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Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
1.0	February 7, 2018	Original version
2.0	February 14, 2018	Amended version
3.0	March 27, 2018	Amended version
4.0	April 13, 2018	Amended version
5.0	May 18, 2018	Amended version
6.0	November 8, 2018	Amended version
7.0	December 7, 2018	Amended version
8.0	December 23, 2018	Amended version: Increase Enrollment to 20 patients
9.0	March 14, 2019	Mavyret initiation once viremia detected

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A SINGLE-CENTER PILOT STUDY OF THE USE OF HEPATITIS C POSITIVE DONORS FOR HEPATITIS C NEGATIVE LUNG TRANSPLANT RECIPIENTS WITH POST-TRANSPLANT TREATMENT WITH MAVYRET

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NYULMC Study Number:	s18-00091
Funding Sponsor:	None
IND/IDE Number:	None
Regulatory Sponsor:	None
Study Product:	Mavyret (glecaprevir/pibrentasvir)
Study Product Provider:	AbbVie, Inc., North Chicago, IL
ClinicalTrials.gov Number	NCT03523871

Initial version: February 7, 2018
Amended: February 14, 2018
Amended: March 27, 2018
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Amended: May 18, 2018
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Amended: March 14, 2019

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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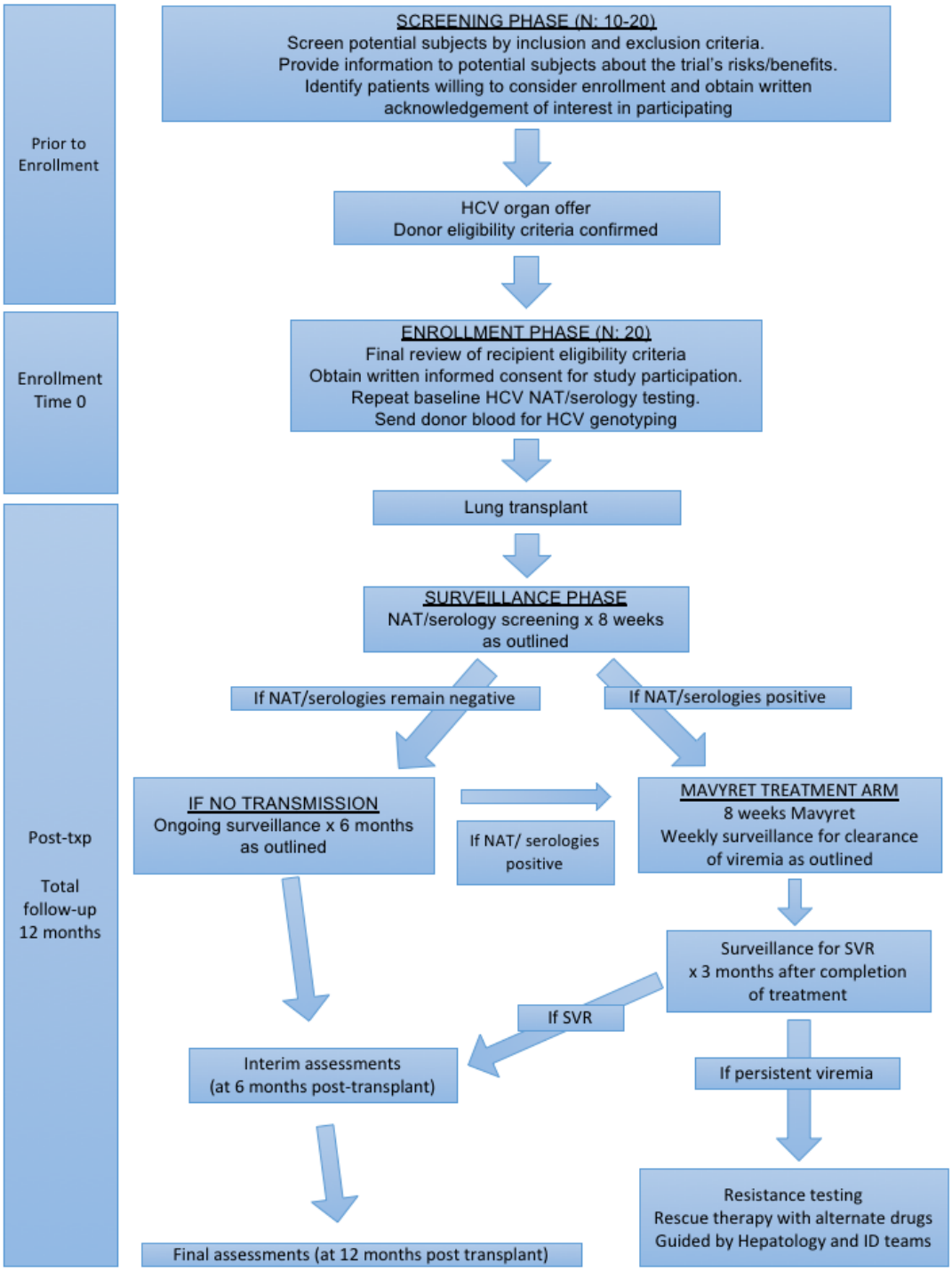
List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PHS	Public Health Service
PI	Principal Investigator
POD	Post-operative day
POW	Post-operative weeks
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
SVR	Sustained virologic response
UNOS	United Network for Organ Sharing
US	United States

Protocol Summary

Title	A single-center pilot study of the use of hepatitis C positive donors for hepatitis C negative lung transplant recipients with post-transplant treatment of hepatitis C viremia with Mavyret
Short Title	HCV positive lung donors
Brief Summary	Patients who are hepatitis C negative and are on the waiting list for a Lung transplant will be enrolled. Study subjects will receive a lung transplant from a deceased donor who has tested positive for hepatitis C and post-transplant surveillance for viral transmission will be performed. All patients who develop hepatitis C viremia will receive therapy with an FDA approved medication, Mavyret, for the treatment of hepatitis C. Mavyret is a pan-genotypic hepatitis C treatment with a cure rate of over 98%. All the recipients will undergo close monitoring and surveillance for the development of hepatitis C viremia post-transplant. They will be monitored in order to ensure that cure of hepatitis C viremia with sustained virologic response has been achieved.
Phase	Pilot study
Objectives	To determine safety and efficacy of the strategy of transplantation of lungs from HCV positive donors (with or without evidence of active HCV viremia). To characterize the incidence of HCV viremia in recipients whose lung donors were HCV positive. For recipients who develop viremia, to characterize the time course of the development of viremia, and subsequent clearance of viremia after treatment with Mavyret.
Methodology	Open label, single treatment arm
Endpoint	Percentage of patients with sustained virologic response after treatment for HCV after lung transplant. Incidence of viremia after receiving a lung transplant from a donor who tests positive for hepatitis C.
Study Duration	Two years
Participant Duration	One year
Duration of IP administration	Eight weeks
Population	Adult patients active on the UNOS waiting list for a lung transplant
Study Sites	Single center (NYU Langone Hospital)
Number of participants	20 patients
Description of Study Agent/Procedure	The lung transplantation will be performed per standard of care techniques, and all post-transplant management of the transplanted organ, including immunosuppression, will be carried out per standard of care. The study-specific interventions will be the treatment of all the patients with an FDA-approved drug, the surveillance for the development of hepatitis C viremia post-transplant, and then surveillance for sustained virologic response post-treatment.
Reference Therapy	Not applicable
Key Procedures	Treatment of all the patients with an FDA-approved drug, the surveillance for the development of hepatitis C viremia post-transplant, and then surveillance for sustained virologic response post-treatment.
Statistical Analysis	In this small pilot study, descriptive statistics will be used.

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

In New York State, 882 patients have received lung transplants since the year 2000. In that time, however 439 patients either died on the waiting list or became too sick for transplant [1]. Thus, for every 2 patients waitlisted in New York, one patient will die or become too sick for transplant before an organ becomes available. The shortage of organs available for lung transplantation directly results in loss of life.

At the same time, since 2000, in New York alone, thousands of donor organs available for transplantation were discarded because of donor history of HCV infection or exposure [2]. With the availability of new and well-tolerated direct-acting antiviral agents, cure rates for chronic HCV infection approach 100% [3]. Treatment of HCV naïve transplant recipients who develop donor-derived HCV infection post-transplant would be expected to be equally successful. Thus, if post-transplant antiviral treatment could enable HCV positive lung donors to be utilized for negative recipients, then the current donor pool has the potential to eliminate waitlist mortality.

There is, in fact, precedent for this as a viable strategy to narrow the gap between organ supply and demand. A recently study in which HCV positive donor kidneys were transplanted into HCV negative recipients demonstrated both excellent outcomes in terms of allograft function, and 100% HCV cure rates among the recipients [4]. Other ongoing and unpublished series of kidney transplant recipients [5] and of heart transplant recipients [6] have observed that only about 70% of HCV negative recipients who receive an organ from a HCV positive donor actually develop HCV viremia post-transplant. This is not surprising since the designation for HCV donor positivity by UNOS is a positive test for *either* anti-HCV antibody *or* HCV RNA. Donors who test positive for HCV antibody alone may have a falsely positive test, or may have had a prior exposure to HCV with subsequent virus clearance; in either scenario, there would be no risk of transmission of HCV infection to a recipient. It is estimated that one-third of donors designated as HCV positive is, in fact, non-viremic [7].

In this pilot study, we propose utilizing HCV positive donors for HCV negative patients on the waiting list for a lung transplant at NYU Langone. Following transplant we will perform serial surveillance for the transmission of HCV viremia from donor to recipient. We will start HCV therapy post-transplant once viremia is detected. The rationale for delaying treatment until viremia is detected is to prevent unnecessary treatment in patients who never develop viremia. The main objective is to determine the safety and efficacy of the strategy of transplantation of lungs from HCV positive donors (with or without evidence of active HCV viremia). To evaluate this clinical objective, we will characterize the incidence of HCV viremia in recipients whose lung donors were HCV positive and for recipients who develop viremia, to characterize the time course of the development of viremia, and subsequent clearance of viremia after

treatment with Mavyret.

With the exception of the use of HCV therapy and the blood testing to evaluate the viremia and the response to therapy, all the other aspects of management of the lung transplant recipients will follow standard of care practices and protocols for lung transplant recipients at NYU Langone Health.

Willingness to participate in this trial will afford patients quicker access to lung transplantation, and will have the potential to reduce if not eliminate waitlist mortality. In particular, the availability of lungs for transplantation in New York State is among the lowest in the country and the evaluation of HCV donors will increase the opportunities for our waitlisted patients to receive organ offers.

2.2 Name and Description of the Investigational Agent

Mavyret (glecaprevir/pibrentasvir)
Manufacturer: AbbVie, Inc., North Chicago IL

Mavyret is an FDA-approved, marketed drug clinically indicated for the treatment of HCV infection in patients without cirrhosis.

Its formulation is as an oral tablet containing two antiviral agents: glecaprevir and pibrentasvir Glecaprevir is an inhibitor of the HCV NS3/4A protease, which is essential for viral replication. Pibrentasvir is an inhibitor of the HCV NS5 protease, which is necessary for RNA replication and virion assembly. Mavyret is active against all known strains of HCV.

2.2.1 Preclinical Data

In vitro studies demonstrating efficacy of glecaprevir and pibrentasvir at preventing replication of all strains of HCV were published prior to the initiation of clinical trials for these agents. In vitro the two agents act synergistically and have high potency with low rates of resistance. [8]

2.2.2 Clinical Data to Date

In Phase 3 clinical trials, 8 weeks of Mavyret therapy achieved high rates (98%) of SVR across all genotypes (1-6) of HCV in patients with HCV infection without cirrhosis. Clinical trials involved over 2300 patients in 27 countries. Based on the results of clinical trials, the FDA approved Mayvret for use in the treatment of HCV (all strains) in patients without cirrhosis. (ClinicalTrials.gov identifiers: NCT02651194, NCT02642432, NCT02640482, NCT02636595, NCT02604017, NCT02446717, NCT02640157, NCT02243293). [9-14]

Included in the clinical trial populations were patients with severe renal impairment (stage 4 or 5 CKD). In this population, Mavyret was found to be effective in achieving a high rate of SVR and no dosing adjustment was required. [15]

2.2.3 Dose Rationale (if applicable)

The dose used will be the standard dosing regimen for its FDA approved indication, three tablets taken once daily with food (total daily dose: glecaprevir 300mg and pibrentasvir 120mg)

2.3 Rationale

There is a vast shortage of available organs for lifesaving lung transplants. Donors with history of HCV represent an unutilized source of organs that could potentially eliminate the current waiting list mortality. With the emergence of new, FDA approved treatments, HCV disease is now curable in nearly 100% of patients who contract it. By transplanting patients with HCV-positive donor lungs, this study will offer the benefit of avoiding waiting list mortality, followed by treatment (with the expectation of cure) of HCV in the event of transmission.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Risks of treatment failure: HCV mutation can lead to drug resistance and treatment failure. In patients administered Mavyret, the risk of this was 2% or less. For patients with treatment resistant HCV, rescue therapy with alternative agents can result in cure of up to 100% depending upon the genotype. Guidelines for the treatment of resistant HCV strains are published and updated regularly. [16]

Risks of treatment intolerance: Over multiple clinical trials. The overall rate of medication related adverse events leading to permanent discontinuation prior to completion of an 8-week course of therapy was 0.1% [17].

Risk of acute hepatitis C infection: Acute hepatitis C is asymptomatic in 66-75% of patients. The risks of acute HCV leading to fulminant hepatic failure are believed to be very low, however case reports of this do exist [18]. To minimize this already very low risk, we are starting treatment in all the patients at the time of transplant before any viremia is even detected.

Risk of chronic hepatitis C infection: Patients who prove refractory to all therapy including rescue therapy and develop persistent viremia are at risk to develop chronic HCV infection, which has the potential to cause cirrhosis/end-stage liver disease, the potential for the need for liver transplantation and/or death. We expect our treatment failure rate in this study to be 0%, therefore we expect the risk of chronic HCV infection to be 0%. In the event of a treatment failure, the risks of developing chronic HCV must be considered. It is estimated that approximately 15-30% of patients with chronic HCV develop cirrhosis/end-stage liver disease over 20-30 years. [19]. This risk should be compared to the risk of death on the lung transplant waiting list. The reported one-year mortality for a waitlisted patient without a transplant is as high 26.7% [20].

The efficacy of HCV treatment with Mavyret is high (98%). The efficacy of rescue therapies approaches 100%. Even in the event of a treatment failure, the risk of cirrhosis and liver disease secondary to chronic HCV are low. We believe that the survival benefit of receiving an earlier lung transplant, by accepting an organ from a HCV-positive donor, far outweighs the risks of HCV exposure and possible treatment failure.

2.4.2 Known Potential Benefits

The benefit of this study is the ability to obtain a lifesaving lung transplant rather than risk death while waiting on the list for a HCV negative organ. In addition, many of the donors with HCV infection have otherwise ideal donor characteristics for lung donation and our patients could benefit from access to better quality organs.

3 Objectives and Purpose

3.1 Primary Objective

This pilot feasibility study is being conducted to determine safety and efficacy of the strategy of transplantation of lungs from HCV positive donors (with or without evidence of active HCV viremia) into HCV-negative recipients on the NYU Langone Health lung transplant waiting list, with subsequent anti-HCV therapy to treat infection in the recipient.

3.2 Secondary Objectives (if applicable)

Secondary objectives will include characterization of the incidence of HCV viremia in recipients whose lung donors were HCV positive.

For those who develop viremia we will also characterize the time course of the development of viremia, and subsequent clearance of viremia after treatment.

4 Study Design and Endpoints

4.1 Description of Study Design

This will be an open-label, single arm, single center trial of the use of HCV positive lung donors for HCV negative recipients, followed by treatment of HCV in recipients.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary endpoint will be percentage of patients with sustained virologic response after treatment for HCV after lung transplant. This endpoint was chosen as primary because it will enable us to evaluate the safety of transient exposure to HCV at the time of lung transplantation. The expectation is that all patients who develop HCV viremia will achieve SVR (cure) following treatment with Mavyret.

4.2.2 Secondary Study Endpoints

Secondary endpoints will include:

1-year patient survival rates in HCV negative lung recipients who receive a lung transplant from a HCV positive donor.

Incidence of acute HCV viremia among HCV negative recipients who receive a lung transplant from a HCV positive donor.

These endpoints will enable us to assess the risks associated with this approach to lung transplantation and will allow us to better understand the risks of this approach to risks associated with remaining on the waiting list for a HCV-negative organ offer.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Listed for an isolated lung transplant at NYU Langone Health
2. Between 18-70 years of age
3. Able to travel to the NYU Langone Health for routine post-transplant visits and study visits for a minimum of 6 months after transplantation
4. No active illicit substance abuse
5. Weight at least 40kg
6. Women of childbearing potential must agree to use birth control in accordance with Mycophenolate Risk Evaluation and Mitigation Strategy (REMS) after transplant due to the increased risk of birth defects and/or miscarriage
7. Both men and women must agree to use at least one barrier method after transplant to prevent any secretion exchange
8. Able and willing to provide informed consent

Furthermore, the deceased donors from whom the organs will be procured must meet the following criteria:

1. Detectable HCV RNA Quantitative (PCR) or positive anti-HCV antibody
2. Donor lung meets standard NYU Langone Health clinical criteria for procurement

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. HCV RNA positive or history of previously treated HCV
2. Evidence of active hepatitis B infection or on active antiviral treatment for HBV
3. Pregnant or nursing (lactating) women
4. Use of strong CYP3A inducers
5. Requires multi-organ transplant

Furthermore, the deceased donors from whom the organs will be procured will be excluded if they meet any of the following criteria:

1. Confirmed HIV positive
2. Confirmed HBV positive (positive hepatitis B surface antigen, and/or detectable Hepatitis B virus DNA)
3. Known previously failed treatment for HCV
4. Donor age >60 years

5.3 Vulnerable Subjects

Vulnerable subjects will not be eligible for enrollment.

5.4 Strategies for Recruitment and Retention

Recruitment of patients will occur during routine evaluation visits to determine candidacy for a lung transplant at NYU Langone Heath. Patients will be informed of the option to enroll in this study, and if interested, detailed information pertaining to the risks and benefits of the trial will be provided.

The signing of the acknowledgment to consider participation in the study will occur in the outpatient clinic. No additional information about potential candidates will be collected to determine interest or candidacy for this trial than would otherwise be normally collected as per standard of care for evaluation for a lung transplant.

Written informed consent for actual enrollment in the study will occur in the inpatient setting once available organ offer has been identified and the patient is admitted for potential transplantation.

The target sample size will be 20 patients.

5.4.1 Use of Data Core/Epic Information for Recruitment Purposes

This study will utilize EPIC to identify subjects.

Any recruitment information sent by email will utilize Send Safe email.

Potential subjects will already be known to the study team, as they will be under their care as candidates and/or waitlist registrants for lung transplant. The study team will conduct an in person consultation with the patients to explain the study as well as discuss the risks, benefits, and alternatives

Approved recruitment language will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

5.5 Duration of Study Participation

Duration of participation is expected to be 12 months minimum, which will be 10 months of follow up post therapy with Mavyret.

5.6 Total Number of Participants and Sites

Twenty patients are expected to be enrolled and transplanted. No sites outside of NYULMC will enroll patients.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

Discontinuation of the study agent is not anticipated, as this will place patients at risk to develop acute or chronic HCV. For patients who do elect to discontinue the study agent Mavyret due to intolerance or SAEs/AEs, the following steps will be taken:

- Hepatology consultation to guide management, which could include:
- Continued surveillance for evidence of HCV viremia in patients who had cleared their viremia
- Conversion to an alternate HCV treatment that can be tolerated by the patient

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and DSMB.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

Mavyret is available in tablet form. The single tablet contains two active agents: glecaprevir (100nmg) and pibrentasvir (40mg).

- No IND is required, as we are not intending to get a new indication for the use of this FDA-

approved agent for the treatment of HCV or to change the marketing for Mavyret.

- This investigation does not involve a route of administration, dosing change, or patient population change compared to what is FDA-approved for Mavyret
- This investigation will be conducted in compliance with the NYULMC IRB review and consenting requirements
- This investigation is not intended to promote or commercialize the product Mavyret.

In this particular situation, it is safe to believe that in most of the cases the transplanted lungs are infected with HCV, more likely with a low viral load but still infected, and that the use of Mavyret is for the treatment of Hepatitis C, even if at the time of the transplant there is no evidence of a HCV viremia. We understand this risk and we will have clear communicating with our patients during the acknowledge introduction of this trial (during listing) and also at the time of the consent for the study that we are transplanting an organ with high likelihood of HCV infection. Then the use of this medication is for the intended use of treating HCV infection. The drug is marketed and will be available through the pharmacy.

6.1.1 Acquisition

These agents are FDA approved and will be obtained from the NYU pharmacy via standard procedure for medication ordering.

6.1.2 Formulation, Appearance, Packaging, and Labeling

This is an open label study and the drug will appear as it provided directly from the manufacturer. The tablets are pink, oblong-shaped, film-coated, and debossed with “NXT” on one side. The drug will be packed in the standard manufacturer’s packing and all standard and package inserts will be retained.

6.1.3 Product Storage and Stability

Mavyret is dispensed from the manufacturer in a 4-week (monthly) or an 8-week carton. Each weekly carton contains seven daily dose wallets. Each monthly carton contains four weekly cartons. Each 8-week carton contains 2 monthly cartons. Each child resistant daily dose wallet contains three 100 mg/40 mg glecaprevir/pibrentasvir tablets. Storage is at room temperature.

6.1.4 Preparation

The drug is a tablet for oral ingestion, which requires no preparation. For patients with prolonged intubation the medication will be crushed and administered to the patient via nasogastric tube.

6.1.5 Dosing and Administration

The dose will be three tablets taken at one time, once daily with a meal. The standard duration of therapy is 8-weeks. Patients requiring administration via nasogastric tube will have the same frequency of the dosing as oral. When the patient has been extubated and are cleared for oral medications, they will be converted to the oral preparation.

6.1.6 Route of Administration

Administered orally or via nasogastric tube.

6.1.7 Dose Adjustments/Modifications/Delays

No dose adjustments are anticipated. Subjects will be counseled as to the importance of strict adherence to the medication regimen. Subjects will be advised to notify the study team of any missed or delayed doses. If a dose is missed and less than 18 hours have elapsed since the scheduled time, patients will be instructed to take the missed dose with the next meal and resume the regular schedule the following day. If a dose is missed and more than 18 hours have elapsed since the scheduled time, then the patients will be instructed not to take the missed dose, but to resume the regular schedule the next day.

6.1.8 Duration of Therapy

The duration of therapy will be 8-weeks.

6.1.9 Tracking of Dose

While in the hospital, nursing staff will give any doses and accountability will be maintained in the electronic medical record. Once outpatient, patients will attend regularly scheduled clinic appointments for routine care following a lung transplant and medication review will occur on each of these visits to ensure that the medication is being taken properly. Laboratory testing for HCV will be performed as described. Clearance of HCV and SVR will serve as clinical evidence that the mediation is being taken properly.

6.2 Study Agent Accountability Procedures

For therapy that is initiated during the inpatient hospitalization post-transplant, the NYU Langone pharmacy will dispense the medication and the bedside nurse will give it to the patient. For outpatient therapy, the drug will be distributed to the study subjects together with the standard of care medications they will require after a lung transplant. The drug is supplied in either 4-week or 8-week batches. Completion of the course will leave no remaining doses. The entire supplied product will be used.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

Note that the medical history and medication history that pertains to candidacy for lung transplantation are considered standard of care procedures and evaluations for lung transplantation, and are not considered here. Patients are not considered candidates for this trial if there is any contraindication to their standard candidacy for a lung transplant. As such, procedures and evaluations specific to participation in this study include:

- Medical history to assess for any history of acute or chronic liver disease, and any prior infection with HCV or HBV(Standard of Care/Per Lung Transplant Protocols)
- Medication history to assess for any potential interacting drugs including (amiodarone, statins, anti-epileptics, hormonal contraceptives, antipsychotics, recreational drugs, immunosuppressant drugs) (Standard of Care/Per Lung Transplant Protocols)
- Physical examination (height, weight, baseline blood pressure, heart rate, oxygen saturation, assess for absence of jaundice/scleral icterus, abdominal examination to assess for absence of hepatosplenomegaly, ascites, abdominal wall varices) (Standard of Care/Per Lung Transplant Protocols)
- Laboratory evaluations. Serum evaluation for HCV and HBV quantitative (PCR) testing. Serum evaluation for HCV and HBV described in detail below.
- A discussion of if the results of any positive blood tests for HCV infection and discussions of response to treatment once treatment has begun.

7.1.2 Standard of Care Study Procedures

Lung transplantation and all associated procedures will be considered standard of care including: the transplant procedure itself and requisite intra-operative procedures and hemodynamic monitoring, post-operative ICU-level care, inpatient hospital unit care, outpatient post-operative care including, standard induction and maintenance immunosuppression, and standard post-transplant anti-infectious prophylaxis (anti-fungal, anti-pneumocystis, and anti-CMV prophylaxis).

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

The following tests will be reviewed for patients who are included in the study but will be performed as standard of care for lung transplant recipients:

- **Hematology:** hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count
- **Biochemistry:** sodium, potassium, CO2, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase
- **Coagulation:** INR
- **Pregnancy test**, usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.
- **HBV quantitative (Hepatitis B Virus DNA, quantitative Real-Time PCR) testing:** PCR test for detection and quantification of HBV viral load, an indicator of active HBV infection. These tests are performed as standard of care for patients who receive transplanted organs from a donor who is designated "PHS increased infectious risk." By definition, all HCV positive organ donors meet criteria for designation as PHS increased infectious risk.
- **HBV serologic testing (HBsAb, HBsAg, HBcoreAb):** serologic testing to evaluate for the presence of immunity to HBV or the evidence of prior infection with HBV. These tests are performed as standard of care for patients who receive transplanted organs from a donor who is designated "PHS increased infectious risk." By definition, all HCV positive organ donors meet criteria for designation as PHS increased infectious risk.
- **HIV serologic testing (HIV1 and 2 antigen/antibody 4th gen):** serologic testing to evaluate for the presence of HIV infection. These tests are performed as standard of care for patients who receive transplanted organs from a donor who is designated "PHS increased infectious risk." By definition, all HCV positive organ donors meet criteria for designation as PHS increased infectious risk.

The following tests will be performed specifically for purposes of this study:

- **HCV genotyping:** to be performed on all donors in parallel with (not prior to) the transplant, and to be performed for any recipient who develops HCV viremia post-transplant. Donor serum will be sent to Quest Laboratories for this testing (Hepatitis C Viral RNA, Genotype, LiPA®). Recipient testing for HCV genotyping will be ordered by standard ordering procedures through Epic as with all other tests.
- **HCV RNA Quantitative (PCR) testing:** PCR test for detection and quantification of HCV viral load
- **HCV serologic testing:** serologic evaluation for the presence of anti-HCV antibodies

7.2.2 Other Assays or Procedures

If after sending the donor serum for HCV genotyping extra donor serum is available, a sample of the donor serum (minimum of 0.5cc), will be banked. This will be retained indefinitely in the event that the donor genotype testing requires repeating at any time. See below for sample handling and labeling details.

7.2.3 Specimen Preparation, Handling, and Storage

Deceased donor blood routinely accompanies organs for transplantation to enable any additional testing a recipient center may wish to perform. For this study, we will utilize donor serum for purposes of HCV genotyping, as outlined above in 7.2.1, because genotyping for HCV positive donors is not performed regularly by UNOS. Donor blood accompanying the lung will be received in a red top tube. The whole blood will be spun in a centrifuge at 2000rpm x 15 minutes at 4°C. Serum will be removed with a pipette and transferred to a cryovials either for storage, or for packaging and shipping to Quest Laboratories for HCV genotype testing. The sample sent to Quest Laboratories will be a minimum of 1mL serum and will be labeled with donor demographic data only, no recipient data. Per standard specimen handling protocols at

Quest Diagnostics, residual samples will not be retained by Quest. Once results are finalized, Quest Diagnostics destroys samples they have tested.

The alternative option for donor blood processing (labeled with donor demographic data only, no recipient data) is having the NYU Laboratory process the samples via standard of care and providing the results to the research team.

The sample banked for storage will be labeled with the donor UNOS identification number (a unique transplant identifier that has no patient- derived identifiers), the recipient's study subject number, at the date collected. Banked samples will be stored in a -80°C freezer, located at 403 E. 34th St, 4th Floor.

See attached documents (Section 19) for detailed standard operating procedures for specimen processing, collection and shipping instructions from Quest Laboratories, as well as for the accreditation documentation for the Transplant Research Lab, where these specimens will be processed and stored. intolerances to Mavyret, due to illness associated with acute HCV infection, HCV resistances) will occur as clinically appropriate and any AEs/SAEs will be documented as described below.

Recipient blood will be processed at the NYU Laboratory while patient is hospitalized and will be processed in local laboratories (Quest, LabCorp) or NYU Laboratory while the patient is outpatient.

7.4 Concomitant Medications, Treatments, and Procedures

The subjects will receive concomitant medications, which would otherwise be given as standard of care for patients undergoing a lung transplant.

7.4.1 Precautionary Medications, Treatments, and Procedures

Treatment with amiodarone, digoxin, atorvastatin, lovastatin, simvastatin, pravastatin, rosuvastatin, flucastatin, pitavastatin requires special consideration and possible dosing adjustments in patients receiving Mavyret and the use of these medications will be discussed by the study team and any dose adjustment plan documented in the CRF.

7.5 Prohibited Medications, Treatments, and Procedures

Treatment with atazanavir, darunavir, lopinavir, ritonavir, efavirenz, rifampin, cyclosporine, ethinyl estradiol-containing oral contraceptives, carbamazepine, dabigatran, St. John's worth will not be permitted.

7.6 Rescue Medications, Treatments, and Procedures

In the event that a subject fails to achieve SVR with Mavyret, rescue therapy with other marketed agents approved for the treatment of HCV will be administered. The rescue treatment will be determined based on genotyping and resistance testing, and the choice of drug(s) used will be prescribed under the direction of a transplant hepatologist and/or transplant infectious diseases physician.

7.7 Participant Access to Study Agent at Study Closure

Not applicable

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events.

For the purpose of this protocol an adverse event is any untoward medical occurrence in a clinical study subject associated with procedures required by this protocol in relation to Mavyret treatment.

An AE does not include the following for this study:

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and before day 1 visit is not an AE.
- Any medical condition or clinically significant laboratory abnormality with an onset date after the consent form is signed that is not related to the study medication.

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the

participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

The Principal Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is notconsistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by the DSMB. All AEs including local and systemic reactions meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All SAEs occurring while on study must be documented appropriately regardless of relationship. All SAEs will be followed to adequateresolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an SAE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. SAEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved serious adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should 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.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

All AEs will be recorded in AE CRFs by a member of the study team. AEs will be recorded within 3 business days of the study team being made aware of the AE. The relationship of the AE to the study interventions will be noted by the PI. AEs that are deemed definitely related or probably related to the study interventions will be reported to the IRB and the DSMB within 3 days of their designation as such. The DSMB will determine the need for an emergency meeting between the DSMB and the study team (see

safety oversight below). AEs that are deemed unrelated or not likely related to the study interventions will be recorded on CRFs as described above and will be reviewed at quarterly DSMB safety review meetings, and at annual review by the IRB.

8.4.2 Serious Adverse Event Reporting

All SAEs will be recorded in SAE CRFs by a member of the study team. SAEs will be recorded within 3 business days of the study team being made aware of the SAE. The relationship of the SAE to the study interventions will be noted by the PI. SAEs that are both unexpected and deemed related to the study interventions will be reported to the IRB and the DSMB within 24 hours of the PI designation as such. The DSMB will determined the need for an emergency meeting between the DSMB and the study team (see safety oversight below) or whether these can be reviewed at quarterly meetings. SAEs that are deemed unrelated or not likely related to the study interventions will be recorded on CRFs, will be reported to IRB and DSMB within 3 days of their designation as such and will be reviewed at quarterly DSMB safety meetings.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UPreport form. It is the site investigator's responsibility to report UPs to their IRB and notify the DSMB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB projectnumber;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, oroutcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 3 days the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 3 days of the investigator becoming aware of the problem.

8.4.4 Reporting of Pregnancy

If any pregnancy occurs in a study subject, the PI will be notified immediately and the IRB will be notified within 3 days of discovery of the pregnancy. No data regarding safety or efficacy of Mavyret in pregnant women are available. Standard of care medications utilized for lung transplant recipients have known contraindications in pregnancies therefore any pregnancies will need to be managed as per standard of care with the lung transplant team. Counseling of pregnant subjects with regard to the risks of continuing versus discontinuing Mavyret will occur with patients once counseling with regard to the contraindications of the standard of care transplant medications has occurred.

8.5 Study Halting Rules

Further enrollment of study subjects will be halted under the following conditions:

- Any patient death occurs and is deemed related to the intervention
- Any SAE deemed related to acute HCV infection occurs
- Any SAE deemed related to Mavyret occurs

The PI will inform the IRB and the DSMB within 24 hours of any of these events. The DSMB and study team will convene an emergency meeting as described below. The DSMB will provide recommendations for proceeding with any further enrollment. Patients who are already enrolled and receiving Mavyret

treatment will continue to receive treatment unless the DSMB determines that an alternate course of therapy should be pursued for already-enrolled subjects.

8.6 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Safety oversight will be under the direction of a DSMB. This DSMB committee for this study will be comprised of individuals with expertise in transplantation, hepatology, infectious diseases and the treatment of hepatitis C, and ethics. These individuals will be:

Rebecca Pellett Madan (DSMB Chair) –Pediatric Infectious Disease Arthur Caplan, PhD – Expert in Medical Ethics

Vasishta Tatapudi, MD – Transplant Nephrologist
Shari B. Brosnahan, MD – Pulmonologist
Nancy Amoroso, MD – Pulmonologist
Sonja Olsen, MD – Hepatologist

The DSMB Charter with specific outlines of DSMB roles and responsibilities is uploaded as a separate attachment in Research Navigator. The DSMB will be notified of all AEs and SAEs as outlined above in 8.4.1 and 8.4.2. Regular meetings of the DSMB and the study team will occur on a quarterly basis to review non-emergent AEs and SAEs.The minimum group required to constitute an adequate DSMB-study team meeting will be (either in person or by teleconference): at least 4 of the DSMB members listed above, the PI, and at least one coinvestigator. At quarterly meetings the DSMB will evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study.

The DSMB and study team will meet on an emergency basis in the following instances:

- Any SAE occurs that is unexpected and deemed related to the study intervention
- Any unanticipated problem occurs that is both serious and deemed related to the study
- intervention
- Any treatment failure occurs or drug resistant HCV strain is identified, and a rescue plan with
- alternate therapy is required

Emergency meetings will occur within one business day of the above-described event occurring or being recognized. Any event that prompts an emergency DSMB-study team meeting will be reported to the IRB within 24 hours of the event occurring or being recognized.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

As this is a single-arm observational study, no SAP will apply.

10.2 Statistical Hypotheses

We hypothesize that 100% of patients who develop HCV viremia will achieve SVR after completing an 8-week course of Mavyret treatment.

10.3 Analysis Datasets

Subjects will be entered into a study subject dataset which includes de-identified information. This will include: donor and recipient demographic data, donor HCV RNA quantitative (PCR), serology, and genotyping information, and results of all recipient HCV RNA quantitative (PCR) , serologic, and genotyping data obtained throughout the course of the study.

10.4 Description of Statistical Methods

Since the anticipated study population will be a small size, statistical analyses will be limited to descriptive statistics. For patients who develop post-transplant viremia we will be able to compare our HCV cure rates to those that are expected for patients who receive treatment with these agents for chronic HCV.

10.4.1 General Approach

The study design will be single arm, open label. Descriptive statistics will include:

- Incidence HCV viremia post-transplant (percentage)
- Time course of exposure to development of clinically detectable viremia in those who develop viremia (median time to viremia with standard deviations)
- Incidence of sustained clearance of HCV (cure) after treatment of viremia (percentage)

- Time course of clearance of viremia after treatment initiation (median time to clearance with standard deviations)
- Incidence of treatment failure/treatment resistant strains of HCV (percentage)
- Characterization of distribution of HCV genotypes in patients who develop viremia (percentages) Comparison of treatment failure rates to expected treatment failure rates for the treatments used (p value for significance will be set at $p<0.05$ and two-tailed t-test will beused)

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint will be percentage of patients with sustained virologic response after treatment for HCV after lung transplant.

We expect that 100% of patients who are treated will achieve SVR. SVR will be defined as the absence of detectable HCV RNA Quantitative (PCR) testing 3 months after the completion of the treatment course. Any failure of therapy will be considered significant and will result in the halting of further enrollment until further discussed by the safety monitors and the IRB.

10.4.3 Analysis of the Secondary Endpoint(s)

Secondary endpoint #1: 1-year patient survival rates in HCV negative lung recipients who receive a lung transplant from a HCV positive donor.
Patients will have regular follow-up as standard of care for all lung transplant recipients. Patients survival will be readily apparent. Furthermore, all deaths of transplant recipients are required to be reported to UNOS.

Secondary endpoint #2: Incidence of HCV viremia among HCV negative recipients who receive a lung transplant from a HCV positive donor.

We will be measuring serial HCV RNA Quantitative (PCR) and serologic testing for a minimum of 6-months post-transplant. A patient will be considered to be viremic when a post-transplant HCV RNA Quantitative (PCR) test is positive. The incidence of viremia will be calculated as a percentage of the patients transplanted with a HCV-positive donor who develop HCV viremia by RNA Quantitative (PCR) testing.

10.4.4 Adherence and Retention Analyses

Adherence to the protocol will be assessed by the study team in direct conversations with thepatients during routing visits, and will be assessed clinically by evaluation of HCV viral loads.

Clearance ofHCV will demonstrate adherence to the regimen. Failure to clear viremia will prompt more detailed direct patient inquiries regarding and will prompt an evaluation of possible treatment resistant strains of HCV as described elsewhere. A rescue course of therapy will be initiated under the direct guidance of a hepatologist and/or transplant infectious diseases specialist.

10.4.5 Baseline Descriptive Statistics

In this study, no designed comparison groups will exist.

10.4.6 Planned Interim Analysis

Interim analysis not applicable

10.4.6.1 Safety Review

Any patient death will result in halting of any further enrollment in the study and an assessment of

whether the death was related to HCV exposure, infection, or treatment. Even in the event of a patient death, currently enrolled patients who are actively being treated for HCV viremia and tolerating therapy will continue to receive therapy so as not to put them at risk for HCV infection and/or the development of resistance as a consequence of interrupted therapy. If the patient death is deemed related to a specific treatment agent, enrolled patients receiving that same agent will be switched to an alternative therapy.

For any patient who is found to experience a treatment, a formal Hepatology consultation will be obtained promptly, and rescue therapy with alternative agents will be initiated under Hepatologyguidance.

10.4.7 Multiple Comparison/Multiplicity

Not applicable.

10.4.8 Tabulation of Individual Response Data

Since this is a relatively small trial, individual participant data, in particular as pertains to the kinetics of the development and clearance of HCV viremia, will be evaluated.

10.5 Sample Size

20 patients are expected to enroll in this trial.
We expect that less approximately 70% of patients will develop evidence of HCV infection transmitted from the HCV-positive donor and will be treated for HCV infection. We expect that 100% of the patients who are treated for HCV viremia will achieve SVR.
This is a single-arm study with no comparison group. The power to detect a difference in observed versus expected depends upon the true efficacy of the therapy. The reported efficacy of the therapy is 98%. With an estimated 7 patients who will be treated, a single treatment failure will be regarded as a significant deviation from the expected outcome.

11 Source Documents and Access to Source Data/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. It is acceptable to use CRFs as source documents.

If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local andregulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The informed consent document to be used is submitted with this protocol.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB- approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality oftheir medical care will not be adversely affected if they decline to participate in this study.
A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented inthe subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.4 Participant and Data 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, byregulation, 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 scheduledstudy period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents.

This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internaluse during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified

by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data will be collected on CRFs and entered electronically into eCRFs in REDCap. The original CRFs will be provided for use as source documents and maintained for recording data for each participant enrolled

in the study. Data reported in the electronic CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be assimilated in the study subject binders. Clinical data will be entered directly from the source documents to electronic CRFs in REDCap.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the investigation is discontinued. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements.

The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, reported to the Monitoring committee and the IRB.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal

manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National

Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA. Study Finances

14.5 Funding Source

Medication costs for the study drug Mavyret will be paid by the Transplant Institute. Study specific laboratory testing will be limited to:

- Serial HCV PCR and serology testing which will be performed at a greater frequency than for standard of care following lung transplantation.
- Genotyping of donor HCV
- Genotyping of recipient HCV among those who develop viremia

The costs of these laboratory tests will be covered by the Transplant Institute.

All other medications and laboratory testing required for this study are routinely conducted as standard of care for all recipients of lung transplants and are not considered components of the study.

14.6 Costs to the Participant

Participants will not incur any costs associated with participating in this trial.

15 Study Administration

15.1 Study Leadership

The Principal Investigator will govern the conduct of the study. The PI, together with at least one coinvestigator will meet in person or by teleconference with the DSMB (at least 4 members) at least quarterly and documentation of the meeting will be maintained.

16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

17 References

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15. Gane, E., et al., *Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment.* N Engl J Med, 2017. **377**(15): p. 1448-1455.
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18 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments. Attached as uploads in the Research Navigator are:

- Sample Consent Form
- Pregnant Partner Consent form
- Pregnant Partner Contact Card
- Sample Willingness to Participate Form
- Sample Fact Sheet
- SOP for specimen handling
- Accreditation for the Transplant Laboratory
- Specimen collection and shipping instructions for Quest Laboratories

19 Schedule of Events: Surveillance post-transplant with an 8 weeks MAVYRET treatment phase included

Activity	Screening visit (POD-365 to -1)	SURVEILLANCE PHASE					
		POD0	**POW1** (+/- 2 day)	**POW2** (+/- 3 days)	**POW3** (+/- 3 days)	**POW4** (+/- 5 days)	**POW5** (+/- 5 days)
Study team procedures							
Acknowledgement of willingness to participate and provision of fact sheet	X						
Medical History		X					
Physical Exam		X					
Height		X					
Weight		X					
Vitals signs		X					
Review all donor and recipient inclusion/exclusion criteria		X					
Signing of informed consent		X					
Study specific interventions							
Lung transplant operation		X					
Mavyret treatment (Start and follow up)		X[1]					
Study specific laboratory tests							
Donor serum HCV genotyping		X					
Recipient serum HCV genotyping		Any time during the study (x1) once there is documentation of positive HCV RNA Quantitative (PCR)					
HCV RNA Quantitative (PCR)	X	X[2]	X	X	X	X	X
HCV serology (HCV Ab)	X	X[2]	X	X	X	X	X

X[1] Mavyret will be initiated post lung transplantation once a viral load is detected
X[2] If screening lab(s) specifically HCV RNA Quantitative (PCR) and HCV serology (HCV Ab) are performed 14 days or less prior to POD 0, those labs will not be repeated at the POD 0 timepoint.

Activity	SURVEILLANCE PHASE			POW9 (+/- 5 days)	POW10 (+/- 5 days)	POW11 (+/- 5 days)
	POW6 (+/- 5 days)	**POW7** (+/- 5 days)	**POW8** (+/- 5 days)			
Study team procedures						
Study specific interventions						
Mavyret treatment (Start and follow up)	X[1]					
Study specific laboratory tests						
Recipient serum HCV genotyping	Any time during the study (x1) once there is documentation of positive HCV RNA Quantitative (PCR)					
HCV RNA Quantitative (PCR)	X	X	X	X	X	X
HCV serology (HCV Ab)	X	X	X	X	X	X

Activity	POW12 (+/- 5 days)	POW 24 - Interim assessment visit (+/- 14 days)	POW 52 - Final assessment visit (+/- 14 days)
Study team procedures			
Mavyret treatment (Start and follow up)	X[1]		
Medical History			X
Physical Exam			X
Height			X
Weight			X
Vitals signs			X
Study specific laboratory tests			
Recipient serum HCV genotyping	Any time during the study (x1) once there is documentation of positive HCV RNA Quantitative (PCR)		
HCV RNA Quantitative (PCR)	X	X	X
HCV serology (HCV Ab)	X	X	X

X[1] Mavyret will be initiated post lung transplantation once a viral load is detected