visits, the following procedures activities will be performed:

- Phlebotomy
- Vital signs
- Physical exam

The study staff will follow procedures and activities closely along with transplant team and this information (vital signs, physical exam, and phlebotomy results) will be collected as a part of data collection. In addition to these standard of care procedures and activities, the study team will also perform specific research related activities at specific time points.

Research laboratory blood draws will take place along with standard of care blood draws. The study staff will call the research subject to coordinate research blood draws appropriately. In addition, study staff will assess for adverse events/side effects and obtain

current medication data. Additional laboratory testing will be performed if the PIs feel it is necessary for patient safety.

Visit 1: Peri-transplant visit

The treating physician will evaluate the patient's overall condition and make a judgment on whether transplantation is safe. The following recipient-donor-kidney match results exclude transplantation in this protocol: a) Blood group incompatibility between donor and recipient; b) Cross match reactivity, or clinically meaningful donor specific antibody, or other immunological reactivity related to an allograft offer deemed a substantial risk for rejection by the responsible investigator. Given the requirement for rapid evaluations and decision-making around the time of kidney transplantation, the treating physician will likely be the transplant surgeon (and/or transplant nephrologist) and will contact study staff in the pre-transplant period about the suitability of the candidate, donor and allograft for the MYTHIC study.

The following research procedures and activities will be performed:

- Obtain medication data
- Assessment of recipient and donor-kidney match for exclusion from transplantation in this protocol

Visit 2: (day 7 ± 2 days)

Visit 2 should occur 7 ± 2 days after the subject's kidney transplant and will immediately follow the subject's regularly scheduled post-transplant follow-up visit. The subject will arrive at the study site outpatient clinic if discharged from hospital or in hospital if not yet discharged. The following procedures and activities will be performed:

- Assess for Adverse Events, and clinical outcomes, including: death, graft failure, acute allograft rejection, delayed graft function ALT elevation > 5x ULN, SAEs, sclerosing cholestatic hepatitis, and extrahepatic manifestations of HCV. Obtain HCV plasma RNA.

- Obtain medication data
- Research Phlebotomy
- Schedule appointments for follow-up visits

The study staff will inform the patient of the results of their HCV RNA within 1 week after their visit. If at any time the patient's HCV RNA becomes detectable, then the patient will move immediately into the "Reactive G/P Treatment Phase".

Visit 3: (week 4 ± 7 days)

Visit 3 should occur 4 weeks ± 7 days after the subject's kidney transplant and will immediately follow the subject's regularly scheduled post-transplant follow-up visit. The subject will arrive at the study site outpatient clinic. The following procedures and activities will be performed:

- Assess for Adverse Events, and clinical outcomes as described in Visit 2 and eGFR and proteinuria
- Obtain medication data
- Standard of care Phlebotomy including plasma HCV RNA test
- Research Phlebotomy
- Schedule appointments for follow-up visits

The study staff will inform the patient of the results of their HCV RNA within 1 week after their visit. If at any time the patient's HCV RNA becomes detectable then the patient will move immediately into the "Reactive G/P Treatment Phase".

Visit 4: (week 8 ± 7 days)

Visit 4 should occur 8 weeks ± 7 days after the subject's kidney transplant and will immediately follow the subject's regularly scheduled post-transplant follow-up visit. The subject will arrive at the study site outpatient clinic. The following procedures and activities will be performed:

- Assess for Adverse Events, and clinical outcomes as described in Visit 2, except that assessments for HCV-related complications will take place only if HCV infection has been detected.
- Obtain medication data
- Schedule appointments for follow-up visits
- Research Phlebotomy, including required plasma and optional PBMCs at sites with capability

Visit 5: (week 24 ± 14 days post kidney transplant)

Visit 5 should occur 24 weeks ± 7 days after the subject's kidney transplant and will immediately follow the subject's regularly scheduled post-transplant follow-up visit. The subject will arrive at the study site outpatient clinic. The following procedures and activities will be performed:

- Assess for Adverse Events, and clinical outcomes as described in Visit 2, except that assessments for HCV-related complications will take place only if HCV infection has been detected, and assess for eGFR and proteinuria.
- Obtain medication data
- Research Phlebotomy, including plasma HCV RNA and other labs as per Table 6, and required stored plasma and optional stored PBMCs at sites with capability
-
- Schedule end of study visit if needed

The study staff will inform the patient of the results of their HCV RNA within 1 week after their visit. If at any time the patient's HCV RNA becomes detectable then the patient will be scheduled for a "Reactive G/P Treatment Visit." If the patient remains HCV RNA negative at visit 5 they will be considered to have not have had HCV transmitted by transplant and will only have passive data collected related to usual care encounters with the health care system.

If study visit 6 ±28 days is equal to or exceeding 365 days after date of enrollment then this will be also the end of study visit (see additional research procedure for end of study visit below in visit 6).

Visit 6: (1 year ±28 days post enrollment and end of study visit)

Visit 6 should occur 1 year ± 28 days after the subject enrolled into the study and is the end of study visit. If possible the visit should follow immediately the subject's regularly scheduled post-transplant follow-up visit. This visit is only necessary if visit 5 occurred before 337 days after date of enrollment.

The following procedures and activities will be performed:

- Assess for Adverse Events, and clinical outcomes as described in Visit 2, except that assessments for HCV-related complications will take place only if HCV infection has been detected. Assess for eGFR and proteinuria.
- Obtain medication data
- Research Phlebotomy, including required stored plasma and optional stored PBMCs at sites with capability
-

The Research Staff should fill out the Study Closeout Form. This form must be signed by the site investigator.

Table 6: Transplantation Phase Study Procedures for Recipients of Kidneys from HCV RNA-Negative/HCV Antibody-Positive Donors in Arm 2A

		Study Visit	Research Visit Activities			Research labs						G/P	Standard of Care					
Week of or after Kidney Transplant	**Day of or after Kidney Trans-plant***	**Visit**	**Assess Adverse Events[6]**	**Current Medications**	**Confirm donor-recipient pair meet trial criteria[1]**	**HCV Antibody**	**Urine Prot./Creat. Ratio**	**HCV RNA[2]**	**Archive blood[7] sample**	**DAA resistance sample**	**Donor blood sample[3]**	**Study drugs dispensed**	**HCV RNA**	**Vitals & PE**	**Clinical Chemistry**	**Hematology**	**Tacrolimus Level[4]**	**Pregnancy Test**
0	**Peri-transplant visit**	V1	✓	✓	✓						✓			**Per standard of care**	**Per standard of care**	**Per standard of care**	**Per standard of care**	**Per standard of care**
1	**7 ± 2 day**	V2	✓	✓				✓										
4	**28 ± 7 days**	V3	✓	✓			✓		✓				✓					
8	**56 ± 7 days**	V4	✓	✓					✓									
24[5]	**168 ± 14 days**	V5	✓	✓		✓	✓	✓	✓									
End of study Visit	**1 year ± 28 days**	V6	✓	✓		✓	✓		✓									
HCV RNA Detected			✓	✓			✓	✓	✓			✓			✓	✓		

1 Includes evaluation of blood type and HLA compatibility
2 First quantifiable HCV RNA should trigger the reactive G/P treatment; First "detectable" but not quantifiable HCV RNA requires a follow-up HCV RNA blood draw and test for confirmation within 1 week of results of 1st "detectable" but not quantifiable RNA result; the second (confirmatory) positive e.g., "detectable or quantifiable" HCV RNA should trigger the reactive G/P treatment
3 If available. Lack of availability of donor blood sample will not preclude donor eligibility. Donor blood sample will be frozen and will be shipped to clinical coordinating center laboratory at MGH as needed for DAA resistance testing. See section 3.5.1.1
4 Includes Tacrolimus level and/or other utilized immunosuppressant that requires therapeutic drug monitoring
5 If subject visit 6 ±28 days would be equal to or exceeds 365 days from date of

enrollment, then visit 5 will be also the end of study visit.
6 Assess for clinical outcomes, including sclerosing cholestatic hepatitis, and extrahepatic manifestations of HCV at Visits 2-6 if treated with G/P.

7 4 Archived plasma samples (required) and PBMC (optional and restricted to sites with collection capability at weeks 8, 24, and end of study) samples are shipped to the clinical coordinating center at Massachusetts General Hospital, see section 5.3.1.1

5.1.8 "Reactive G/P Treatment Phase" -- only for subjects who experience HCV infection after transplantation of a kidney from a HCV RNA-negative/HCV antibody-positive donor in Arm 2A

Reactive Visit 1 (within 2 weeks of positive HCV RNA)

Reactive Visit 1 should occur approximately within 2 weeks after the subject's first positive HCV RNA. The first quantifiable HCV RNA should trigger the reactive G/P treatment. If the first positive HCV RNA is "detectable" but not quantifiable, then, to confirm the result, a follow-up HCV RNA blood draw is required as soon as possible. A second (confirmatory) positive, e.g., "detectable or quantifiable", HCV RNA should trigger the reactive G/P treatment. The subject will arrive at the study site outpatient clinic. The following standard of care procedures and activities will be performed:

- Assess for Adverse Events, and clinical outcomes, including: death, graft failure, acute allograft rejection, delayed graft function ALT elevation > 5x ULN, SAEs, sclerosing cholestatic hepatitis, and extrahepatic manifestations of HCV.
- Obtain medication data
- Physical examination, vital signs
- Phlebotomy
- Where applicable, pregnancy testing must be performed prior to starting G/P, and G/P should not be started when pregnancy test is positive
- Schedule appointments for follow-up visits
- Dispense G/P

The following information of standard-of care follow up visits after reactive Visit 1 will be collected retrospectively, abstracted from subject records and recorded in study eCRFs: Any SAE and relatedness of SAE to G/P during G/P treatment from the 1st dose of G/P to 30 days post last dose of G/P treatment; any G/P treatment emergent laboratory abnormality ≥ Grade 3 until 2 days post last day of G/P treatment; any early discontinuation of G/P,; HCV plasma RNA before start of G/P treatment and post G/P treatment week 12; reason for not achieving SVR12 if applicable.

5.1.9 Additional Visits

Additional visits will only be necessary in the case of G/P treatment failure of subjects who received an HCV RNA-positive kidney. After treatment failure has been confirmed, a suitable retreatment regimen will be provided by the MYTHIC study. The retreatment regimen will be chosen at the discretion of the overall PI, Ray Chung, MD with input from the site investigator. The retreatment of study subjects, however, will be followed by the site investigator and as per local center standard of care. The following information of standard-of care visits for retreatment of a subject who failed G/P in this study will be obtained: Any SAE and relatedness of SAE to retreatment regimen from the 1st dose of retreatment regimen to 30 days post last dose of retreatment regimen; Any retreatment regimen emergent laboratory abnormality ≥ Grade 3 until 2 days post last dose of retreatment regimen; any early discontinuation of retreatment regimen, reason for not achieving SVR12; HCV plasma RNA before start of re-treatment regimen and 12 weeks after end of re-treatment.

5.1.10 Schedule of events for patients who receive no transplant or standard of care kidney transplant

Enrolled subjects who undergo a standard of care kidney transplant or who remain on the transplant waiting list will have limited study visits and procedures. These subjects will be followed for a minimum of 1 year post enrollment if they did not receive a transplant during that time. Subjects who received a standard of care kidney transplant will be

followed for 24 weeks post transplant or a minimum of 1 year post enrollment, whichever is longer.

After enrollment and while on the waiting list, there will be telephone contacts with study subjects every two months to ascertain interim events of importance to protocol-data collection, including non-SAE hospitalizations, SAEs, change in wait list status. For those who have a standard of care kidney transplant, death, graft failure, acute allograft rejection, delayed graft function ALT elevation > 5x ULN, eGFR, proteinuria (as available) and SAEs will be obtained from the subject's medical record. eGFR will be measured at each standard of care clinic visit, with particular focus on the 6-month visit. These data will be entered into study eCRFs.

5.1.11 Future Research

De-identified plasma samples, and/or PBMC samples collected for research purposes from subjects may be sent only to study investigators for their research. These samples may include information such as sex, age, health history, or ethnicity. These samples will not be sold. Some future studies may need health information (such as smoking history or present health status) that may require contacting the subject to obtain further information. If future contact with study subjects is contemplated after when this study has ended, the patient must consent to allow contact after the study has ended.

5.2 Selection of Study Population

The study population consists of HCV RNA-negative patients on the kidney transplant waiting list.

Subjects who meet all the transplant candidate inclusion criteria and none of the transplant candidate exclusion criteria will be eligible for enrollment into the study. As noted elsewhere in the protocol, the study will be divided into the screening phase, the waiting list phase, and the post-transplantation phase.

5.2.1 Inclusion/Exclusion Criteria for kidney transplant candidates

5.2.1.1 Inclusion Criteria for kidney transplant candidates

1. Age ≥21 and ≤65 years at consent
2. Estimated glomerular filtration rate < 15 ml/min/1.73m^2 (calculated using the 4-variable MDRD equation) at the time of consent
3. Listed for an isolated kidney transplantation
4. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements, and must voluntarily sign and date an informed consent
5. No available medically acceptable, compatible living kidney donor
6. Subject must agree to use an effective method of birth control as outlined in Appendix D, and starting on the day of transplant
7. Assent from the patient's primary transplant nephrologist that participation would be reasonable for the patient
8. Attended an educational session on use of HCV positive allografts

5.2.1.2 Rationale for Main Inclusion Criteria

The rationale for each criterion is listed in the order of inclusion criteria.

1. The rationale for the age inclusion criteria is that participants ≥ 65 years may have more severe responses to acute HCV infection
2. While listing for kidney transplantation is allowed when eGFR<20 ml/min/1.73m^2, some patients with an eGFR in the 15 – 20 ml/min/1.73m^2 range continue to have good quality of life. Participants with eGFR <15 ml/min1.73m^2 are more likely to be at risk of renal disease-related complications than participant with eGFR>=15 ml/min/1.73m^2. As a result, it is consistent with the ethical principle of beneficence to require eGFR<15 ml/min/1.73m^2 for study entry.
3. Multi-organ transplant recipients often have poor post-transplant life expectancy and elevated risk for peri-transplant contraindications.
4. Respect for autonomy necessitates that all participants have a full understanding of the risk of participation.

5. Living kidney donor transplantation often offers substantial advantages over deceased donor kidney transplantation. Patients with the option of a living donor transplant need not accept the risk of acute HCV infection and treatment.
6. Acute HCV infection or the use of study drug and/or mycophenolate mofetil might carry risks to a pregnancy that must be avoided.
7. The primary transplant nephrologist's assent for participation should help the study sites leadership to identify suitable participants for the trial because the transplant nephrologists and their staff can weigh study participation in light of
    a. the subject's other options for renal replacement therapy,
    b. risk of developing FSGS or recurrent GN post-transplantation, and
    c. ability to adhere to the study regimen
8. This education requirement provides an additional tool for candidate subjects to learn about and comprehend about HCV infection that would be transmitted from the donor organ and is aimed to further their understanding of risks and benefits associated with the study.

5.2.1.3 Exclusion Criteria for kidney transplant candidates

1. History of severe, life-threatening or other significant sensitivity to immunosuppressants utilized in kidney transplant.
2. Female who is pregnant, planning to become pregnant during the study, or breast feeding
3. HIV RNA-positive or HIV antibody positive
4. HCV RNA-positive
5. HBV surface Ag-positive or detectable HBV DNA
6. Primary focal segmental glomerulosclerosis (FSGS) or disease process with increased risk of causing early graft failure as assessed by the transplant nephrologist and/or investigator team.
7. Absence of clinically significant liver disease evident after review of history, labs and fibroscan imaging

a) Persistently elevated liver enzymes (ALT >2 times upper limit of normal) of unknown cause

b) Liver fibroscan result >8kPA, or >F2 on liver biopsy

8. Transplant candidate requires antibody desensitization protocol for transplantation
9. Most recent calculated panel reactive antibody (cPRA) >80%. For this purpose, the cPRA assessed will be the cPRA most-recently reported to UNOS at the time of waitlisting.
10. Prior recipient of a non-renal solid organ transplant
11. Subject has any other medical condition that, in the opinion of the Investigator, would adversely affect the participant's participation in the study. Specifically, the investigator may exclude any patient with a pre-existing cancer that does not have a high probability of cure or control and increase the risk or decrease the benefit for the transplant as per local transplant center guidance
12. Requirement for and inability to safely discontinue the medications or supplements listed in Table 7 of the protocol at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of any study drug.
13. Participation in another interventional study of any investigational agent or approved medication, or participation in another kind interventional study that the responsible investigator deems to be an exclusion from period 6 months prior to screening to last study visit

5.2.1.4 Rationale for Exclusion Criteria

The rationale for each criterion is listed in the order of exclusion criteria.

1. To minimize participant risks, we will exclude participants with a history of adverse drug reactions to commonly used transplant drugs.
2. To reduce risks to pregnancies and nursing children from HCV or study medications.
3. Participants with HIV are at elevated risk of rejection after transplant and may need medications with complex drug-drug interactions.
4. Patients with HCV should not participate because they already commonly accept HCV RNA-positive kidneys; the study does not offer them a new option.

5. We will exclude participants with these serologies in order to limit the risks of acute HCV infection on the liver.
6. Case series and other preliminary data suggest the possibility that donor-derived HCV infection or its treatment could increase the risk of post-transplant FSGS; therefore, we will not accept patients who plausibly have an elevated pre-existing risk of GN. Primary FSGS can recur in a transplant kidney requiring intensification of immunosuppression or early graft failure.
7. We will exclude participants with evidence of liver disease in order to limit the risks of acute HCV infection on the liver.
8. Desensitization treatment is associated with elevated risk of rejection and the need for additional immunosuppression treatment
9. Elevated PRA is associated with elevated risk of rejection and the need for additional immunosuppression treatment. Additionally, patients with high PRA are often able to get enhanced access to deceased donor organs under the US organ allocation system.
10. Prior non-renal solid organ transplant recipients commonly have substantial comorbidities and elevated risk of post-transplant complications, including death.
11. Investigators may identify reasons (not otherwise identified in the criteria) why candidates are not suitable for participation, but which cannot be comprehensively enumerated prior to the start of the trial. For example, the investigator team will confirm that prior malignancies have been appropriately considered by the primary treating clinical team as unlikely to recur and be uncontrolled after transplantation.
12. The medications listed in Table 7 interact with G/P and could increase the risk of adverse events, and/or reduce antiviral activity of G/P.
13. The effects of other interventions could confound interpretation of the study results and add risks to the participant.
    - Investigator evaluation of candidacy shall also include assessment of the candidate's ability and willingness to receive high quality post-transplant care without using any of the contraindicated medications or supplements listed in Table 7.

5.2.2 Main Inclusion Criteria for kidney donors and allografts

1. Deceased donor organ with kidney donor profile index (KDPI) ≤ 0.85
2. HCV RNA positive*

5.2.2.1 Rationale for Main Inclusion Criteria for HCV RNA-positive kidney donors and allografts

1. To offset the risks associated with HCV infection and treatment, participants should derive the plausible benefit of a good quality allograft.

5.2.2.2 Main exclusion criteria for HCV RNA-positive kidney donor and allograft

1. Known prior HCV treatment with direct acting antiviral medications
2. HIV RNA-positive
3. HBV Surface antigen positive or HBV-DNA positive

* Kidney offers from HCV RNA-negative/HCV antibody-positive donors or HCV RNA-negative/HCV antibody-negative donors are allowed to be accepted by enrolled subjects; for study-eligible HCV RNA-negative/HCV antibody-positive donor offers, all other donor inclusion and exclusion criteria above apply, except the donor is not HCV RNA-positive. No study allograft criteria apply to standard of care allografts and their donors.

5.2.2.3.4 Rationale for Main Exclusion Criteria for HCV RNA-positive kidney donors and allografts

Rationales are listed in the same order as exclusion criteria.

1. Prior failed HCV treatment with DAAs of the donor virus increases the risk of HCV treatment failure with DAA retreatment due to potential viral resistance to the DAAs.
2. Donor-derived HIV could substantially elevate the risk of transplantation.
3. Donor-derived HBV could elevate the risk of transplantation.

5.2.3 Prior and Concomitant Therapy

During screening, the investigator/clinician designee should review all concomitant medications for any potential interactions with G/P via the Sponsor-provided drug-drug interaction tool. With the permission of the treating physicians, the patients should be changed from any prohibited medications or supplements listed in Table 7. The subject must be able to safely discontinue any prohibited medications or supplements listed in Table 7 at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of G/P.

During the period after HCV treatment ends, all medications taken will be recorded in the medical record at subsequent clinic visit until the 12 month post-transplant endpoint. During the transplantation phase, any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from the time of transplantation study drugs are stopped, must be recorded in the medical record along with the reason for use according to standard medical care. Where the reason for use of a concomitant medication is missing from the submitted medical records, the site will be queried.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior HCV Therapy

Enrolled subjects can be HCV treatment-experienced but must have been cured from prior HCV infection.

5.2.3.2 Concomitant Therapy

The investigator should confirm that a concomitant medication/supplement can be safely administered with study drugs. Some concomitant medications may require dose adjustments due to the potential for drug-drug interactions.

During the Post-Treatment Period, investigators should reassess concomitant medications/supplements, and subjects may resume previously prohibited

medications/supplements or revert to pre-study doses 2 weeks following discontinuation of study drugs as applicable.

5.2.3.3 Prohibited Therapy

Subjects must be able to safely discontinue any prohibited medications or supplements listed in Table 7 at least 2 weeks or 10 half-lives (whichever is longer) prior to the first dose of study drug G/P and not use these during the entire Treatment Period and for 2 weeks following discontinuation of study drugs.

Table 7: Prohibited Medications and Supplements

Medication or Supplement Name
red yeast rice (monacolin K), St. John's Wort
Ethinyl estradiol
Atorvastatin, lovastatin, simvastatin*
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Astemizole, cisapride, terfenadine

* The HMG-CoA reductase inhibitors atorvastatin, lovastatin, or simvastatin should not be taken with the study drugs. Subjects receiving these statins should either switch to pravastatin or rosuvastatin prior to the first dose of study drugs. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drugs.

Use of high dose (0.035mg) ethinyl estradiol containing oral contraceptives with G/P combination was associated with asymptomatic ALT increases (one Grade 3, and one Grade 2) without concurrent bilirubin increases in 2 healthy female subjects. Therefore hormonal contraceptives (including oral, topical [including vaginal rings], injectable or implantable varieties) containing any ethinyl estradiol may not be used from 2 weeks prior to the first dose of study drug until 2 weeks after the end of study drug dosing. Progestin-only contraceptives, such as those containing norethindrone, desogestrel, or levonorgestrel, without ethinyl estradiol, may be used with G/P. Post-menopausal hormone replacement therapy, such as with esterified or conjugated estrogens, i.e., not containing ethinyl estradiol, may be used with G/P at the discretion of the Investigator.

G/P may be initiated in subjects receiving cyclosporine ≤ 100 mg per day. **Concomitant administration of G/P with cyclosporine doses of greater than 100mg per day is <u>not</u> recommended.**

5.3 Efficacy, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described in this protocol for the screening phase are summarized in section 5.1.3. and Table 4, for the waiting list phase in section 5.1.4.1., and for the transplantation phase in sections 5.1.4.2 and Tables 5, 6.

5.3.1.1 Study Procedures

Informed Consent

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed.

Subjects will be required to first attend an educational session about HCV and the study. After completion, the subjects will be eligible for a screening visit. The following procedures and activities will be performed during the screening process (and outlined in Table 4), after the informed consent is signed:

- Review medical history
- Vital signs
- Physical exam
- Review current medications
- Review labs/phlebotomy: hepatic function panel, HCV RNA, HBV DNA, HBV Core Antibody will be checked in patients during screening, if not checked previously; HIV serologies
- Serum pregnancy test (for women of childbearing potential)
- Fibroscan
- Provide instructions on recording of new medications and dose changes

Medical History, Physical Examinations, Vital Signs and Weight, Clinical Assessment in the Post-Transplant phase

Study sites will enter data into electronic CRFs obtained from study visits, AEs related to post-transplant events, and testing results, as appropriate.

Clinical Laboratory Tests

Clinical tests that will be performed during the screening period as a part of routine care are shown in Table 8.

Table 8: Clinical Laboratory Tests Performed at Baseline or as Part of Wait-listing Evaluation as Standard of Care

Hematology	**Clinical Chemistry**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands, if detected Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin[c] Alanine aminotransferase[c] (ALT) Aspartate aminotransferase[c] (AST) Alkaline phosphatase[c] Sodium Potassium Calcium Total protein Glucose Albumin Chloride Bicarbonate eGFR by MDRD equation
Other Tests	
Urine and Serum Human Chorionic Gonadotropin (hCG) for females[b] (pregnancy) HCV RNA HCV genotype HBsAg, anti-HBc, anti-HBs, HBV DNA[a] HCV Ab HIV Ab	

[a] If HBsAg neg, antiHBc positive at Screening
[b] In women of childbearing potential serum hCG test will be performed at screening, and after enrollment if urine testing is not feasible [c] Liver function test panel

During the post-transplant period, the blood tests obtained during follow-up visits are shown in Tables 5 –6.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator will request that the transplant center repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study, or requires a subject to receive treatment will be recorded as an adverse event.

The management of laboratory abnormalities that may occur during the study is described in Section 6.1.7.

Contraception Recommendations and Pregnancy Testing

A serum pregnancy test will be performed for all female subjects of childbearing potential at Screening as per transplant center protocol. Additional urine pregnancy tests will be performed if feasible, or if not serum pregnancy tests will be performed as indicated by center protocol and at any time that HCV treatment is started. Pregnancy testing is not required for females of non-childbearing potential. Determination of postmenopausal status will be made during the Screening period, based on the subject's history.

Concomitant Medication Assessment

Excluding the medications and substances listed in Table 7, use of medications (prescription or over-the-counter, including vitamins, herbal supplements, and vaccines) from the time of signing the consent, through the post-transplantation phase and 30 days after study drugs are stopped must be recorded in the medical record according to the local standard of care.

The concomitant medication listing will be updated in the standard of care medical record at the time of informed consent. All original clinic notes and telephone notes collected prior to, during, and post HCV treatment period will be abstracted to identify concomitant medication(s) that were prescribed as part of standard of care practice.

Enrollment and Assignment of Subject Numbers

Screening numbers will be unique numbers and will be assigned sequentially at the site beginning with the first digits representing the investigative site, and the last digits representing the subjects at that site. Enrolled subjects will keep their screening number as their subject number throughout the study.

All screening activities of transplant candidate subjects must be completed and reviewed prior to enrollment and advancement of the subjects into the waiting list phase of the study. Prior to enrollment in the waiting list phase, subject eligibility will be verified by the lead CCC at MGH. The site will submit sufficient data to be verified for meeting enrollment eligibility criteria.

Study Drug Compliance for Kits

G/P will be provided for subject dosing to the site. Each subject will have compliance documented by the site in the subject's source records for G/P. At each study drug accountability visit in Table 5, the overall number of tablets of G/P remaining will be recorded if the patient brought their G/P to the visit.

HCV Genotype and Subtype

Study sites will make reasonable efforts to collect donor plasma samples for HCV genotype and subtype determination from the kidney donor. Donor HCV genotype and subtype will subsequently be assessed using the Versant® HCV Genotype Inno LiPA Assay, Version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY). If the LiPA assay is

unable to assign a genotype, genotyping will be determined by a Sanger sequencing assay of the HCV NS5B region at MGH.

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Tables 4-6. The central laboratory at MGH will be using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for this assay (regardless of genotype) are both 15 IU/mL.

HCV Resistance Testing Sample

Where available, a plasma sample for HCV resistance testing will be collected from the kidney donor at day 0 and for study subjects with confirmed virological failure at the required lab collection visits indicated in Tables 5, and 6. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory at MGH.

Archived Plasma Sample and PBMC Samples

Archived plasma samples will be collected at the study visits, indicated in Tables 4, 5, 6 from all subjects and stored frozen. At sites with collection capability, optional PBMC collection and archiving will also be performed at selected time points as indicated in Tables 5 and 6. These samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, HCV RNA levels, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, immune response to HCV infection, and other possible predictors of response, as determined by AbbVie and the sponsor. Specific instructions for preparation and storage of archive samples will be provided by the central laboratory at MGH. Archived plasma and PBMC samples which have not been utilized for additional analyses as described above or in future research as described in section 5.1.11 by 3 years after the last subject visit of the study will be destroyed.

5.3.1.2 Meals and Dietary Requirements

Tablets of G/P should be taken with food.

5.3.1.3 Handling/Processing of Samples

Specific instructions for collection, preparation, and shipment of those blood samples, plasma samples, PBMC samples, and tissue samples which will be analyzed, and /or stored at the central laboratory at MGH will be provided by the sponsor to all participating sites..

5.3.2 Efficacy Variables

Virologic response will be assessed by plasma HCV RNA levels in IU/mL at various time points from Day 3 of treatment through 24 weeks post treatment for all recipients of HCV-RNA-positive kidneys.

5.3.2.1 Primary Efficacy Variable

The primary efficacy variable is SVR_{12} (HCV RNA < LLOQ) 12 weeks after the last actual dose of study drug) among subjects receiving study-eligible HCV-RNA positive kidneys treated with G/P (Arm 1).

5.3.2.2 Secondary Efficacy Variables

The secondary efficacy endpoints will be calculated among subjects receiving study eligible HCV-RNA-positive kidneys treated with G/P (Arm 1).

- The percentage of subjects with on-treatment virologic failure;
- The percentage of subjects with post-treatment relapse.

5.3.3 Resistance Variables

The following resistance information will be analyzed for subjects receiving G/P who do not achieve SVR_{12} and who have a post-baseline sample with HCV RNA ≥ 1000 IU/mL in

Arms 1 and 2A. The HCV NS3 and NS5A amino acid sequences from the sample closest in time after virologic failure or treatment discontinuation with an HCV RNA level of ≥ 1000 IU/mL will be determined by population sequencing or NGS, and a listing by subject of all substitutions at GLE and PIB signature amino acid positions relative to the appropriate prototypic reference sequence of NS3 and NS5A will be provided.

5.3.4 Safety Variables

Separate safety data will be collected for patients while on the waiting list versus after transplantation. Because subjects are unlikely to suffer adverse events related to study participation while on the waiting list, adverse event ascertainment will take place every two months by phone as well as during an in-person evaluation every 6 months while on the waiting list. The following clinical outcomes will be collected from subjects while on the waiting list: SAEs, non SAE hospitalizations, delisting from waitlist, death. (see section 6.1.4).

For all transplanted subjects in Arm 1 or Arm 2, the following data will be collected: death, graft failure, acute allograft rejection, delayed graft function, ALT elevations ≥5 times upper limit of normal, eGFR, proteinuria, and SAEs. Events of fibrosing cholestatic hepatitis and extrahepatic manifestations of HCV infection will also be collected for subjects who received an HCV RNA-positive kidney in Arm 1, and from subjects who became HCV viremic after transplant of a kidney from an HCV RNA-negative/HCV antibody-positive donor in Arm 2A.

Adverse events after kidney transplantation will be categorized as to whether the event was caused by transplantation generally, or caused by HCV infection and/or HCV therapy as applicable.

All subjects who receive at least one dose of G/P in Arm 1 will have additional safety collected as specified in section 8.1.5, and 8.1.6.

5.4 Removal of Subjects from Therapy or Treatment Duration Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

If, during the course of study drug administration, the subject prematurely discontinues, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 5 and Table 6. Ideally this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the site investigator's best clinical judgment, and input from the study's principal investigator. The last dose of any study drug and reason for discontinuation will be recorded in the medical record and submitted for centralized abstraction.

The subject should then begin a period of post-transplant monitoring for 24 weeks for HCV RNA, the emergence and persistence of resistant viral variants. The subject will be assessed at 1-year post transplant for kidney graft function and anti-HCV antibody (only if HCV Ab negative at screening).

If a subject is discontinued from study drugs or the Post-Treatment Period with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.
In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the Treatment Period, the administration of DAAs to that

subject may be continued at site investigators discretion and in consultation with the study's principal investigator after discussion with the subject, if the benefit of continuing DAAs is felt to outweigh the potential risk. Specific instructions regarding subject pregnancy can be found in Section 6.1.5. If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Section 6.1.5.

5.4.1.1 Virologic Stopping Criteria

Individual patient

Virologic stopping criteria are defined as one of the following:

1. Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during treatment.

2. Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment.

When confirmatory testing is required, it should be completed as soon as possible and the subject should remain on study treatment until the virologic stopping criteria has been confirmed. Subjects meeting virologic stopping criteria will be discontinued from study drug and will continue to be followed in the Post-Treatment Period for the emergence and persistence of resistant viral variants until 12 weeks post-treatment.

5.4.2 Discontinuation of Entire Study

The sponsor, in agreement with AbbVie, may terminate this study prematurely, either in its entirety or the sponsor may terminate this study at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to the sponsor in advance of the intended termination.

Advance notice is not required by either party if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator by telephone and subsequently provide written instructions for study termination. If 3 virologic treatment failures are observed among the first 10 recipients of kidneys from HCV RNA-positive donors, or 5 virologic treatment failures are observed among the first 20 recipients of kidneys from HCV RNA-positive donors, then no further offers of HCV RNA-positive kidneys will be accepted as part of the study.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of study drug (G/P) will be dispensed in the form of co-formulated G/P tablets at the visits listed in Tables 5 and 6 (and as needed). Subjects will be instructed to take study drugs at the same time every day with food.

G/P will be provided to the investigator as G/P 100 mg/40 mg tablets. G/P will be taken orally as three tablets once daily with food, which corresponds to G/P 300 mg/120 mg QD. The maximal dose of G/P is 300mg/120mg for 8 weeks (56 doses, given once daily). There is no dose adjustment for G/P for any reason in this study.

All subjects who receive at least one dose of study drug and meet the virologic stopping criteria defined in Section 5.4.1.1 will be discontinued from treatment.

5.5.1.1 G/P Initial Treatment Failures

Study subjects with treatment failure, defined as meeting virologic stopping criteria (Section 5.4.1.1) or virologic relapse (unquantifiable viral load after completion of treatment that during the post-treatment follow-up period becomes quantifiable) will be provided with either 1) Open-label Sofosbuvir + G/P ± Ribavirin or 2) Open-label sofosbuvir/velpatasvir/voxilaprevir +/- Ribavirin. The regimen will be chosen at the discretion of study's Principal Investigator (Ray Chung, MD), with input from the site investigator where the patient is located. The retreatment of study subject will be followed

by the site investigator and as per local center standard of care. Outcomes of HCV re-treatment will also be collected. AbbVie will provide G/P, and funds for purchasing sofosbuvir, ribavirin, or funds for purchasing Vosevi (sofosbuvir/velpatasvir/voxilaprevir) for retreatment.

5.5.2 Identity of Investigational Products

Information about the study drugs to be used in this study is presented in Table 9.

Table 9: Identity of Investigational Products

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Tablets/bottle
Glecaprevir/ Pibrentasvir	AbbVie	Oral	Tablet	100 mg/40 mg	30

5.5.3 Packaging and Labelling

All study drug will be supplied in bottles. Each bottle will be labelled as required per FDA. The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

5.5.3.1 Storage and Disposition of Study Drugs

The study drug (G/P 100 mg/40 mg) is for investigational use only and is to be used only within the context of this study. The storage conditions are 15° to 25°C (59° to 77°F). The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use, destroyed on-site, or returned to AbbVie (or designee).

5.5.4 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, all subjects will be assigned a unique subject number assigned sequentially by the study site. Enrolled subjects will keep their screening number as their subject number throughout the study.

For subjects who do not meet the study selection criteria, the site personnel will identify the subject as a screen failure by submitting adequate records about the reason for screen failure to the DCC using electronic CRFs.

For enrollment of eligible wait-listed subjects into the study, subject eligibility will be verified centrally by the CCC. At a minimum of 5 business days prior to activating the patient for offers of organs from donors who are seropositive for HCV, the site will submit the subject's medical record to be verified for meeting enrollment eligibility criteria related to the subject as a candidate for kidney transplantation. After being centrally verified as meeting the eligibility criteria, subjects will be entered centrally via the study system. At the time of transplantation, final eligibility of the subject and the organ will be made by the responsible site PI. The local study site will inform the MGH lead clinical site staff and the DCC about each transplant event within 24 hours of the transplant (preferably sooner).

Once a patient has consented to study participation and approved by the CCC as meeting criteria, study drug will be shipped as a bulk supply from AbbVie to that study site so that G/P may be provided to any patient subsequently offered an eligible kidney from an HCV RNA-positive donor.

5.5.5 Selection and Timing of Dose for Each Subject

G/P study drug is a fixed-dose combination tablet of 100 mg glecaprevir and 40 mg pibrentasvir. The dose used for all subjects in this study is 300 mg/120 mg G/P, 3 tablets given together once daily with food. The maximum dose of G/P will not exceed 300 mg/120 mg per day for 8 weeks (i.e. 56 daily doses) for initial treatment.

Kidney transplant recipients of kidneys from deceased donors that are HCV RNA-positive should be administered G/P starting on day 3 after transplantation. Subjects will receive a

supply of G/P, with dosing instructions. The default approach will be to provide a supply of 4 weeks of pills at the time that G/P is first prescribed.

5.5.6 Blinding

This is an open-label study.

5.5.7 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/ dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

At the start of the study, each subject should receive counselling regarding the importance of dosing compliance with the treatment regimen with regard to virologic response and potential development of resistance due to poor compliance.

At each post baseline visit during the Treatment Period denoted in Table 5, subjects will be instructed to bring all study drug containers (full, partial or empty) for assessment of treatment compliance by pill count and the site will discuss adherence with the subject. At Weeks 4 and 8 only, study site personnel will assess subject compliance by pill count (where available) or by talking to participants about their adherence history, and, where possible, record the exact number of remaining tablets of G/P in the source. In between the Week 4 and Week 8 study visits, a Week 6 phone call will be conducted to discuss ongoing compliance with the subject.

5.5.8 Drug Accountability & Destruction

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. A current and accurate inventory of study drug will be kept by the investigator or his/her representative and will include lot number, kit number, number of tablets dispensed, subject number, initials of person who dispensed study drug,

and date dispensed for each subject. An overall accountability of the study drug will be performed and verified by the study monitor. Final accountability will be verified by the monitor at the end of study drug treatment at the site or via alternate approved method (e.g. video conferencing).

Study drug start dates for each drug and the last dose of the regimen will be documented in the subject's source documents. Upon completion of or discontinuation of G/P therapy, all original study drug bottles containing unused study drugs will be destroyed at the study site, or returned to AbbVie (or its designee). All unused study drugs can only be destroyed after being inspected and reconciled by clinical site staff and verified by the Clinical Coordinating Center. The number of tablets of each type of study drug returned will be noted in a drug accountability log. Labels must remain attached to the containers.

On-site destruction is preferred, provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site’s SOPs and a copy provided to the Clinical Coordinating Center.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of all unused and/or partially used study drug to AbbVie.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. Empty containers can only be destroyed on-site after being inspected and reconciled by the Study Monitor at the site or via alternate approved method (e.g. video conferencing).

5.5.8.1 Risk of Development of Resistance-Associated Substitutions During Combination DAA Trials

In subjects treated with a DAA, variants with amino acid substitution(s) in the targeted protein conferring resistance to the DAA can be selected. Among the 2258 TN and TE-PRS subjects chronically infected with GT1-6 and treated with G/P 300/120 mg included in the integrated resistance analysis from the Phase 2 and Phase 3 studies, only 22 (0.97%) experienced virologic failure. Among these 22 subjects, treatment-emergent substitutions were detected in NS3 in 54.5% (12/22) and in NS5A in 81.8% (18/22). Subjects frequently had multiple substitutions in NS5A at the time of failure indicating that, in contrast to first generation NS5A inhibitors, single substitutions in NS5A do not confer sufficient resistance to allow the virus to overcome PIB drug pressure. These results support the prediction that the risk of development of resistance-associated variants with glecaprevir and pibrentasvir combination treatment is low.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution. Complaints associated with any component of G/P must be reported to the Sponsor (Section

6.2.2). For adverse events, please refer to Section 6.1. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study in accordance with standard medical practice and the AASLD HCV treatment guidelines as well as kidney transplant protocols at the clinical centers. The adverse events and actions taken (concomitant therapy, etc.) identified centrally in the submitted medical records generated as part of clinical care will entered into study CRFs using the electronic interface that will be developed by the DCC. The DCC Abstraction Conventions manual will be used to assign adverse event start dates for any event without a specific start date noted. After adverse event data are submitted, the site investigator/clinician designee will be provided an adverse event listing to assess relationship of the adverse event to study drug. Site investigator/designee will also be provided an adverse event listing to determine adverse event stop dates/continuation for any adverse events for which no end date is evident in the submitted medical records during the treatment period and up to 30 days post treatment.

6.1.1 Definitions

6.1.1.1 Adverse Event

Adverse event (AE): Any untoward medical occurrence associated with the protocol procedures, whether or not considered product or process related. Any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Inter-current illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious AE
- is associated with clinical signs or symptoms

- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to the sponsor as a SAE within 24 hours of the site being made aware of the serious adverse event:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any

of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note that criteria as described above apply to all SAEs that occur after consent for the trial. All SAEs in the trial will be categorized as pre-transplant vs post-transplant, as well as pre-study drug vs post study drug.

Sites will use the SAE reporting template provided by the sponsor to report all SAEs. If an SAE is observed in the submitted clinical records during data abstraction that was not previously reported by the site, the site will be queried for the report and supporting records. The query must be responded to within 24hrs.

Minimum supporting records required for all SAE reports:

1. Admit and Discharge note
2. Consults with VS/PE as available
3. All labs
4. Imaging/procedure reports
5. Medication administration record

For serious adverse events with the outcome of death, the date and cause of death (if known) will be recorded on the appropriate case report form. The site will make all reasonable efforts to obtain a death or autopsy certificate, if available.

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the mild-moderate-severe severity scale below. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) using the following definitions:

1. **MILD:** Adverse events and/or symptoms recorded in the medical record where no therapy was given to treat the event or where an over-the-counter medication/intervention ONLY was given to treat the event.

2. **MODERATE**: Adverse events and/or symptoms recorded in the medical record requiring prescription medication treatment.

3. **SEVERE:** Adverse events and/or symptoms requiring any study drug discontinuation will be defined and coded as severe. ANEMIA events requiring blood transfusion will be coded as severe.

6.1.3 Relationship to Study Drug

Assessment of relatedness will be made with respect to the stage of the trial that the subject is in (screening, waiting list, or post-transplantation) and further with respect to whether the event was related to G/P where applicable. The investigator will use the following definitions to assess the relationship of the adverse event to the use of G/P:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, the sponsor will consider the event associated.

For serious adverse events, if an investigator's opinion of relatedness is "no reasonable possibility of being related to study drug" an "Other" cause of event must be provided by the investigator. After adverse event data is abstracted from the submitted records, the site investigator/ clinician designee will be provided an adverse event listing to assess relationship of the adverse event to study drug.

6.1.4 Adverse Event Reporting

For this study, the AE reporting period will be divided based on the three phases of the study.

Pre-Treatment Phase

Screening phase: When all screening tests have been done, we will assess for any AEs related to the screening tests at the time of communication with the subject about whether he/she is official eligible or ineligible for the study.

Pre-existing Condition: A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

Waitlist phase: We will only capture AEs that are pertinent to the study. Specifically, the following will be captured:

1. Patient death,
2. Patient develops a condition that would exclude that subject from the study,
3. Patient is de-listed (taken off the kidney transplant waitlist)
4. Patient is made inactive on the transplant waitlist
5. Serious Adverse events and non-SAE hospitalizations; these will be categorized as "pre-transplant" (vs. "post-transplant") and "pre-study drug" (vs. "post-study drug")

In order to ascertain these events, we will review the patient's medical history by phone every 2 months and in person every 6 months that they are on the wait list.

Treatment Phase in Arm 1

Immediate Post-transplant phase:

From the date of transplant with a HCV RNA-positive kidney to 1 day before first administration of the study drug, we will collect SAEs and clinical outcomes and data, including death, graft failure, acute allograft rejection, delayed graft function, eGFR, ALT elevation > 5 x ULN, SAEs.

HCV Treatment Phase

The following additional data will be collected from Day 1 of HCV treatment to 30 days following last dose of HCV treatment:

All adverse events will be collected and clinical outcomes, including death, graft failure, acute allograft rejection, delayed graft function, ALT elevation > 5 x ULN, SAEs, sclerosing cholestatic hepatitis and extrahepatic manifestations of HCV, and data of eGFR and proteinuria. An assessment for causality to transplant, HCV infection, or study drug G/P will be made**.** Grade 3 or greater treatment-emergent laboratory abnormalities from the first dose of G/P through 2 days post dosing will also be collected and summarized. Events of sclerosing cholestatic hepatitis and extrahepatic manifestions of HCV infection will only be collected in ARM 1 subjects and subset of ARM 2A subjects who develop HCV viremia.

Post-Treatment Phase in Arm 1

Post HCV treatment Phase: From 30 days post last dose of HCV treatment to 1 year post kidney transplant (last study visit), the following outcomes and other data will be collected: death, graft failure, acute allograft rejection, delayed graft function, ALT elevation > 5 x ULN, SAEs, sclerosing cholestatic hepatitis and extrahepatic manifestations of HCV. eGFR and proteinuria will be collected at specific visits. All SAEs will be assessed at every clinic visit when the subject is seen by a member of the study team.

All unresolved AEs considered possibly, probably, or definitely related to the study drug or to HCV infection should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained.

The investigator will notify the IRB of any death or SAE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The IRB will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

6.1.5 Serious Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify the Sponsor within 24 hours of the site being made aware of the serious adverse event by submitting the available serious adverse event data to:

Email to: mythicSAE@mgh.harvard.edu

For safety concerns, contact the physician listed below:

Hannah Gilligan, MD
Office: 617-643-2257
Mobile: 781-552-1870
Email: Hgilligan@mgh.harvard.edu

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be submitted within 24 hours using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

The MGH designated Medical Monitor or delegate from the sponsor must also report any serious adverse event in a subjects on G/P treatment (on G/P treatment period includes day 1 of G/P dosing to 30 days after last G/P dose) to AbbVie within 24 hours after receipt of the serious adverse event information from the study site.

6.1.6 Pregnancy

Female subjects should avoid pregnancy starting with screening and through 30 days after completion of study drug.

Pregnancy in a study subject must be reported to the sponsor within 1 working day of the site becoming aware of the pregnancy. Administration of study drug may be continued at the investigator's discretion after discussion with the subject, if the benefit of continuing therapy is felt to outweigh the risk (Section 5.4.1). If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for pregnancies occurring up to 30 days after the end of treatment.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to the sponsor within 24 hours of the site becoming aware of the event.

In the peri-transplant and post-kidney transplantation period, standard of care is to avoid pregnancy during the first year because of potential negative effects on the allograft and because of the common utilization of teratogenic medications such as mycophenolate mofetil. In the post-transplant period, clinical sites will follow their own standard of care protocols regarding screening for pregnancy and robust contraceptive counselling.

6.1.7 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator. Only lab abnormalities that are deemed clinically significant or require intervention are classified as adverse events. All adverse events and laboratory abnormalities will be managed and followed to a satisfactory clinical resolution. A toxicity is deemed "clinically significant" based on the medical judgment of the investigator.

To facilitate this process in a pragmatic study, after adverse event data is abstracted from the submitted records, the site investigator/clinician designee will be provided an adverse event listing to assess relationship of the adverse event to study drug. The site will also upload signed central lab reports where the investigator completed the evaluation of clinical significance of abnormal results. Actions taken for clinically significant abnormal

laboratory results and/or adverse events will be recorded in the site medical record or source, and entered into the eCRFs.

6.1.8. Management of ALT elevations while on study drug G/P

If a subject experiences a post-baseline increase in ALT to > 5 × ULN which is also > 2 × baseline value, the subject should have a confirmatory ALT measurement performed.

If the ALT increase is confirmed to be > 5 × ULN which is also > 2 × baseline value, the recommendations below should be followed:

- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate (e.g., hepatitis B panel).
- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs if any of the following is observed at any time:
  - ALT level is ≥ 20 × ULN in the absence of an alternate etiology.
  - Increasing direct bilirubin or INR or onset of symptoms/signs of hepatitis.

At the discretion of the investigator alternate management of ALT increases is permitted with approval of the Principal Investigator (Ray Chung) at MGH.

6.1.9. Management of suspected kidney rejection while on study drug G/P

If at any time a site investigator suspects rejection of the transplanted kidney while the subject is receiving study drug, then dose adjustment of immunosuppressants may be performed per the site investigator's usual practice and the event captured on eCRF. If the abnormality is non-responsive to immunosuppressant adjustment and/or if the site investigator wishes to empirically augment the immunosuppressive regimen, e.g., by

commencement of high dose steroids or to add specific anti-rejection agents but without the availability of a biopsy of the transplanted organ confirming rejection, then change in follow-up procedures and antiviral treatments may be considered by the site investigator, as appropriate.

If the site investigator wishes to pursue alternative management of study drugs in this setting the Principal Investigator should be contacted to obtain approval.

If a biopsy of the transplanted kidney is performed as part of the evaluation of rejection and the histologic findings are consistent with rejection as determined by the local pathologist, the site investigator should follow the usual management of rejection and continuation of study drugs should be per investigator discretion. If the site investigator wishes to pursue alternative management of study drugs in the setting of histologically confirmed rejection, then the Principal Investigator should be contacted to obtain approval. Biopsy tissue from the transplanted organ obtained during the trial to evaluate rejection or other pathologic process should be read locally and the result recorded in the subject source documents. Because of the potential impact of discontinuation (or interruption) of study drugs on immunosuppressant levels, investigators should ensure that a plan for appropriate immunosuppressant dose modification is in place and that this plan is communicated to the subject.

6.2. Product Complaint

6.2.1 Definition

A product complaint is any complaint (see Section 6.0 for the definition) related to the study drug product(s). For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labelling, labelling discrepancies/inadequacies in the labelling/instructions (e.g. printing illegible), or missing components/product, or packaging issues. Any product complaints identified centrally in the submitted medical records will be abstracted into the study database.

6.2.2 Reporting

Product complaints concerning the investigational product must be reported to the sponsor within 24 hours of the time it is observed. If the data is abstracted centrally from the submitted medical records, it should be reported via the product complaint form. Product complaints occurring during the study will be followed up to a satisfactory conclusion via specific query to the site for any available clinical information. All follow up information is to be reported to the sponsor and documented in the source medical record. Product complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator/site to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Major Protocol Deviations

The investigator should not implement any major deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following personnel:

Hannah Gilligan, M.D.

If by e-mail: hgilligan@mgh.harvard.edu

If by phone: 617-643-2257

Such contact must be made as soon as possible to permit a review by the sponsor to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

In some analyses below, Arm 2 will be further broken down by category:

A. subjects who receive a kidney from a study-eligible HCV RNA-negative/ HCV Ab-positive donor
B. subjects who receive a standard of care kidney transplant
C. subjects who were not transplanted within 1 year of consent

8.1 Statistical and Analytical Plans

The data analysis will be generated using SAS version 9.4 or higher for windows and/or STATA software version 14.0 or higher (StataCorp LP, College Station, TX). SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. All statistical tests (if applicable) and confidence intervals will be two-sided with an alpha level of 0.05. Descriptive statistics will be provided, such as the number of observations (N), mean, and standard deviation (SD) for continuous variables and counts and percentages for discrete variables.

The efficacy and safety of the "reactive" G/P treatment of patients who become HCV RNA-positive after receiving a kidney from a study eligible HCV RNA-negative/HCV Ab-positive donor in Arm 2A are not an objective of this study, and they are not included in assessments of efficacy or safety described below. The time to transplant and clinical outcomes and data post-transplant from patients in Arm 2A are included in those secondary endpoints.

The primary analysis will occur after all recipients of HCV RNA-positive kidneys in Arm 1 have completed post-treatment week 12 visit (corresponding to SVR_{12} data collection) or prematurely discontinued study. The primary analysis of SVR_{12} will be performed on the intention-to-treat (ITT) population defined as all enrolled subjects who received a study eligible HCV RNA-positive kidney and received at least one dose of G/P according to actual treatment received (Arm 1).

No data will be imputed for any efficacy or safety analysis except for analyses of SVR endpoints (HCV RNA data). HCV RNA values will be selected for the analyses of all SVR endpoints (e.g., SVR_4 and SVR_{12}, SVR_{24}) based on defined visit windows. A backward imputation method will be used to impute missing responses for SVR analyses. Additional details of analyses to be performed will be specified in the Statistical Analysis Plan.

8.1.1 Demographics

Demographics and baseline characteristics will be summarized for all enrolled subjects by arm (Arm 1 and Arm 2) with further breakdown by categories of Arm 2 (2A, 2B and 2C), and overall. Baseline characteristics include age, weight, height, BMI, gender, race, ethnicity, cause of end-stage kidney disease, dialysis vintage, prior solid organ transplantation, liver fibroscan results, and any HCV treatment history (for participants previously cured of HCV infection) and match run position for kidney transplant recipients. For subjects in Arm 2B, further breakdown by the subgroups allowed in Arm 2B will be summarized - 2B1 to 2B5.

Donor variables will include donor age, sex, race, terminal serum creatinine, cause of death, PHS increased risk status, KDPI score, cold ischemia time, and where available, characteristics of the donor HCV including genotype.

Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI), and the number and percentage of subjects will be presented for categorical variables (e.g., sex and race).

Study drug G/P exposure and compliance will be summarized for Arm 1. Treatment compliance to study drug will be calculated based on the percentage of tablets taken relative to the total tablets expected to be taken, where these data are available. A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum. The percentage of compliant subjects will be summarized.

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population, unless otherwise specified. Plasma HCV RNA levels will be determined for each sample and measured using standard of care in the clinical site labs. HCV RNA ≥ the lower limit of quantification (LLOQ) are all quantifiable values.

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoints is the proportion of ITT subjects who achieved SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

The number and percentage of subject achieving SVR_{12} will be summarized along with a two-sided 95% confidence interval calculated using Wilson's score method. A summary of reasons for SVR_{12} non-response (e.g., on-treatment virologic failure, relapse, other) will be provided.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints to be summarized for all ITT subjects who are:

- the number and percentage of subjects with on-treatment virologic failure (confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment);
- the number and percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment, excluding subjects with reinfection).

For the analysis of relapse, completion of treatment is defined as any subject with study drug duration of 49 days or greater for 8-week treatment.

8.1.2.3 Sensitivity Analysis

As a sensitivity analysis, the percentage of subjects in the modified intention-to-treat-virologic-failure (VF) population (ITT population excluding those who did not achieve SVR_{12} for reasons other than on treatment VF and relapse) achieving SVR_{12}, will be summarized.

8.1.2.4 Subgroup Analysis

The percentage of ITT subjects with SVR_{12} will be calculated, as will the corresponding two-sided 95% Wilson score intervals by the following subgroups:

- HCV GT
- Timing of HCV treatment initiation after transplant
- Study drug compliance

Further details about subgroup analyses will be described in the Statistical Analysis Plan

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized for the ITT population:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects with SVR4;
- The percentage of subjects with SVR24 and the concordance between SVR12 and SVR24

In the above analyses for SVR, the percentage of subjects and a two-sided 95% Wilson score interval will be summarized.

8.1.3 Resistance Analyses

The following analyses will be performed for subjects in Arms 1 and 2A who do not achieve SVR_{12} and who have post-baseline resistance data available: The HCV NS3 and NS5A amino acid sequences from the sample closest in time after virologic failure or treatment discontinuation with an HCV RNA level of ≥ 1000 IU/mL will be determined by population sequencing or NGS, and a listing by subject of all substitutions at GLE and PIB signature amino acid positions relative to the appropriate prototypic reference sequence of NS3 and NS5A will be provided.

8.1.4 Secondary Clinical Outcomes

Secondary clinical outcome analyses will be performed for subjects prior to kidney transplant in both Arms 1 and 2, and post kidney transplant for those who receive a kidney transplant in Arms 1 and 2. For details on safety reporting and periods of safety reporting see section 6.1.4.

The cumulative incidence function curves of time to kidney transplant will be created for each type of kidney transplant (Arms 1, 2A, 2B), and cumulative incidence and standard error (SE) will be calculated for each type of kidney transplant.

An exploratory analysis will create cumulative incidence function curves of time to kidney transplant for the subgroups of Arm 2B if sufficient subjects are enrolled in Arm 2B.

The number and percentage of subjects with clinical outcomes while on waitlist and after study consent (SAEs, delisting from waitlist, death) among subjects who receive an HCV RNA-positive kidney (Arm 1) and among those subjects who do not receive an HCV RNA-positive kidney (all Arm 2 subjects) overall and with breakdown by category of Arm 2 (2A, 2B, 2C). In addition, the total number of inpatient hospital days while on waitlist in those who did receive an HCV RNA-positive kidney (Arm 1) and total inpatient hospital days in those who did not (Arm 2) overall and with breakdown by category of Arm 2 with be summarized descriptively with mean, median, standard deviation (SD), minimum and maximum.

We will match MYTHIC trial participants 1:3 to comparators derived from the Organ Procurement and Transplantation Network database. Matching will be based on demographics and baseline characteristics known to influence waiting time, including waiting list priority, blood group, geographic region, and sensitization. A comparison of time to kidney transplantation between the kidney transplant candidates enrolled in the MYTHIC trial and OPTN comparators will be performed using a Cox proportional hazards model.

Clinical outcomes post-transplant will include death, graft failure, acute allograft rejection, delayed graft function, ALT elevation > 5 times the upper limit of normal, and SAEs. In addition, HCV-infection related events of fibrosing cholestatic hepatitis and extrahepatic manifestations of HCV infection collected for Arm 1 subjects and only for Arm 2A subjects who develop HCV viremia will also count as clinical outcomes. The number and percentage of subjects with each and any clinical outcomes will be summarized for those who receive an HCV RNA-positive kidney (Arm 1) versus Arm 2 subjects combined and broken down (2A and 2B) as applicable. The difference in the overall percentage of subjects with clinical outcomes post-transplant in Arm 1 vs Arm 2A + 2B will be assessed by logistic regression with Arm as a factor and including appropriate covariates to adjust for possible differences between Arms including waiting list priority, blood group,

geographic region and sensitization, as appropriate given sample size and other statistical considerations. In addition, to include any clinical outcomes due to being treated with G/P, another summary of clinical outcomes post-transplant will include any study drug (G/P) related severe treatment emergent adverse events for Arm 1 subjects, and another will include events of treatment emergent Grade ≥ 3 laboratory values and related severe treatment emergent adverse events as clinical outcomes for Arm 1 subjects.

Analyses of the eGFR outcome will be calculated eGFR using the 4-variable MDRD equation. Mean (SD) eGFR will be summarized at appropriate visits and compared between Arms. Specifically, mean eGFR at 24 weeks/6-months post-transplant and 1 year post transplant will be compared between Arm 1 transplant recipients and the combined group of Arm 2A and 2B transplant recipients (2B1-2B4). As a secondary approach, mean eGFR at 24 weeks/6-months post-transplant will be compared between Arm 1 recipients and Arm 2A and 2B kidney recipients limited to those 2A and 2B recipients who did not develop HCV infection.

We will also compare estimated proteinuria between Arms 1 and 2A, including a count of individuals with >1000 mg/day estimated proteinuria. Proteinuria will be estimated using spot protein:Cr ratio.

An exploratory analysis will summarize the number and percentage of subjects with clinical outcomes post kidney transplant for the subgroups of Arm 2B.
Exploratory analyses will also make comparisons between groups in which recipients of non study-eligible HCV RNA-positive and non study-eligible RNA-negative/HCV Ab-positive kidneys are censored at transplantation.

These clinical outcomes post-transplant will be further summarized by relatedness to study drug or HCV infection for Arm 1 subjects, and relatedness to transplant for each group Arm 1, Arm 2A, and Arm 2B subjects.

In addition, for subjects in study Arm 2 receiving HCV antibody-positive/ HCVRNA-negative kidneys, the rate and timing of HCV transmission will be summarized.

8.1.5 Safety Analyses for Arm 1

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade for the severity grade table and the most related for the relationship to study drug table. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC. An adverse event will be considered treatment-emergent if it begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing. Related adverse events are those considered at least possibly related to study.

Laboratory data will be summarized from the first dose of G/P through 2 days post dosing. Laboratory values will be rated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4) which is available on the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf Grade 3+ laboratory values are those that are Grade 3 or 4.

8.1.6 Additional Adverse Event Analyses for Arm 1

For subjects treated with G/P, the number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) for each treatment arm. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug, kidney transplantation, or HCV infection also will be provided.

8.1.7 Additional Clinical Laboratory Data for Arm 1

Clinical laboratory tests will be summarized by transplant phase (e.g., awaiting a transplant, after receipt of a transplant) and treatment arm. Additional evaluations will be performed for subjects who received study drug as part of the protocol (Arm 1). The baseline value will be the last non-missing measurement prior to the initial dose of study drug. Mean changes from baseline to each post-baseline visit, including the Final Treatment Visit, will be summarized descriptively for Arm 1 as feasible.

In addition, the number and percentage of subjects with post-baseline laboratory values of interest equal or greater than Grade 3 of the CTCAE scale will be summarized overall and by Arm.

8.2 Determination of Sample Size

This study is primarily designed to demonstrate feasibility and to generate preliminary data related to cure rates (defined as SVR_{12}) from treating donor-derived HCV infection post kidney transplantation using G/P. For this reason, the sample size was not determined with reference to power to detect differences between groups for the primary objective. The lower bound of a one-sided 95% confidence interval using the Wilson's score method, for various SVR12 rates with a total sample size of 30 subjects are provided in Table 10.

Table 10: Estimated Lower Bound for 95% Confidence Interval for Cure Rate Based on Observed Number of Cures

Sample Size	No. of Observed Cures	Observed Cure Rate	Lower Bound for 95% CI of Cure (Wilson's Score)
30	30	100.0%	93.8%
30	29	96.7%	85.4%
30	28	93.3%	81.0%
30	27	90.0%	76.9%
30	26	86.7%	73.0%

As a secondary objective, we will compare time to kidney transplantation between the estimated 75 - 90 kidney transplant candidates enrolled in this trial with 225-270 matched kidney transplant candidates from the OPTN list (1:3 match). We estimate that at least 40

patients (44%) of 90 enrolled patients will undergo kidney transplantation versus 20% (or less) of comparators from OPTN list during an estimated 6 months of follow-up, with 80% power to detect a difference between groups.

8.3 Assignment of Participants to Study Arms: Methods

This is a two-arm study. All eligible subjects who entered the study will be observed. Observed subjects who accept a study-eligible HCV RNA-positive kidney allograft offer will be assigned to the G/P treatment Arm 1 and followed in that Arm up until 1 year post-transplant. All other enrolled study subjects will remain in Arm 2 of the study (see Figure 1A).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the MAVYRET USPI,[10] the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB at each site will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports

required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to the sponsor

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.2.1 Ethics Analysis

The main ethical considerations in this trial are non-maleficence, respect for persons, and autonomy. Our selection criteria are designed to select subjects who are at substantial risk of death and health complications because of end-stage renal disease and chronic dialysis treatment. Transplantation with a HCV RNA-positive kidney and then treatment for HCV also involve risks, but it is plausible that survival and quality of life will still improve after transplantation compared to the alternative of additional years on dialysis. Our informed consent procedures are designed to enable individuals to make decisions that are consistent with their values. We will enumerate the many possible risks and plausible benefits. The processes of informed consent in this study will be conducted so that patients can ask questions, confer with their primary nephrologists and develop a full understanding of the trial procedures and risks, all of which is consistent with respect for persons. Lastly, subjects in the trial will retain the ability to consider organ offers and decide whether to accept an organ based on their own judgment about the value of that particular organ and after getting advice from their transplant team.

9.3 Subject Information and Consent

The processes of informed consent in this study are designed to give potential participants several opportunities to learn about HCV, the study and to understand risks and benefits. As

described in section **5.1.3 Screening**, study staff will discuss the study during an initial phone call, a subsequent educational session and finally during the informed consent session when subjects will have the opportunity to sign the informed consent document.

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A signed copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

9.4 Potential Risks and Benefits

9.4.1 Risks of Study Procedures

There are several areas of potential risk in this study. We will obtain several blood samples from each subject. There is a risk of bruising, hematoma, and infection after phlebotomy, which are possible but not considered serious AEs. Fainting may occur, which is unlikely but considered a serious AE. The removal of <70 cc of blood every 1-4 weeks during the 40-week post-transplant period is a potential risk; however this amount is routinely taken from subjects for clinical indications without adverse effect. Study medications will be delayed until after phlebotomy on each study day.

Because we may store subjects' blood samples, there may be confidentiality risks associated with the storage and analysis of those samples or the information resulting from the analysis of those samples. Samples may be used for genetic testing. Under some circumstances, it can be a risk for genetic information to be known. To help ensure confidentiality, samples will be coded and stored in a secured facility. While situations

cannot be foreseen where potentially sensitive genetic information is revealed or where people who should not have this information could obtain it (representing a loss of confidentiality), however, it is possible that presently unforeseen situations may arise where this could happen.

The risk of undergoing screening includes potential identification of new health problems that subjects were unaware of. If we discover new health problems, we will answer subjects' questions and try to arrange appropriate treatment if any is needed. If new health problems are discovered, it is possible that subjects would not be able to enter this study. It is also possible that subjects would no longer be eligible for kidney transplantation based on the results.

The risks associated with a Fibroscan are that the probe used on the abdomen during the Fibroscan may lead to mild soreness in the area for about a day.

The risks of any kidney transplant surgery include blood loss, infections, and deep vein thrombosis. There are also risks related to immunosuppression and standard anti-infective therapy. The risks of any kidney transplant also include primary graft non-function, delayed graft function, acute rejection, and death. Re-admissions within 30 days after a kidney transplant are expected in approximately 40% of patients.

There may also be a small risk of developing Focal and Segmental Glomerulosclerosis (FSGS) after receiving a kidney from HCV-RNA-positive donor and/or being treated for HCV after transplantation. However, this condition can also develop in patients who do not have HCV. There have been case reports of FSGS among patients receiving treatment for HCV after kidney and liver transplantation. It is possible that such cases were related to HCV treatment. After transplant, we will monitor all patients for FSGS and similar conditions by checking proteinuria at every study visit post-transplant.

There may also be a small risk of developing symptoms of acute HCV infection, or extrahepatic manifestations of HCV infection if the start of HCV treatment is delayed. After transplant, we will monitor all patients and will initiate HCV treatment as early as feasible on or after day 3 post-transplant.

Taking part in a research study may cause psychological distress or excess worry. A subject may experience discomfort if asked questions about the subject's medical history that the subject deems to be private.

9.4.2 Risk of Study Drugs and Mycophenolate Mofetil

Glecaprevir/Pibrentasvir

In subjects receiving G/P for 8, 12, or 16 weeks, the most commonly reported adverse reactions of all intensity (greater than or equal to 5% were headache, fatigue and nausea.[10] The majority of subjects experienced an AE, which were mostly considered to be mild in severity by the investigator (Grade 1).

For this trial, the greatest risk is failure to achieve SVR12 after treatment with G/P, leading to chronic HCV.

Glecaprevir/Pibrentasvir and/or Mycophenolate Mofetil

It is not known whether G/P causes fetal harm in humans. There is a risk of fetal harm and birth defects should any woman taking G/P. Mycophenolate mofetil can cause fetal harm and birth defects. To mitigate this risk, all pre-menopausal women with a uterus will be screened for pregnancy before enrollment and instructed to use a highly effective form of birth control (e.g. abstinence, intrauterine device, etc.). The applicable methods of birth control that are required in this protocol are outlined in Appendix D, and based on whether the subjects will take mycophenolate mofetil after kidney transplantation or not.

9.4.3 Risk of Developing HCV Infection

The risks of chronic HCV include severe acute inflammation of the liver that could lead to liver failure requiring a liver transplant. HCV may also cause a severe type of acute infection called fibrosing cholestatic HCV, that can cause severe liver injury, jaundice (yellowing of the eyes and skin), and progressive liver dysfunction, and may cause damage to other organs, including and not limited to the kidneys, heart, skin. Chronic HCV infection has also been associated with certain cancers, autoimmune diseases, and depression.

There is a small risk of transmission of HCV from the study subject to intimate partners during sexual activity. This risk is very low and should be reduced even further due to requirements for subjects to use barrier protection during sexual activity.

9.4.4 Potential benefits

The results from the study could be applied in the future to subjects (including those in the study) who stand to benefit from the information. Subjects will experience clinical benefits as their kidney function and quality of life should vastly improve following transplant. The study involves the risks of phlebotomy, echocardiography, Fibroscan, development of chronic HCV, and loss of confidentiality, but there is a potential for future benefit for both subjects in the study and for future subjects, the risk/benefit ratio is favorable.

9.4.5 Alternatives

The use of the medications for this study requires that certain other medications not be used (Table 7). Therefore, the alternative is to not participate in this study and to continue having the option to take these medications.

10.0 Study Administration, Data Handling, and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial as appropriate and applicable to the study.

10.3 Case Report Forms

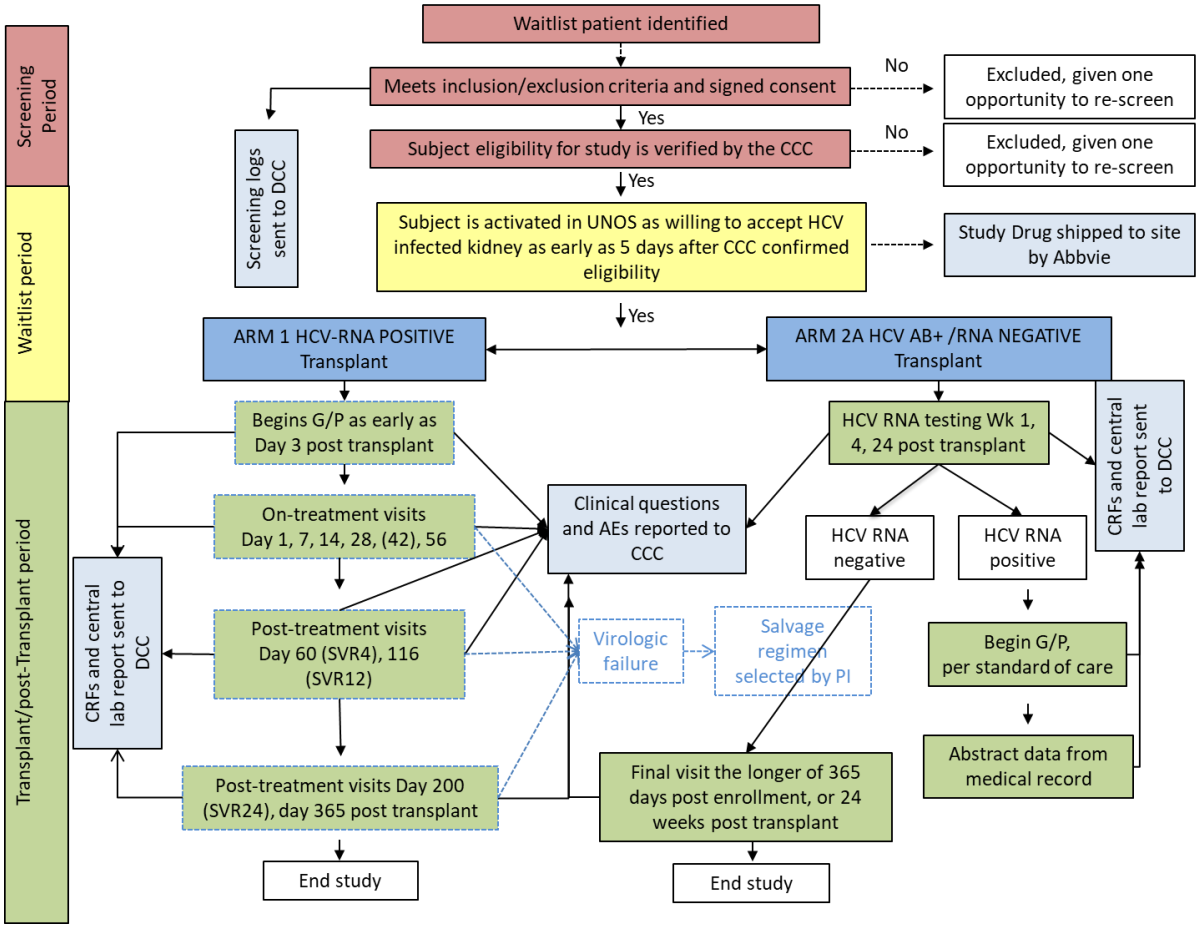
The study case report form (CRF) is the primary data collection instrument for the study. Data will be collected using CRFs developed specifically for the (study name) trial as well as standardized instruments. Forms will be made available for completion on paper as well as directly into the electronic data management system. Data will be collected from in-person and telephone interviews with study participants, and from clinical information contained in medical records. When possible during the follow-up phase of telephone interviewing, data collected will be entered directly into the electronic data management system. Hard copy CRFs will be available in case of the electronic data management system (DMS) is inaccessibility.

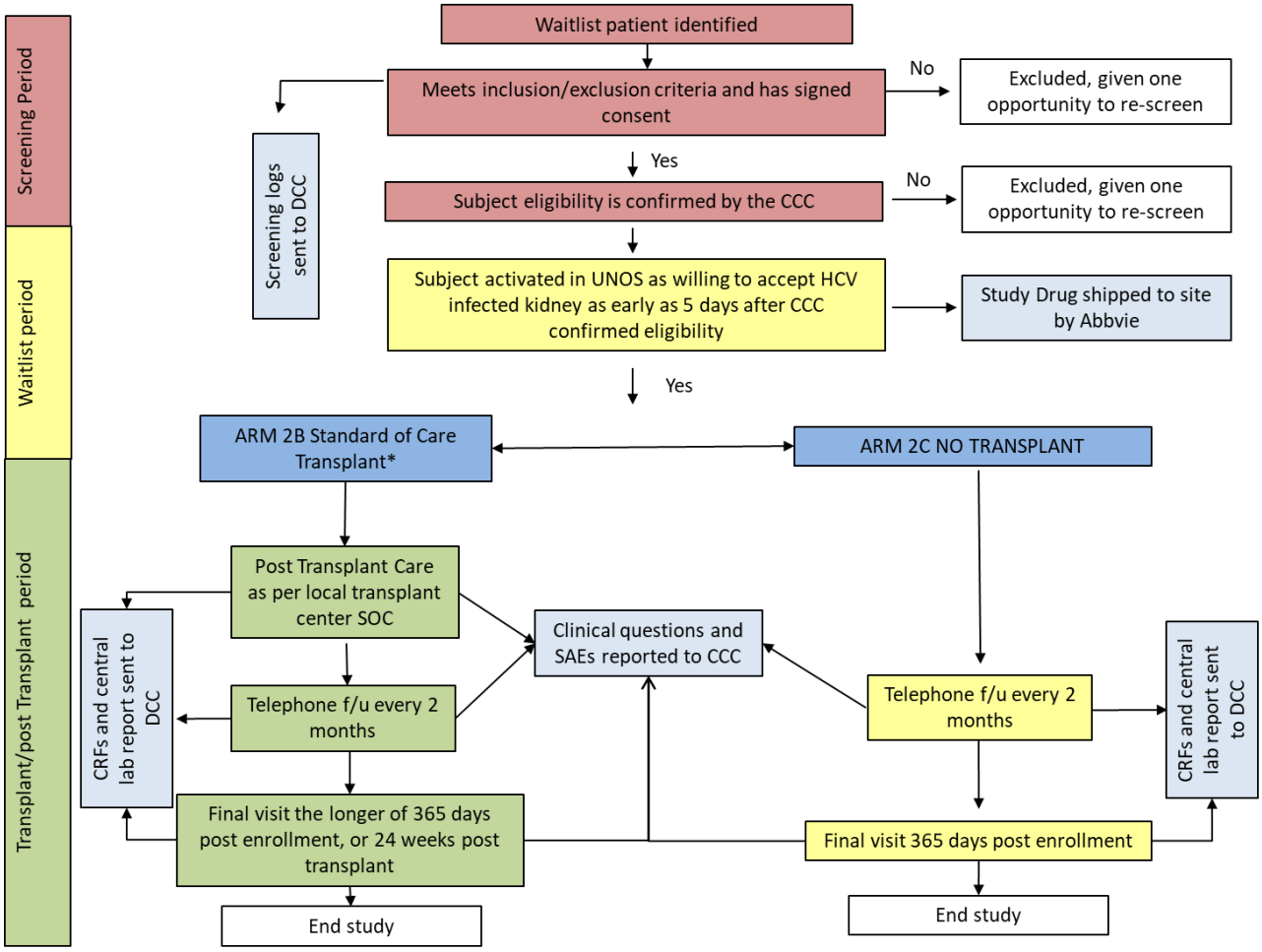
10.4 Data Collection and Management

Data Collection Procedures. All data collection procedures for this Multi Center, Open-Label Study of Glecaprevir/Pibrentasvir to Treat Recipients of Transplanted Kidneys from Deceased Donors with Hepatitis C Virus are outlined in **Section 5.0** ("Investigational Plan")

Figure 2 shows flow of patients through the 4 patient scenarios, data collection and data transfer activities. The first diagram depicts patient and data flow for enrolled subject who receive a study-eligible HCV RNA positive kidneys (left, ARM 1) and subjects who receive a study-eligible HCV RNA-negative/HCV Ab-positive kidney (right, ARM 2A). The second diagram shows patient and data flow for enrolled subject who receive a standard-of- care kidney (left, ARM 2B) and subject who are not transplanted during the duration of the trial (right, ARM 2C).

Figure 2: Subject flow, data collection and data transfer activities during the trial


Screening Period
Waitlist period
Transplant/post-Transplant period
Waitlist patient identified
Meets inclusion/exclusion criteria and signed consent
No
Excluded, given one opportunity to re-screen
Yes
Subject eligibility for study is verified by the CCC
No
Excluded, given one opportunity to re-screen
Yes
Screening logs sent to DCC
Subject is activated in UNOS as willing to accept HCV infected kidney as early as 5 days after CCC confirmed eligibility
Study Drug shipped to site by Abbvie
Yes
ARM 1 HCV-RNA POSITIVE Transplant
ARM 2A HCV AB+ /RNA NEGATIVE Transplant
Begins G/P as early as Day 3 post transplant
HCV RNA testing Wk 1, 4, 24 post transplant
CRFs and central lab report sent to DCC
On-treatment visits Day 1, 7, 14, 28, (42), 56
Clinical questions and AEs reported to CCC
HCV RNA negative
HCV RNA positive
CRFs and central lab report sent to DCC
Post-treatment visits Day 60 (SVR4), 116 (SVR12)
Virologic failure
Salvage regimen selected by PI
Begin G/P, per standard of care
Abstract data from medical record
Post-treatment visits Day 200 (SVR24), day 365 post transplant
Final visit the longer of 365 days post enrollment, or 24 weeks post transplant
End study
End study



*A "standard of care" transplant is defined as any of the following kidney transplants: a deceased donor HCV RNA-positive kidney transplant that did not meet donor criteria for Arm 1 or HCV RNA-positive kidney transplant that place after last transplant allowed for Arm 1 but met criteria for Arm 1 inclusion (2B1); a deceased donor HCV RNA-negative/HCV Ab-positive kidney transplant that either did not meet donor criteria or took place > 6 months after the last Arm 1 transplant (2B2); a deceased donor HCV RNA-negative/HCV Ab-negative transplant at a MYTHIC

clinical site (2B3); any living donor kidney transplant at a MYTHIC clinical site (2B4); or any kidney transplant at a different center than the 7 clinical sites (2B5).
Arm 2B5 recipients will be censored at transplantation.

Data management procedures. The Data Coordinating Center (DCC) at the University of Pennsylvania will develop a data management system for the collection, validation, storage and management of trial data. The data management system will use a combination of tools to perform the following study functions:

• Subject tracking – to monitor screening and enrollment and produce subject visit schedules
• Eligibility determination - to evaluate screening data to determine subject eligibility
• Comprehensive data collection modules to accommodate all types of trial data

Data management system. All research data for this trial will be stored in an electronic database that is managed by the Clinical Research Computing Unit (CRCU) of the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics (CCEB). The Data Management System will be developed using Oracle Corporation's suite of pharmaceutical applications, including Oracle Clinical® and Oracle Clinical Remote Data Capture®. The Oracle Clinical system, which has been installed, tested and validated in compliance with the FDA part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR Part 11), meets the requirement for IND/IDE studies. The database will be hosted on secure computing servers and will be restricted to only those individuals who are authorized to work on the trial. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies.

The DMS will exist within an appropriate database structure to support the requirements of the DMS and to promote data security and integrity. Electronic audit trails of changes to database contents will be incorporated into the design and will capture and record those changes automatically. In addition to the trial database where actual results will be maintained, a development database will be created. The development database is a working environment that facilitates the development, testing, troubleshooting, enhancement, and training for the DMS without adversely affecting the integrity of the collected project data. CRCU servers exist within highly secure computing environments of the CCEB that are the responsibility of the Penn Medicine Academic Computing Services group. This group focuses on providing hardware and software services, systems administration, business continuity, and security services to research projects within the CCEB and other departments in Penn Medicine.

Data Security Measures: The research computing environment has a security component required due to HIPAA; federal, state, and research compliance regulations; and CCEB best practices for safeguarding research data. The CCEB secures its logical network using virtual private network (VPN) protocols and network address translation (NAT) protocols layered on top of the single logical virtual local area network (VLAN). The VPN protocols provide encrypted “data in motion” protections and “fire-walled” connections between each of the physical network segments of the logical network. Applying VPN/VLAN encrypted connections allow all internal CCEB data to “tunnel through” and traverse the University’s thus ensuring the privacy of the CCEB data and the availability of the data to only CCEB managed resources and users.

In addition to the VLAN and VPN technologies, the CCEB network utilizes the NAT protocols to provide private network addressing within the logical CCEB network. This additional precaution ensures that all network protocols running into or out of the logical CCEB network are essentially “proxy” connections that are only passed through one of several CCEB firewall devices. Providing a proxy service allows the CCEB to monitor, log

and control all data and network protocols coming into and going out of its logical network. The physical building environment for supporting the computing environments required by the CRCU is co-located within a formal data center facility that is managed by University of Pennsylvania; Penn Medicine and Information Systems and Computing personnel. The data center also has uninterrupted power supply (UPS)/diesel subsystems to ensure that adequate and constant electrical power requirements are met at all times, even during prolonged power outages. The data center has secured and limited physical access and is constructed with walls and doors to prevent break-through efforts and/or illegal entry.

Data entry. The CRCU will configure the Oracle Clinical® remote data capture (RDC) module to allow remote data entry from the participating trial sites. The RDC module will be available to any computer with a persistent internet connection and will be run using standard web browser software. The data entry screens will look like the data collection forms as closely as possible to allow visual referencing during data entry, enhancing accuracy and efficiency. Data entry checks will be included in the entry screen designs where appropriate to limit the opportunity for erroneous entries due to mistyping. Such data entry checks would include value range comparisons, valid data type checks, required value checks, and skip pattern enforcement. This data entry module will be configured for single data entry.

Data Quality Module: The CRCU will configure a module to assess data entered in to the database in relation to a set of rules that describe expectations for those data items. This set of data validation rules will be defined by CRCU clinical data management personnel and the study PI and Biostatistician to identify data items that may have been collected incorrectly or entered into the database inaccurately. The module will run automatically to inspect all newly entered or modified data. Clinical site personnel will review the results of the data validation and take any required corrective action for invalid data. Queries will be recorded and tracked in the data quality module. Corrections identified for individual data

items will be managed by the clinical sites. All changes made will be recorded in an electronic audit trail and documented using change control procedures.

The DCC and CCC teams will establish specific training and certification procedures to ensure that all study personnel are well trained in the performance of study procedures, data collection and data entry processes.
A Manual of Procedures (MOP) will provide detailed instruction for the performance of screening, enrollment, treatment, and follow-up procedures. The MOP will provide instruction in data collection, case report form completion, and use of the electronic data management system.

Reports Module: The CRCU will develop a set of standard reports to clearly illustrate the results of trial recruitment efforts and study events, and to document any safety concerns that have occurred during the study. Additional reports may be developed where regular feedback is desirable. Such additional reports may include data entry timeliness and data quality assessments.

10.5 Medical record review/verification

Clinical Site RCs will complete a detailed chart abstraction to include all original clinic notes, telephone notes, safety and efficacy labs/evaluations collected during standard of care treatment and in the post treatment observation period. Data required by the protocol will be entered into the online Data Management System. Hard copy forms will be stored in secure locked cabinets within offices controlled by study personnel and locked when not in use.

As needed, clinical site staff will provide medical record/source documents with identifying information redacted to the CCC to confirm eligibility of all screened patients, as soon as possible after the screening process. The CCC will assess the accuracy of eligibility determination and provide feedback to the clinical site staff. The CCC may determine that

additional documentation and/or training may be may be required, as determined by the results of the chart review. Sites will redact all personal identifying information prior to sending. All documentation from medical charts will be permanently disposed of by shredding. Eligibility will be confirmed again by the site PI immediately before transplant. The CCC may request the corresponding medical records of treated patients in order to further verify data accuracy.

10.6 HIPAA Privacy Rule for Elements of PHI and Uploaded Records

Established in 1996, the U.S. Department of Health and Human services issued the Privacy Rule as part of the Health Insurance Portability and Accountability Act to establish a national set of standards for the protection of certain health information. This rule protects all "individually identifiable health information" held or transmitted by a covered entity or its business associate in any form or media whether electronic, paper, or oral. A list of 18 Identifiers was established:

1. Names
2. All geographical subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
4. Phone numbers
5. Fax numbers

6. Electronic mail addresses
7. Social Security numbers
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code (note this does not mean the unique code assigned by the investigator to code the data)

Records submitted for Centralized Abstraction and through RED-I are redacted for these PHI identifiers *except for dates of service*/*activities*. In instances where a PHI identifier other than a date of service is present on a redacted record delegated CCC personnel will redact that information.

11.0 Monitoring

The study monitor – to be selected by MGH leadership - will review data centrally (remote monitoring) to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

The study monitor must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On-site they will review study records, the Investigator Site File, and study medication; discuss the conduct of the study with the investigator; and verify that the facilities remain acceptable.

The investigator must notify the sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the sponsor.

12.0 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact the sponsor prior to destroying any records associated with the study. The sponsor will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to the sponsor.

13.0 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable

- amount returned to AbbVie, if applicable
- dates and initials of person responsible for Investigational Product dispensing/ accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

14.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the electronic CRF.

15.0 Data Safety Monitoring Committee

An independent DSMB will be constituted by the sponsor. The DSMB will be comprised of 3 members who have current experience in the management of kidney- and/or liver transplant patients, clinical trials, GCP, HCV treatment with direct acting antivirals, and preferably have prior DSMC experience (not required). After the 5th kidney transplant from an HCV RNA-positive donor, the DSMC will have at least one interim meeting during which efficacy and safety, including adverse events data as well as data related to response of HCV infection to therapy, will be reviewed. The DSMC will continue monitor ongoing efficacy and safety data during the study until the time of its conclusion. The DSMC charter will outline DSMC constitution, scope, operation, and function per relevant FDA Guidance Documents.

16.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and sponsor. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and sponsor. The investigator will provide a final report to the IEC/IRB

following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify the sponsor to arrange alternative archiving options.

The end-of-study is defined as the date of the last subject's last visit.

17.0 Investigator's Agreement

1. I have received and reviewed the MAVYRET USPI.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Multi-Center, Open-Label Study of Glecaprevir/Pibrentasvir to Treat Recipients of Transplanted Kidneys from Deceased Donors with Hepatitis C Virus

Protocol Date: February 13, 2019

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

18.0 Reference List

References

1. Centers for Disease Control and Prevention. Viral Hepatitis Statistics and Surveillance. URL: https://www.cdc.gov/hepatitis/statistics/index.htm. Accessed September 26 2017.
2. World Health Organization Global Hepatitis Report 2017: Executive Summary URL: http://appswhoint/iris/bitstream/10665/255017/1/WHO-HIV-201706-engpdf?ua=1 Accessed September 26, 2017.
3. Cardoso A-C, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. Journal of Hepatology 2010;52:652-7.
4. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clinical Gastroenterology and Hepatology 2011;9:509-16. e1.
5. Pawlotsky JM. New hepatitis C therapies: the toolbox, strategies, and challenges. Gastroenterology 2014;146:1176-92.
6. Organ Procurement and Transplant Network. National Data on Kidney Transplant US Waiting List. Accessed September 18, 2017. Available at: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#. .
7. Veatch RM, Ross LF. Transplantation Ethics. 2nd ed. Washington, D.C.: Georgetown University Press; 2015.
8. Bloom RD, Sayer G, Fa K, Constantinescu S, Abt P, Reddy KR. Outcome of hepatitis C virus-infected kidney transplant candidates who remain on the waiting list. American journal of transplantation 2005;5:139-44.
9. Goldberg DS, Blumberg E, McCauley M, Abt P, Levine M. Improving Organ Utilization to Help Overcome the Tragedies of the Opioid Epidemic. Am J Transplant 2016;16:2836-41.
10. Mavyret US Package Insert, AbbVie Inc., 2017. URL: http://www.rxabbvie.com/pdf/mavyret_pi.pdf. Accessed October 11 2017
11. Gane EJ, Lawitz E, Pugatch D, et al. Glecaprevir and Pibrentasvir in patients with HCV and severe renal impairment. NEJM 2017; 377:1448-55.
12. Hall IE, Reese PP, Doshi MD, et al. Delayed Graft Function Phenotypes and 12-Month Kidney Transplant Outcomes. Transplantation 2017;101:1913-23.
13. Davis MI, Chute DF, Chung RT, Sise ME. When and how can nephrologists treat hepatitis C virus infection in dialysis patients? Semin Dial 2 2018 31(1):26-36.
14. Reau N, Kwo P, Rhee S, et al. LBO-03-MAGELLAN-2: safety and efficacy of rentasvir in liver or renal transplant adults with chronic hepatitis C genotype 1–6 infection. Journal of Hepatology 2017;66:S90-S1.
15. Goldberg DS, Abt PL, Blumberg EA, et al. Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients. N Engl J Med 2017;376:2394-5.
16. 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 2017;17:2790-802.

17. Zeuzem S, Foster GR, Asatryan A, Gane E, Feld JJ et al. Glecaprevir-Pibrentasvir for 8 and 12 weeks in HCV genotype 1 or 3 infection. New England Journal of Medicine 2018: 378: 354-69.A
18. Asselah T, Kowdley CV, Zadeikis N, Wang S, etal. Effiacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2,4,5 or 6 infection without cirrhosis. Clin Gatroenterol H epatol. 2018 in press. DOI: https://doi.org/10.1016/j.cgh.2017.09.027
19. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999;341:1725-30.
20. Merion RM, Ashby VB, Wolfe RA, et al. Deceased-donor characteristics and the survival benefit of kidney transplantation. JAMA 2005;294:2726-33.
21. Reese PP, Shults J, Bloom RD, et al. Functional status, time to transplantation, and survival benefit of kidney transplantation among wait-listed candidates. Am J Kidney Dis 2015;66:837-45.
22. Reese PP, Abt PL, Blumberg EA, Goldberg DS. Transplanting Hepatitis C-Positive Kidneys. N Engl J Med 2015;373:303-5.
23. Durand C, Brown D, Wesson R, et al. EXPANDER-1: Exploring Renal Transplants Using Hepatitis-C Infected Donors for HCV-Negative Recipients. American Journal of Transplantation 2017;17 (suppl 3).
24. Cacoub P, Comarmond C, DomontF, et al Extrahepatic manifesations of chronic hepatitis C virus infection. Ther Adv Infect Dis. 2016 3:(1) 3-14.
25. Sherman AC and Sherman KE. Extrahepatic manifestations of hepatitis C infection: navigating CHASM. Curr HIV/AIDS Rep. 2015 12(3): 353-361.
26. American Association for the Study of the Liver Disease (AASLD) Clinical Practice Guidelines: Recommendations for Testing, Managing, and Treating Hepatitis C. Available at: http://www.hcvguidelines.org. Accessed August 15, 2017.

Appendix A: Educational material to be distributed at MYTHIC trial education session

What is hepatitis C infection?
Hepatitis C is a virus that circulates in the blood, attacks liver cells, changes the way that the liver functions and causes inflammation of the liver.

How can a person get hepatitis C infection?
Hepatitis C virus is passed by blood to blood contact with another person who has Hepatitis C virus infection. The most common way that it is passed from one person to the next is by intravenous drug use and sharing needles. Some people may get Hepatitis C virus infection by sexual contact. After the virus is passed, it moves through the bloodstream and replicates and lives in blood and the liver.

What happens when you get hepatitis C?
Once you are infected with hepatitis C, the virus begins to grow. Some people's immune system can fight off Hepatitis C virus, but for most people the virus remains active in their body. Liver cells are the most commonly affected cells. With the virus present, liver cells become injured and inflamed. Once Hepatitis C virus has lived in your body for many years (usually more than 20 years), the liver may not be able to function and Hepatitis C virus can cause cirrhosis of the liver, which can lead to liver failure and liver cancer. Cirrhosis can cause yellowing of the skin, fluid retention, confusion, gastrointestinal bleeding, and may lead to the need for a liver transplant or death.

Are there any other effects of Hepatitis C on other parts of the body?
Rarely, hepatitis C can cause inflammation in other parts of the body, including the joints (arthritis), skin (rashes), nerves (numbness or nerve pain), or kidney (kidney failure).

Could you get hepatitis C from being in this study?
Yes, if the donor you receive has virus circulating in their blood then when the kidney is transplanted to you, you would likely catch their hepatitis C virus if you didn't take any treatment. We believe that starting medication right away at the time of transplant will kill the virus and that by the time the treatment is done there is only a small chance that you would still have Hepatitis C virus circulating in your body. The study medications are being used are more than 95% effective at curing Hepatitis C.

What is a Hepatitis C antibody test? What is a Hepatitis C viral load test?

A Hepatitis C antibody test detects if you have ever been exposed to the virus. Even if you had the virus but your body or a medicine cured it, your antibody test will stay positive in your blood for the rest of your life. The Hepatitis C viral load test will measure if the virus is still circulating in your blood. If your viral load test is positive then you have an active Hepatitis C infection. If your viral load test is negative then you do not have a Hepatitis C infection.

Why would a donor have a positive Hepatitis C antibody test but a negative viral load? Can I still catch Hepatitis C from this donor?

A donor with a positive Hepatitis C antibody but negative virus 1) may be false positive antibody test, or 2) may have had the infection in the past but cleared by either their immune system or by taking Hepatitis C treatment or 3) may have a false negative viral load test. You are unlikely to catch Hepatitis C from this donor, even without treatment, but there is still a small chance, so we will carefully test you for Hepatitis C virus at regular intervals. You will be tested 1 week, 4 weeks, 24 weeks and 1 year after the kidney transplant from a Hep C antibody positive but HCV RNA negative donor. If you were going to get Hepatitis C from such transplant, we expect it would happen right away. If you are clear 24 weeks after your transplant then there is almost no chance the virus will spread to you from the transplant.

Are there any treatments for hepatitis C infection?

Yes, there are many therapies that have been approved by the FDA as safe and effective for treating chronic hepatitis C. Newer medications are curing more than 95 out of 100 people who get treatments. Even patients who fail their first round of Hepatitis C treatment can be treated with an alternative treatment and be cured.

Can people with hepatitis C donate a kidney?

Yes, but right now a person with hepatitis C can only donate to another person who already has hepatitis C infection. Right now patients who are on dialysis and have hepatitis C usually have a much shorter wait time because they can accept these donors.

How do you know that a kidney donor has hepatitis C infection?

Any potential deceased kidney transplant donor goes through many blood tests to determine if they have infections that may be spread. The hospital tests the blood of the donor for Hepatitis C virus.

Why are there many donors with Hepatitis C infection?

One of the major causes of Hepatitis C virus is sharing needles during intravenous drug use. There are many people now taking opioid medications and using injection drugs. There has been a large increase in the number of people who die from opioid overdose and have hepatitis C. This is part of the reason why there are so many kidneys available with Hepatitis C.

What are the different types of hepatitis C?
There are six common types of Hepatitis C. These variations are categorized into groups known as genotypes. There are a total of 6 common genotypes seen throughout the world. Genotype 1 is the most common in the United States. Approximately 75% of Americans infected with hepatitis C have a genotype 1 viral infection.

Does glecaprevir/pibrentasvir (G/P) treat all types of Hepatitis C?
The study medication, glecaprevir and pibrentasvir (G/P), is approved to treat all 6 common genotypes of hepatitis C. The use of G/P in patients receiving organs from donors with HCV infection is investigational.

When would the G/P treatment begin?
If you receive a transplant from a donor with HCV infection, then you will take your first dose of G/P within the first week of transplant. Your doctors and study team will decide when you are ready to start G/P given as oral tablets.

If you receive a transplant from a donor with a positive HCV antibody but a negative viral load then you will be monitored after transplant and you will only start G/P if your Hepatitis C viral load test becomes positive within 24 weeks after the transplant.

How long will I take G/P?
You will take 3 G/P tablets at one time with food daily for 8 weeks

What are the side effects of G/P?
The most common side effects were fatigue, headache and nausea (occurring in approximately 1 in 10 patients). Less than 1 in 100 patients had side effects so severe that had to stop treatment due to a side effect.

What happens if G/P doesn't work and the Hepatitis C comes back?
If, after taking G/P for 8 weeks the Hepatitis C virus is detected in your blood you will have the option to be given an additional course of Hep C treatment at no cost to you. The study investigators will choose which kind of therapy is best for you at the time.

How long will I be a part of this study?
You will start the screening process soon after you sign the consent form. You will meet with the transplant team and we will ensure you are healthy enough for a kidney transplant, once you pass these tests you will be accepted into the study. We estimate that you will receive a kidney transplant within 6 months after enrolling into the study. Once you received the transplant, we will follow you for one year. We estimate your total time in the study will be 1.5 years.

When will my study visits take place?
You will schedule your screening visits with our study team at your convenience and meet in the transplant clinic. Your visits after the transplant will take place after your regularly scheduled medical visits to the transplant clinic.

Will participating in this study effect my transplant medications or my transplant care?
Your transplant doctor will know that you are participating in this study, but your care after the transplant should not be affected by being a part of this study. You will get the same transplant immunosuppression drugs that are most commonly used at our transplant program.

Does being a part of this study affect my standing on the kidney transplant list? If I decide not to participate does this affect my standing on the kidney transplant list?
You will still be eligible to receive a kidney transplant from a donor without Hepatitis C should one become available for you. However, if you decide to participate in this study it is more likely that you will be called about a transplant from a Hepatitis C donor first. If you decide not to participate, this will not affect your standing on the regular transplant list.

Has anyone like me who does not have Hepatitis C ever received a kidney transplant from a patient with Hepatitis C before?
Yes, patients have previously received kidney transplants from patients with hepatitis C and the virus was transmitted from the donor to the recipient. Recently, 20 patients at the University of Pennsylvania (as well as 10 patients at Johns Hopkins and other patients at Massachusetts General Hospital) had a kidney transplant from donors with Hepatitis C and they all developed the Hepatitis C virus in their system within 3 days. They were treated

with a different combination of Hep C medicines for 12 weeks and all were cured of Hepatitis C virus.

What are the risks to being in this study?

Risks include contracting Hepatitis C from the donor kidney. You may experience liver disease right after the transplant or years later if you have Hepatitis C, however we would not expect you to have liver disease from Hepatitis C as long as the G/P treatment works to cure Hepatitis C. The study procedures including blood draw may lead to bruising. Although G/P is generally well tolerated, it is possible you experience a more severe side effect. There is also a possibility of detecting a new health problem during screening for this study that you may need to address. Participating in a study may lead to psychological stress. Risks will be reviewed again in the informed consent session.

What are the benefits to being in this study?

Participation in this study may allow you to receive a good quality kidney and shorten your wait time on the kidney transplant list. If you are willing to accept a kidney from a donor who has hepatitis C virus infection we expect you will wait 6 months. This is much shorter than you would otherwise be expected to have to wait.

Appendix B: Responsibilities of the Clinical Investigator

Clinical research studies sponsored by MGH are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 17.0 of this protocol, the investigator is agreeing to the following:

Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying the sponsor, except when necessary to protect the safety, rights or welfare of subjects.

Personally conducting or supervising the described investigation(s).

Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.

Reporting adverse experiences that occur in the course of the investigation(s) to the sponsor and the site director.

Reading the information in the Mavyret US package insert/safety material provided, including the instructions for use and the potential risks and side effects of the study drug(s)

Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.

Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of the sponsor and/or the appropriate regulatory agency, and retaining all study-related documents until notification from the sponsor.

Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and the sponsor.

Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix C: Medicare National Coverage Decision for Clinical Trials

This national coverage policy is based upon the authority found in §1862(a)(1)(E) of the Social Security Act (Act). It is binding on all Medicare carriers, fiscal intermediaries, Peer Review Organizations, Health Maintenance Organizations, Competitive Medical Plans, Health Care Prepayment Plans, and Medicare+Choice organizations (§1852(a)(1)(A) of the Act). In addition, an administrative law judge may not disregard, set aside, or otherwise review a national coverage decision issued under §1862(a)(1) of the Act. 42 C.F.R. §405.860.

Clinical Trials

Effective for items and services furnished on or after September 19, 2000, Medicare covers the routine costs of qualifying clinical trials, as such costs are defined below, as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials. All other Medicare rules apply.

Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national noncoverage decision) that are provided in either the experimental or the control arms of a clinical trial except:

- the investigational item or service, itself,
- items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan); and
- items and services customarily provided by the research sponsors free of charge for any enrollee in the trial.

Routine costs in clinical trials include:

- Items or services that are typically provided absent a clinical trial (e.g., conventional care);

- Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and
- Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service--in particular, for the diagnosis or treatment of complications.

This policy does not withdraw Medicare coverage for items and services that may be covered according to local medical review policies or the regulations on category B investigational device exemptions (IDE) found in 42 C.F.R. §405.201-405.215 and §411.15 and §411.406. For information about LMRPs, refer to www.lmrp.net, a searchable database of Medicare contractors' local policies.

For noncovered items and services, including items and services for which Medicare payment is statutorily prohibited, Medicare only covers the treatment of complications arising from the delivery of the noncovered item or service and unrelated reasonable and necessary care. (Refer to MCM 2300.1 and MIM 3101.) However, if the item or service is not covered by virtue of a national noncoverage policy in the Coverage Issues Manual and is the focus of a qualifying clinical trial, the routine costs of the clinical trial (as defined above) will be covered by Medicare but the noncovered item or service, itself, will not.

Requirements for Medicare Coverage of Routine Costs

Any clinical trial receiving Medicare coverage of routine costs must meet the following three requirements:

1. The subject or purpose of the trial must be the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids).

2. The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.
3. Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers. Trials of diagnostic interventions may enroll healthy patients in order to have a proper control group.

The three requirements above are insufficient by themselves to qualify a clinical trial for Medicare coverage of routine costs. Clinical trials also should have the following desirable characteristics; however, some trials, as described below, are presumed to meet these characteristics and are automatically qualified to receive Medicare coverage:

1. The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes;
2. The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;
3. The trial does not unjustifiably duplicate existing studies;
4. The trial design is appropriate to answer the research question being asked in the trial;
5. The trial is sponsored by a credible organization or individual capable of executing the proposed trial successfully;
6. The trial is in compliance with Federal regulations relating to the protection of human subjects; and
7. All aspects of the trial are conducted according to the appropriate standards of scientific integrity.

Qualification Process for Clinical Trials

Using the authority found in §1142 of the Act (cross-referenced in §1862(a)(1)(E) of the Act), the Agency for Healthcare Research and Quality (AHRQ) will convene a multi-

agency Federal panel (the "panel") composed of representatives of the Department of Health and Human Services research agencies (National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), AHRQ, and the Office of Human Research Protection), and the research arms of the Department of Defense (DOD) and the Department of Veterans Affairs (VA) to develop qualifying criteria that will indicate a strong probability that a trial exhibits the desirable characteristics listed above. These criteria will be easily verifiable, and where possible, dichotomous. Trials that meet these qualifying criteria will receive Medicare coverage of their associated routine costs. This panel is not reviewing or approving individual trials. The multi-agency panel will meet periodically to review and evaluate the program and recommend any necessary refinements to CMS.

Clinical trials that meet the qualifying criteria will receive Medicare coverage of routine costs after the trial's lead principal investigator certifies that the trial meets the criteria. This process will require the principal investigator to enroll the trial in a Medicare clinical trials registry, currently under development.

Some clinical trials are automatically qualified to receive Medicare coverage of their routine costs because they have been deemed by AHRQ, in consultation with the other agencies represented on the multi-agency panel to be highly likely to have the above- listed seven desirable characteristics of clinical trials. The principal investigators of these automatically qualified trials do not need to certify that the trials meet the qualifying criteria, but must enroll the trials in the Medicare clinical trials registry for administrative purposes, once the registry is established.

Effective September 19, 2000, clinical trials that are deemed to be automatically qualified are:

1. Trials funded by NIH, CDC, AHRQ, CMS, DOD, and VA;

2. Trials supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, CMS, DOD and VA;

3. Trials conducted under an investigational new drug application (IND) reviewed by the FDA; and

4. Drug trials that are exempt from having an IND under 21 CFR 312.2(b)(1) will be deemed automatically qualified until the qualifying criteria are developed and the certification process is in place. At that time the principal investigators of these trials must certify that the trials meet the qualifying criteria in order to maintain Medicare coverage of routine costs. This certification process will only affect the future status of the trial and will not be used to retroactively change the earlier deemed status.

Medicare will cover the routine costs of qualifying trials that either have been deemed to be automatically qualified or have certified that they meet the qualifying criteria unless CMS's Chief Clinical Officer subsequently finds that a clinical trial does not meet the qualifying criteria or jeopardizes the safety or welfare of Medicare beneficiaries.

Should CMS find that a trial's principal investigator misrepresented that the trial met the necessary qualifying criteria in order to gain Medicare coverage of routine costs, Medicare coverage of the routine costs would be denied under §1862(a)(1)(E) of the Act. In the case of such a denial, the Medicare beneficiaries enrolled in the trial would not be held liable (i.e., would be held harmless from collection) for the costs consistent with the provisions of §1879, §1842(l), or §1834(j)(4) of the Act, as applicable. Where appropriate, the billing providers would be held liable for the costs and fraud investigations of the billing providers and the trial's principal investigator may be pursued.

Medicare regulations require Medicare+Choice (M+C) organizations to follow CMS's national coverage decisions. This NCD raises special issues that require some modification of most M+C organizations' rules governing provision of items and services in and out of network. The items and services covered under this NCD are inextricably linked to the

clinical trials with which they are associated and cannot be covered outside of the context of those clinical trials. M+C organizations therefore must cover these services regardless of whether they are available through in-network providers. M+C organizations may have reporting requirements when enrollees participate in clinical trials, in order to track and coordinate their members' care, but cannot require prior authorization or approval. For the initial implementation, Medicare contractors will pay providers directly on a fee for service basis for covered clinical trial services for beneficiaries enrolled in M+C plans.

Appendix D: Methods of Contraceptives

D1 Contraception requirement for all subjects who will not receive mycophenolate mofetil following transplantation.

The below listed methods meet the requirements for contraception as per the CTFG guidance.[18]

If female, subject must be either postmenopausal defined as:

- Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause.
- Age < 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

OR

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

*OR for Women of Childbearing Potential who **do not** receive mycophenolate mofetil immunosuppressant after kidney transplantation*

- Agreeing to practice one effective method of birth control while receiving G/P (as outlined in the subject information and consent form or other subject information documents), starting with Day of transplant and for at least 30 days after stopping G/P.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
  - Bilateral tubal occlusion/ligation.
  - Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
  - Non-ethinyl estradiol hormone-releasing Intrauterine device (IUD)
  - Non-ethinyl estradiol hormone-releasing Intrauterine hormone-releasing system (IUS)
    - Male or female condom with spermicide (male and female condom must not be used together)
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Contraceptive sponge with spermicide

- True abstinence:
  Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods, "rhythm method," or pre-ejaculation withdrawal,are not acceptable forms of contraception).
- Sexually active with female partners only

Male Subjects

Subject must be surgically sterile (vasectomy with medical assessment confirming surgical success)

OR

Have a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy)

OR

if sexually active with female partner(s) of CBP must agree to practice one effective method of birth control while receiving G/P (as outlined in the subject information and consent form or other subject information documents), starting with Day 1 and for 30 days after stopping G/P.

- Any approved and commercially available hormonal contraception for female partners
- Any approved and commercially available, including any hormone-eluting, devices for female partners of male subjects
- Male or female condom with spermicide (male and female condom must not be used together)
- Female partner using a diaphragm with spermicide
- Female partner using a cervical cap with spermicide
- Female partner using a contraceptive sponge with spermicide
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, "rhythm method", or pre-ejaculation withdrawal are not acceptable forms of contraception).
- Sexually active with male partners only

D2 Contraception requirements for all subjects who will receive mycophenolate mofetil post kidney transplant

All Women of child bearing potential subjects or male subjects with child bearing potential women partners who receive mycophenolate mofetil following kidney transplantation are required to utilize highly effective methods of birth control as per transplant center standard of care and consistent with the transplant center mycophenolate mofetil Risk Evaluation and Mitigation Strategy (REMS).

Appendix E: Extrahepatic Manifestations of HCV infection

Infection with hepatitis C virus (HCV) can lead to both acute and chronic hepatitis. The hepatitis C virus mainly affects the liver, but there are many other conditions that are associated with hepatitis C. Extrahepatic manifestation of HCV infection denotes diseases or conditions that affect organs other than the liver. Extrahepatic manifestations of hepatitis C infection can be found in the skin, eyes, joints, immune system, nervous system and kidneys.[24,25] Some of the extrahepatic manifestations of HCV infection are more common- such as cryoglobulinemia, while others are not common. Furthermore, it is not well understood whether extrahepatic manifestations of HCV can already manifest during the phase of acute HCV infection. In this study the below listed diseases/conditions are recognized as extrahepatic manifestations of HCV infection and new onset/diagnosis of respective diseases/conditions following the transplant of an HCV-positive kidney during the study will be collected:

-Mixed cryoglobulinemia
-B cell non-hodgkin's lymphoma
-Monoclonal gammopathy
-Sjögren syndrome/sicca symptoms
-Polyarteritis
-Autoimmune thyroiditis
- Immune thrombocytopenia (ITP)
-membranoproliferative glomerulonephritis type 1
-Porphyria cutanea tarda
-Lichen planus