THE ROLE OF C1 ESTERASE INHIBITOR IN ANTIBODY MEDIATED RENAL ALLOGRAFT REJECTION-AN OPEN LABEL, PHASE II, SINGLE-ARM, SINGLE CENTER TRIAL

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List of Abbreviations

Study Summary

Title	The role of C1 Esterase inhibitor in antibody mediated renal allograft rejection- an open label, Phase ii, single-arm, single center trial
Short Title	Berinert AMR trial
Protocol Number	s16-01851
Phase	Phase II
Methodology	Open label, single-arm
Study Duration	6 months
Study Center(s)	Single-center
Objectives	The primary objective will be measurement of clinical and histologic resolution refractory acute of antibody mediated rejection (AMR) of kidney transplant. The secondary objective will be to estimate graft survival and to characterize the development of transplant glomerulopathy (TG) in patients who receive Berinert for AMR.
Number of Subjects	Five
Diagnosis and Main Inclusion Criteria	Diagnosis: Antibody mediated rejection; Inclusion criteria: Patients with AMR that is refractory to standard therapy.
Study Product, Dose, Route, Regimen	C1 esterase inhibitor, Berinert, 25-50 units/kg, intravenous, 7 doses on days 1, 3, 5, 7, 9, 11, 13 and 50 units/kg twice weekly for a total study period of 6 months.
Duration of administration	6 months
Reference therapy	10 Historical controls with refractory AMR who received standard of care (SOC) therapy with a combination of any or all of the following therapies – Plasmapheresis, IVIG, Rituximab, pulse steroids, Thymoglobulin.
Statistical Methodology	The primary outcome measure will be clinical and histologic resolution of AMR. Time to event distributions will be estimated by using the Kaplan-Meier method. The significance will be evaluated by the log-rank test.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

Antibody mediated rejection (AMR) is a major risk factor for accelerated graft loss in recipients of kidney transplants. This type of rejection is associated with the presence of donor specific antibody (DSA) before a transplant or an anamnestic response usually in the first month after transplantation. If left untreated, the acute inflammation in AMR leads to transplant glomerulopathy (TG) characterized by interstitial fibrosis, tubular atrophy, and rapid graft failure. If treated promptly, however, renal allografts can be salvaged. The standard of care for treatment of AMR has been clearing donor specific antibodies by plasma exchange or immunomodulating with high dose IVIg and anti-CD20, but this process takes time and does nothing to minimize inflammation resulting from antibody that has already bound. The inflammation in AMR is known to be regulated by the complement system, and therefore complement inhibitors have been explored as a potential means by which to interrupt the antibody-mediated injury at the level of the target tissue. Studies from independent groups demonstrate that complement inhibition can be effective at salvaging kidneys after severe acute AMR. Chronic AMR from either preformed DSA de novo antibody occurring after the first 3 months post-transplant often does not respond to SOC therapy. These patients have a significantly reduced graft half-life. This is a significant unmet need. We hypothesized that C4d positive AMR recalcitrant to SOC treatment might benefit from the addition of a complement inhibitor as add-on therapy.

1.2 Investigational Agent

CLINICAL PHARMACOLOGY

Mechanism of Action
C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, alpha1-protease inhibitor, alpha2-antiplasmin, and heparin cofactor II. As with the other inhibitors in this group, C1 esterase inhibitor has an important inhibiting potential on several of the major cascade systems of the human body, including the complement system, the intrinsic coagulation (contact) system, the fibrinolytic system, and the coagulation cascade. Regulation of these systems is achieved through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation of both and consumption of the C1 esterase inhibitor. C1 esterase inhibitor, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1 esterase inhibitor is the only known inhibitor for the subcomponent of the complement component 1 (C1r), C1s, coagulation factor XIIa, and kallikrein. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade[1].

Pharmacodynamics and Pharmacokinetics in Hereditary Angioedema (HAE)
Onset of symptom relief: Median: 15 minutes per attack (for HAE).

Duration of action: Time to complete resolution of HAE symptoms: Median: 8.4 hours.

Half-life elimination: Children and Adolescents: 22 hours (range: 20 to 24 hours).

Adults (following a single dose): 22 hours (range: 17 to 24 hours)[2].

1.3 Preclinical Data

Xavier Tillou et al previously published a baboon model of preimmunization of prevention of acute antibody-mediated rejection by an early inhibition of the classical complement pathway using human recombinant C1-inhibitor. Baboons were immunized against peripheral blood mononuclear cells from allogeneic donors and, once a specific and stable immunization had been established, they received a kidney from the same donor. Rejection occurred at day 2 post-transplant in untreated presensitized recipients, with characteristic histological lesions and complement deposition. As recombinant human C1-inhibitor blocks in vitro cytotoxicity induced by donor-specific antibodies, other alloimmunized baboons received the drug thrice daily intravenously during the first 5 days after transplant. Rejection was prevented during this treatment but occurred after discontinuation of treatment. They showed that early blockade of complement activation by recombinant human C1-inhibitor can prevent acute antibody-mediated rejection in presensitized recipients[3].

1.3 Clinical Data to Date

Montgomery et al published a phase 2b, multicenter double-blind randomized placebo-controlled pilot study to evaluate the use of human plasma-derived C1 esterase inhibitor (C1 INH) as add-on therapy to standard of care for AMR. Eighteen patients received 20,000 units of C1 INH or placebo (C1 INH n = 9, placebo n = 9) in divided doses every other day for 2 weeks. No discontinuations, graft losses, deaths, or study drug-related serious adverse events occurred. While the study's primary end point, a difference between groups in day 20 pathology or graft survival, was not achieved, the C1 INH group demonstrated a trend toward sustained improvement in renal function. These finding suggest that C1 INH may be useful in the treatment of AMR[4].

1.4 Dose Rationale

The dosing that we propose to use in this study is based on the regimen employed in the study by Montgomery that is quoted in the section above. In that study patients received C1 INH every other day for 2 weeks (total of seven doses) as adjunct therapy to standard of care (SOC) with plasmapheresis(PP), IVIg, and/or anti-CD20 therapy (Rituximab). Based on PK modeling in HAE patients and assuming that AMR patients have ongoing C1 INH consumption, the goal was to aim for twice physiological C1 INH levels by dosing patients with an intravenous infusion of 5000 U C1 INH (maximum of 100 U/kg) day 1 after the diagnosis of AMR, followed by 2500 U C1 INH (maximum of 50 U/kg) or placebo on days 3, 5, 7, 9, 11, and 13. Most patients in this study also received PP every other day with one volume exchange replaced with albumin and crystalloid in most cases or fresh frozen plasma when indicated by coagulation studies at the time of an invasive procedure. We propose a similar dosing regimen for this open-label study.

1.5 Research Risks & Benefits

1.5.1 Risk of Study Drug

Risk of Study Drug

Adverse Reactions
Frequency >10%:
Headache, Nausea

Frequency 1% to 10%:
Dizziness, itching, skin rash, abdominal pain, altered sensation of taste, vomiting, dry mouth, fungal infection (vulvovaginal), flu-like symptoms, nasopharyngitis, upper respiratory tract infection, fever, infusion-related reaction.

Frequency <1% (Limited to important or life-threatening):

Anaphylaxis (severe allergic reaction), cerebrovascular accident (stroke), chest pain, deep vein thrombosis(clot in vein), erythema(redness) at injection site, hypersensitivity reaction (allergic reaction), migraine, pain at injection site, pain (not otherwise specified), shock (severe blood pressure instability), swelling, transient ischemic attacks (mini stroke).

We hope to prevent these aforementioned allergic reactions by pre medicating patients with antihistamines and low dose steroids prior to study drug infusion.

Patients at greater than average risk for thrombotic events will be excluded from the study.

All patients will receive prophylaxis for fungal infections and PCP pneumonia.

1.5.2 Other Risks of Study Participation

The primary risk, beyond study drug exposure, will be lack of efficacy of the drug and loss of the kidney transplant due to uncontrolled antibody mediated rejection. We plan to minimize this risk by continuing all standard of care therapy in addition to the study drug. This includes any or all of plasmapheresis, IVIG, rituximab, splenectomy.

1.5.3 Potential benefits

Untreated or inadequately treated antibody mediated rejection can lead to failure of the kidney transplant and necessitate initiation or resumption of dialysis. Study subjects who receive Berinert may experience an improvement in their antibody mediated rejection of kidney transplant. This could salvage the kidney transplant and preclude all the risks associated with dialysis.

2 Study Objectives

The primary objective will to assess the efficacy of C1 inhibitor, Berinert in inducing clinical and histologic resolution refractory acute of antibody mediated rejection (AMR) of kidney.

The secondary objective will be to estimate the glomerular filtration rate, six month graft survival, to characterize incidence of transplant glomerulopathy (TG) and to assess the safety and tolerability of the proposed regimen of C1 inhibitor.

A clinical investigation of a marketed drug is exempt from the IND requirements since all of the following criteria for an exemption in § 312.2(b) are met:
• The drug product is lawfully marketed in the United States.
• The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
• In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
• The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).

3 Study Design

3.1 General Design

- Phase II, open label, single-arm study.
- Expected duration of subject participation-6 months.
- As part of the study, patients will undergo 7 sessions of plasmapheresis. After each session of plasmapheresis, the patients will receive IVIg (100mg/kg) and the study drug, Berinert (50 units/kg

after the first and final sessions of plasmapheresis and 25 units/kg after the other sessions). Subsequently, subjects will receive Berinert 50 units/kg twice weekly for 5 additional months. The patients will also receive IVIg (2gm/kg) monthly for the subsequent 5 months. The patients will undergo a biopsy of the kidney transplant 21 days after the initiation of the study. If the biopsy shows persistent AMR, the patients will receive IVIg (2gm/kg) and Rituximab (375mg/m2), as per standard of care. Blood will be drawn for laboratory testing prior to every session of plasmapheresis and at periodic intervals thereafter as part of the study. Patients will be required to have a follow up clinic visit every 14 days for the first 2 months of the study period and monthly for the remainder of the study period.

3.2 Primary Study Endpoints

Clinical and histologic resolution of acute AMR of the transplanted kidney will be the primary endpoint. Clinical resolution will be defined as return of serum creatinine to within 150% of baseline serum creatinine level. Histologically, AMR will be defined by the Banff 2013 criteria for renal allograft pathology. Histologic resolution will be defined by absence of AMR by the same criteria.

3.3 Secondary Study Endpoints

Estimated glomerular filtration rate (eGFR by MDRD 6 equation), overall patient and graft survival, death censored graft survival, incidence of transplant glomerulopathy and a composite score of chronic pathologic lesions severity as defined by Banff 2013 criteria will be assessed as secondary end points.

3.4 Primary Safety Endpoints

Incidence of minor and serious adverse events will be recorded as safety measures and will be included as primary safety study endpoints.

4 Subject Selection and Withdrawal

Inclusion Criteria

- Living or deceased donor kidney transplant recipients at least 18 years of age.
- Both male and female patients are eligible for enrollment.
- Weight ≥50 kg.
- Biopsy-proved AMR as defined by the Banff 2013 classification of renal allograft pathology that has not responded to standard of care therapy including any or all of the following – intravenous steroids, thymogobulin, plasmapheresis, IVIg, Rituximab.
- All episodes of antibody mediated rejection should have occurred more than three months after transplantation.
- Patients may have blood type incompatibility with their donor, HLA incompatibility or both.
- Subjects should be capable of giving informed consent.

Exclusion Criteria

- Pathologic findings on kidney allograft biopsy with Banff classification ≥2 for arteriosclerosis, interstitial fibrosis, tubular atrophy.
- Confounding surgical or medical condition.
- Concurrent infection causing hemodynamic compromise.
- A history of abnormal bleeding, clotting, or any coagulopathy (excluding a history of clotted hemodialysis access or superficial thrombophlebitis in the absence of medically confirmed coagulopathy).
- A white blood cell count $<0.5 \times 10^9$/L or $>20 \times 10^9$/L or a platelet count $<25 \times 10^9$/L or $>600 \times 10^9$/L within 48 h before dosing with study drug.
- Pregnant or breastfeeding women.

- Patients who received any C1 INH (plasma-derived or recombinant), eculizumab, ecallantide, bortezomib within 1 month before the first dose of study drug.

4.1 Subject Recruitment and Screening

Subjects will be recruited from investigator or sub-investigator clinical practices. Patients who meet the inclusion criteria detailed above will be recruited for the study.

Subjects 18 years of age or older can be included. The study is open to male and female subjects and individuals of all races and ethnic groups.

Kidney transplant recipients who are being followed at NYU transplant institute in the practice of the primary investigator or one of the sub-investigators will be screened for the study. Those that meet the inclusion criteria and do not meet any of the exclusion criteria will be recruited to the study. The consent will be obtained from the study subjects by the primary investigator or one of the sub-investigators. Informed consent will be obtained either at the transplant ambulatory care clinic or at Tisch Hospital. The subjects will be given ample opportunity to peruse the informed consent documents. Any and all questions that the subjects may have will be addressed by the investigators. The subjects are free to decline their consent to participate in the study. Once the consent document is signed by the subject, it will be filed in the clinical charts. It will also be scanned into the subject's chart in the EPIC electronic medical records and be clearly labeled for identification as a research study consent document.

The following precautions will be observed to protect the privacy of the subjects:

• The consent will be obtained at the NYU transplant institute ambulatory care clinics or at the inpatient service of NYU Langone Medical Center's Tisch Hospital.
• The subjects will be asked to provide their name, age and medical history.
• Patient specific information will be accessible only the primary investigator, sub investigators, study coordinator and the study statistical analyst.

4.2 Early Withdrawal of Subjects

4.2.1 When and How to Withdraw Subjects

Subject may be withdrawn from the study prior to the expected completion if

- The subject withdraws consent.
- Violation of study protocol.
- Serious adverse events including but not limited to drug related serious systemic infections and thrombotic events.
- Failure of renal allograft due to progressive rejection or any other cause of renal allograft injury.

4.2.2 Data Collection and Follow-up for Withdrawn Subjects

This will be an intention to treat study and even though subjects may be withdrawn prematurely from the study. We will collect survival data on such subjects throughout the protocol defined follow-up period for that subject and if the subject is not lost to follow up, we will collect all primary efficacy and safety end point data as well as secondary end point data. If a subject withdraws consent to participate in the study, attempts will be made to obtain permission to record at least patient and graft survival data up to the protocol-described end of subject follow-up period. Attempts will be made to obtain at least patient and graft survival data on all subjects lost to follow-up. In order to consider a subject lost to follow up, the subject must not be reachable despite 6 phone calls to the subject over a period of 4 weeks in addition to phone 4 phone calls over a period of 2 weeks to any listed next-of-kin.

5 Study Drug

4.3 Description

C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins). As with the other inhibitors in this group, C1 esterase inhibitor has an important inhibiting potential on several of the major cascade systems of the human body, including the complement system and the fibrinolytic system. Berinert works by blocking the effects of complement protein, C1. C1 esterase inhibitors are approved for the treatment and prevention of attacks of hereditary angioedema by the FDA. The complement system is a group of proteins that are normally present in human blood. These proteins play an important role in immunity against infectious disease. However, they also participate in rejection of transplanted organs. During rejection of a kidney transplant, activation of the complement system leads to injury and if insufficiently treated, ultimately to failure of the transplant. Therefore, inhibiting C1 is expected to prevent ongoing injury in kidney transplant that is being rejected and improve kidney function. Although the FDA has approved the use of C1 esterase inhibitors in hereditary angioedema, its use in individuals with antibody mediated rejection of the kidney transplant has not been approved by the FDA. A few patients with severe antibody mediated rejection have safely received this drug as part of research studies. However more evidence is needed before this drug can be approved by the FDA for routine use in patients with antibody mediated rejection. Therefore subjects that are consented and enrolled to be part of this study will receive C1 esterase inhibitor for an off label indication.

Each Berinert vial contains 500 IU of C1 esterase inhibitor as a lyophilized concentrate for reconstitution with 10 mL of Sterile Water for Injection, USP provided.

4.4 Treatment Regimen

C1 esterase inhibitor, Berinert, 25-50 units/kg, intravenous, 7 doses on days 1, 3, 5, 7, 9, 11, 13 and 50 units/kg twice weekly for a total study period of 6 months.

4.5 Method for Assigning Subjects to Treatment Groups

This is an open-label, single arm study. Successive patients at the investigator or the sub-investigator's practice who meet the inclusion criteria and are not ruled out by the exclusion criteria will be recruited for the study.

4.6 Preparation and Administration of Study Drug

The following are instructions provided by the drug manufacturer[1].

DOSAGE AND ADMINISTRATION

For Intravenous Use Only.

Berinert is provided as a freeze-dried powder for reconstitution with the Sterile Water for Injection, USP provided. Store the vial in the original carton in order to protect from light. Do not freeze.

Preparation and Handling

• Check the expiration date on the product vial label. Do not use beyond the expiration date.
• Prepare and administer using aseptic techniques.
• Use a silicone-free syringe for reconstitution and administration of Berinert.
• After reconstitution and prior to administration, inspect Berinert visually for particulate matter and discoloration. The reconstituted solution should be colorless, clear, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.
• The Berinert vial is for single use only. Berinert contains no preservative. Any product that has been reconstituted should be used promptly. The reconstituted solution must be used within 8 hours. Discard partially used vials.
• Do not freeze the reconstituted solution.

Reconstitution and Administration

Each Berinert vial containing 500 IU of C1 esterase inhibitor as a lyophilized concentrate for reconstitution with 10 mL of Sterile Water for Injection, USP provided.

4.7 Subject Compliance Monitoring

The study drug will be infused under direct supervision of a health care provider at Tisch Hospital, an NYU Langone Medical Center acute care facility or at the an NYU infusion center. This will allow subject compliance monitoring.

4.8 Prior and Concomitant Therapy

- The following concomitant medicines/therapies are permitted during the study – intravenous methylprednisolone, oral prednisone, thymoglobulin, plasmapheresis, IVIg and Rituximab. Standard of care maintenance immunosuppressive therapy will be continued during the course of the study – the drugs used may include Tacrolimus, Cyclosporine, Mycophenolate, Azathioprine Prednisone. Certain individuals may require surgical intervention in the form of splenectomy.
- Patients who received any C1 INH (plasma-derived or recombinant), eculizumab, ecallantide, or bortezomib within 1 month before the first dose of study drug are excluded for the study.

4.9 Packaging

• Berinert is supplied in a single-use vial.
• 500 IU vial of Berinert for reconstitution with 10 mL of Sterile Water for Injection, USP.
• The components used in the packaging for Berinert are latex-free.

Each product presentation includes a package insert and the following components:
• Berinert in a single-use vial
• 10 mL vial of Sterile Water for Injection
• Mix2Vial filter transfer set
• Alcohol swab

4.10 Blinding of Study Drug

This is an open label study and does not involve blinding.

4.11 Receiving, Storage, Dispensing and Return

4.11.1 Receipt of Drug Supplies

The drug will be shipped directly from the manufacturer, CSL Behring, and will be received by the investigational pharmacy at NYU. This is located at 160 East 34th Street, Room 610, New York, NY 10016.

4.11.2 Storage

• When stored at temperatures of 2-25°C (36-77°F), Berinert is stable for the period indicated by the expiration date on the carton and vial label (up to 30 months).
• Keep Berinert in its original carton until ready to use.
• Do not freeze.
• Protect from light.

4.11.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

4.11.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

5 Study Procedures

Visit 1: Day 1, 6 hours

- Blood draw: 3-4 teaspoons. Blood will be used to assess kidney function. Donor reactive antibody titers will be measured to assess the effectiveness of plasmapheresis to remove the pathogenic antibodies. Blood counts will be assessed to determine if they are at safe levels to allow performance of plasmapheresis.
- Plasmapheresis
- IVIg infusion
- Berinert infusion, 50 units/kg
- Measurement of vital signs

Visit 2: Day 3, 6 hours

- Blood draw: 3-4 teaspoons. Blood will be used to assess kidney function. Donor reactive antibody titers will be measured to assess the effectiveness of plasmapheresis to remove the pathogenic antibodies. Blood counts will be assessed to determine if they are at safe levels to allow performance of plasmapheresis.
- Plasmapheresis
- IVIg infusion
- Berinert infusion, 25 units/kg
- Measurement of vital signs

Visit 3: Day 5, visit duration 6 hours

- Blood draw: 3-4 teaspoons. Blood will be used to assess kidney function. Donor reactive antibody titers will be measured to assess the effectiveness of plasmapheresis to remove the pathogenic antibodies. Blood counts will be assessed to determine if they are at safe levels to allow performance of plasmapheresis.
- Plasmapheresis
- IVIg infusion
- Berinert infusion, 25 units/kg
- Measurement of vital signs

Visit 4: Day 7, visit duration 6 hours

- Blood draw: 3-4 teaspoons. Blood will be used to assess kidney function. Donor reactive antibody titers will be measured to assess the effectiveness of plasmapheresis to remove the pathogenic antibodies. Blood counts will be assessed to determine if they are at safe levels to allow performance of plasmapheresis.
- Plasmapheresis
- IVIg infusion
- Berinert infusion, 25 units/kg
- Measurement of vital signs

Visit 5: Day 9, visit duration 6 hours

- Blood draw: 3-4 teaspoons. Blood will be used to assess kidney function. Donor reactive antibody titers will be measured to assess the effectiveness of plasmapheresis to remove the pathogenic

antibodies. Blood counts will be assessed to determine if they are at safe levels to allow performance of plasmapheresis.
- Plasmapheresis
- IVIg infusion
- Berinert infusion, 25 units/kg
- Measurement of vital signs
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Visit 6: Day 11, visit duration 6 hours

- Blood draw: 3-4 teaspoons. Blood will be used to assess kidney function. Donor reactive antibody titers will be measured to assess the effectiveness of plasmapheresis to remove the pathogenic antibodies. Blood counts will be assessed to determine if they are at safe levels to allow performance of plasmapheresis.
- Plasmapheresis
- IVIg infusion
- Berinert infusion, 25 units/kg
- Measurement of vital signs

Visit 7: Day 13, visit duration 6 hours

- Blood draw: 3-4 teaspoons. Blood will be used to assess kidney function. Donor reactive antibody titers will be measured to assess the effectiveness of plasmapheresis to remove the pathogenic antibodies. Blood counts will be assessed to determine if they are at safe levels to allow performance of plasmapheresis.
- Plasmapheresis
- IVIg infusion
- Berinert infusion, 50 units/kg
- Measurement of vital signs

Visit 8: Day 21, visit duration 12 hours

- Ambulatory procedure – ultrasound guided kidney transplant biopsy
- Blood draw: 3-4 teaspoons. Blood will be used to assess kidney function. Donor reactive antibody titers will be measured to assess the effectiveness of plasmapheresis to remove the pathogenic antibodies. Blood counts and coagulation panel will be assessed to determine if they are at safe levels to allow performance of kidney transplant biopsy.

- Berinert 50 units/kg infusion at NYULMC infusion center twice weekly x 5 months.
- IVIg (2g/kg) infusion at NYULMC infusion center – once a month x 5 months.
- High dose IVIg(2gm/kg) and Rituximab 375 mg/m^2 if biopsy on day 21 shows persistent rejection.
- Weekly blood draw (3-4 teaspoons) x 1 month
- Blood draw (3-4 teaspoons)every month x 6 months

6 Statistical Plan

6.1 Sample Size Determination

We expect to enroll 5 patients in this study.

6.2 Statistical Methods

Clinical, serological and histological data will be compared between the two groups of AMR treatment (study arm and historical controls) using for categorical data, Fisher's exact test or Pearson's chi-square test. For continuous data, comparisons will be made using standard t -tests. Kaplan–Meier survival

estimates will be calculated for graft loss (dialysis or GFR ≤ 15 mL/min/1.73 m2). Graft survival curves were compared between the two groups using the log-rank test. Univariate analysis will be performed to evaluate the association of clinical and morphologic parameters with Outcome by standard techniques.

6.3 Subject Population(s) for Analysis

Data pertaining to any subject enrolled into the study that received at least one dose of study drug will be analyzed.

7 Safety and Adverse Events

7.1 Definitions

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).

Adverse Event
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. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- 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

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***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as six months following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved 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.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded

immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

7.3.1 Investigator reporting: notifying the study sponsor

The following describes events that must be reported to the study sponsor in an expedited fashion.

Initial Report: within 24 hours:
The following events must be reported to the study sponsor by telephone within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

Additionally, an FDA Form 3500A (MEDWATCH Form; see Attachment 2) must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the study site.

Sponsor:
Robert A. Montgomery, MD DPhil
530 First Avenue, HCC Suite 7A
New York, NY 10016
Office phone: 646-501-2418
Office fax: 646-501-2419

Follow-up report: within 48 hours:

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

7.3.2 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected**:** An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures**:** An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*

- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the Reportable New Information submission" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

7.4 Unblinding Procedures

This study will be an open label study and will not require unblinding since all enrolled patients and investigators are aware of the drug assignment.

7.5 Stopping Rules

The study will be stopped in the event of a patient death related to infusion of the study drug. The study will be stopped if serious adverse events occur in multiple patients without evidence of any benefit.

7.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. 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 (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

7.7 Confidentiality and HIPAA

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.
- All study subject related medical information will be extracted by review of NYU electronic medical records by the primary investigator and the sub-investigators. Pertinent data will entered and saved in excel spreadsheet format as password protected files. Only the primary investigator and the sub-investigators will have access to the data files. No other personnel will be granted access to the data files. De-identified data will be supplied to a study statistician who will analyze the data.

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.

7.8 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.

7.9 Case Report Forms

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.

7.10 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

8 Study Monitoring, Auditing, and Inspecting

8.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

The study will be conducted in accordance with a data safety monitoring plan that entails a systematic, periodic review of data pertaining to study subjects to ensure safe and proper conduct of the study. The data safety monitors will determine whether the study should continue with or without modifications or be stopped based on the outcome of the reviews and whether stopping criteria have been met.

The data safety monitoring plan is outlined below:
The following individuals will have the responsibility of monitoring the data

1. Study sub-investigator - Vasishta Tatapudi, MD,
   Clinical Instructor of Medicine, Division of Nephrology, Department of Medicine, New York University School of Medicine.
2. Study sub-investigator - Bonnie Lonze, MD PhD
   Assistant Professor, Department of Surgery, NYU Langone Transplant Institute.

Data safety monitoring reviews will be conducted every six months throughout the duration of the study and ad hoc reviews will be conducted in the event of occurrence of major unexpected events in the study population. The study period is defined as the period from the initiation of study drug in the first subject to the end of the study treatment follow-up in the last enrolled subject. For this study, the study treatment follow-up is defined as six months following the last administration of study treatment.
Following every semi-annual data safety monitoring review, the study-monitors with compile a report and submit it to the NYU IRB.
The following parameters will be scrutinized by the study monitors

1. Kidney allograft (transplant) loss or failure.
2. Patient/study subject death.
3. Incidence of serious adverse events including but not limited to major study drug related infusion reactions, infections, malignancies or hospitalizations.
4. Drop-out/withdrawal rate from the study.

Unanticipated problems and serious adverse events related to study participation will be reported to the study sponsor in an expedited fashion as outlined in the study protocol.
As required by federal regulations, unanticipated problems posing risks to subjects or others will be reported by investigators to their NYU IRB in a timely fashion as outlined in the study protocol.
In addition to abiding by the aforementioned processes, the study investigators with apply stopping rules as outlined in the study protocol. The study will be stopped in the event of a patient death related to infusion of the study drug. The study will be stopped if serious adverse events occur in multiple patients without evidence of any benefit.

8.2 Auditing and Inspecting

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.

9 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) or independent Ethics Committee (EC) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB/EC members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment 1 for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB/EC for the study. The formal consent of a subject, using the IRB/EC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

In addition, describe who will obtain consent and how the process of informed consent will be structured to be conducive to rational and thoughtful decision making by the subject/subject's legally authorized representative. If children and/ or cognitively impaired adults will be subjects, include a specific plan to assess comprehension during assent or the subject's agreement Individuals who are authorized to obtain consent must be listed on the protocol (or FDA form 1572) and consent form document. If necessary to use 'Auditor/Witness' and/or translator, these roles would be described in this section.
Include a plan for assessing subject capacity in cognitively impaired subjects. Describe the anticipated degree of impairment relative to their ability to consent and the anticipated direct benefits to the subjects.

10 Study Finances

10.1 Funding Source

There will be no monetary funding provided for this trial. CSL Behring will supply all drug for the study at no cost to the participants or the Institution. Subjects will not be paid for participating in the study nor will they be charged for participation.

10.2 Conflict 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 a properly constituted Conflict of Interest Committee 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 University conflict of interest policies.

11 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

12 References

1. http://www.fda.gov/downloads/%E2%80%A6/UCM186268.pdfAuthor, Title of work, periodical and associated information.
2. UpToDate®.
3. Tillou X, Poirier N, Le Bas-Bernardet S, et al. Recombinant human C1-inhibitor prevents acute antibody-mediated rejection in alloimmunized baboons. Kidney Int. 2010 Jul;78(2):152-9.
4. Montgomery RA, Orandi BJ, Racusen L et al. Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study. Am J Transplant. 2016 May 16.

13 Attachments

1. Consent From
2. FDA Form 3500A
3. Study Procedures Flowchart/Table

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Attachment: [3]

Activity	Screening	AMR treatment regimen [Day 1, 3, 5, 7, 9, 11, 13]	DSA screen [Day 1]	DSA screen [Day 13]	Kidney transplant biopsy [Day 21]	Ritux, IVIG for persistent rejection [Window – 1 week post biopsy]	C1 INH periodic infusion visit [Twice weekly, ending at 6 months]	Periodic blood draw [Monthly ending at 6 months]
Study team procedures								
Consent	X							
Medical History	X							
Physical Exam	X							
Height	X							
Weight	X							
Vitals signs	X	X	X	X	X	X		
Study drug dispensation		X					X	
Procedures/Infusions								
C1 INH		X					X	
Plasmapheresis		X						
IVIG 2g/kg						X		
IVIG 100 mg/kg		X						
Rituximab						X		
Kidney transplant biopsy					X			
Laboratory Assessments								
Chemistry panel	X	X				X		X
CBC with differential	X	X				X		X
Tacrolimus level		X	X	X	X	X		X
Urine protein/creatinine			X	X	X			X
Donor specific antibody (DSA) screening	X		X	X	X	X		
Imaging Assessments								
Ultrasound guidance for biopsy					X			