An Open-Label, Single-Arm, Multicenter Trial to Determine Safety and Efficacy of Eculizumab in the Prevention of Antibody Mediated rejection (AMR) in Sensitized Recipients of a Kidney Transplant from a Deceased Donor

Unique Protocol ID:	C10-002
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Date of Protocol:	08 October 2013

ECULIZUMAB
PROTOCOL NUMBER: C10-002

AN OPEN-LABEL, SINGLE-ARM, MULTICENTER TRIAL TO DETERMINE SAFETY AND EFFICACY OF ECULIZUMAB IN THE PREVENTION OF ANTIBODY MEDIATED REJECTION (AMR) IN SENSITIZED RECIPIENTS OF A KIDNEY TRANSPLANT FROM A DECEASED DONOR

FINAL VERSION 2.0
8 OCTOBER 2013
EUDRA CT NUMBER: 2010-019631-35

Version: 2.0

SPONSOR/MEDICAL MONITOR:

PPD

8 Oct 2013

Date

Alexion Pharmaceuticals, Inc.

352 Knotter Drive, Cheshire CT USA 06410

Telephone: PPD

Mobile: PPD

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CLINICAL LABORATORY:

Local investigative site laboratories will be used for safety, clinical assessment and treatment – Local Laboratories will be used for Entry Criteria.

EUROPE:

HLA Central Lab

PPD

Leiden University Medical Center

Department Immunohematology and Blood Transfusion

Eurotransplant Reference Laboratory

Albinusdreef 2

2333 ZA Leiden

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AUSTRALIA:

HLA Central lab

PPD

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Puget Sound Blood Center

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CENTRAL PATHOLOGY LABORATORY:

EUROPE:
Biomedical Systems
Waversesteenweg
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Telephone: PPD
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UNITED STATES:
Biomedical Systems
77 Progress Parkway
Building One
Maryland Heights, MO 63043
Telephone: PPD
Toll Free: PPD
Fax: PPD

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for eculizumab. I have read the protocol number C10-002 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	PPD	PPD Alexion International Av du Tribunal Fédéral 34 1005 Lausanne, Switzerland Tel: PPD Mobile: PPD Fax: PPD email: PPD
Clinical Study Leader	PPD	PPD Alexion Pharmaceuticals 352 Knotter Drive Cheshire CT USA 06410 Tel: PPD Mobile: PPD Fax: PPD email: PPD
Responsible Physician	PPD	PPD Alexion Pharmaceuticals 352 Knotter Drive Cheshire CT USA 06410 Tel: PPD Mobile: PPD Fax: PPD email: PPD
Drug Safety Physician	PPD	PPD Alexion Pharmaceuticals 352 Knotter Drive Cheshire CT USA 06410 Tel: PPD email: PPD
24-Hour Emergency Contact	24 Hour Telephone Number	PPD

2. SYNOPSIS

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc. 352 Knotter Drive Cheshire, CT 06410	
Name of Investigational Product: Eculizumab	
Name of Active Ingredient: h5G1.1-mAb	
Title of Study: An Open-Label, Single-Arm, Multicenter Trial to Determine Safety and Efficacy of Eculizumab in the Prevention of Antibody Mediated Rejection (AMR) in Sensitized Recipients of a Kidney Transplant from a Deceased Donor.	
Study Center(s): Approximately 20 kidney transplant centers in Europe and Australia.	
Principal Investigator: N/A **Investigators: N/A**	
Study Period (years): Estimated date first patient enrolled: 2nd Q2012 Estimated date last patient, first visit: 2nd Q2014 Estimated date last patient last visit: 2nd Q2015 Estimated date of last patient completing 3 year follow-up data collection: 2nd Q2017	**Phase of Development:** Phase II
Study Rationale: Over 25% of kidney transplant candidates have antibodies (are sensitized) to potential organ donors. As a result, antibody mediated rejection (AMR) has emerged as a significant clinical problem. Currently, the options to prevent AMR are limited and marginally successful. No products are approved for the treatment of AMR. Eculizumab, an inhibitor of C5, has been shown in hypothesis-generating studies to successfully reduce the incidence of AMR following kidney transplantation of sensitized living donor recipients. This phase II study is designed to assess the effect of eculizumab on the incidence of AMR in recipients who receive kidney allografts from deceased donors to whom they are sensitized.	
Primary Objective: To evaluate the safety and potential efficacy of eculizumab to prevent AMR in sensitized recipients of deceased donor kidney transplants.	
Study Design: Multicenter, open-label, Phase II, single-arm study.	
Methodology: Please see below in "Statistical Methods" section of the protocol synopsis.	
Number of Patients (planned): An estimated total of 80 patients will be enrolled in the study based on a single-arm study for the primary efficacy endpoint variable (See Statistical Methods). Recruitment will be closed latest by end of June 2014.	
Pre-screening, Screening and Enrollment: **Pre-screening:** Investigator will pre-screen highly sensitized patients on their transplant waiting list in order to identify those patients that may be suitable for this protocol**.** **Screening:** Patients who are candidates for deceased donor kidney transplantation and who are sensitized to their deceased donors and who meet the following baseline parameters for "sensitized" at time of screening will proceed to obtain the necessary blood draws to confirm candidacy:	

1. Sensitizing event (history of prior exposure to human leukocyte antigens [HLA]):
    a. Prior solid organ or tissue allograft
    b. Pregnancy
    c. Blood transfusion
    d. Prior exposure to donor's HLA

If history is consistent with donor specific antibody (DSA) exposure then:

2. Patients must have
    - Had an historical positive complement-dependent cytotoxicity (CDC). **Patient must be CDC negative at time of transplant.**

    and/or
    - Current B cell flow cytometric cross match (BFXM) or T cell flow cytometric cross match (TFXM) ≥ 300 and ≤ 500 mean channel shift (mcs). **No patient may have either a BFXM or TFXM > 500 mcs.**

    and/or
    - DSA identified by single antigen bead (SAB) assay (Luminex Labscreen assay) with a single MFI > 3000

    a. **The Local Laboratory specimens will be used to select patients for study entry**
    b. A duplicate set of samples will be analyzed at the Central HLA laboratory.

Enrollment: If all inclusion criteria and none of the exclusion criteria are met, patients will be vaccinated against *N. meningitidis*. Furthermore, all patients that were not already vaccinated within the time period of active coverage specified by the vaccine manufacturer must be re-vaccinated 30 days after initial vaccination. Tetravalent conjugated vaccines for *N. meningitidis* must be used. If patients were not already vaccinated at least 14 days prior to receiving the first dose of eculizumab, they will receive prophylactic treatment with an appropriate antibiotic for 14 days after the vaccination.

Diagnosis and Main Criteria for Inclusion:
All patients must adhere to the following inclusion/exclusion criteria:
Inclusion Criteria:

1. Male or female patients ≥ 18 years old
2. Patients with Stage V chronic kidney disease who will receive a kidney transplant from a deceased donor to whom they are sensitized
3. History of prior exposure to HLA:
    a. Prior solid organ or tissue allograft
    b. Pregnancy
    c. Blood transfusion
    d. Prior exposure to specific donor's HLA
4. Historical positive CDC cross match **and/or** BFXM or TFXM ≥ 300 and ≤ 500mcs (no

patient may have a BFXM or TFXM > 500mcs) **and/or** DSA identified by single antigen bead (SAB) assay (Luminex Labscreen assay) with a single MFI > 3000 as determined by local laboratory.

5. Negative CDC at time of transplantation
6. Able to understand the informed consent form and willing to comply with study procedures
7. Female patients of child-bearing potential must have a negative pregnancy test (serum beta-hCG) and must be practicing an effective, reliable and medically approved contraceptive regimen while on eculizumab treatment and for up to 5 months following discontinuation of treatment

Exclusion Criteria:

1. Has received treatment with eculizumab at any time prior to enrolling in this study
2. ABO incompatible with deceased donor
3. History of severe cardiac disease (e.g., New York Heart Association [NYHA] Functional Class III or IV, myocardial infarction ≤ 6 months of enrollment, ventricular tachyarrhythmias requiring ongoing treatment, unstable angina or other significant cardiovascular diseases)
4. Prior splenectomy
5. Has a known bleeding disorder
6. Has any active bacterial or other infection which is clinically significant in the opinion of the Investigator and is a contraindication to transplantation
7. Has participated in any other investigational drug study or was exposed to an investigational drug or device within 30 days of screening
8. Has received rituximab (Mabthera®) ≤ 3 months prior to screening
9. Has received bortezomib (Velcade®) ≤ 3 months prior to screening
10. Has received alemtuzumab (Campath®) ≤ 6 months prior to screening
11. Hypersensitivity to murine proteins or to one of the product excipients
12. History of illicit drug use or alcohol abuse within the previous year
13. Unresolved meningococcal disease
14. Pregnancy or Lactation
15. Current cancer or a history of cancer within the 5 years prior to study entry, with the exception of patients who have successfully treated nonmetastatic basal or squamous cell carcinoma of the skin; carcinoma in situ of the cervix; or breast carcinoma in situ
16. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the study, poses an added risk for the patient, or confounds the assessment of the patient
17. Active infection with Hepatitis B (HBV), Hepatitis C (HCV) or human immunodeficiency virus (HIV)

Prohibited Medications/Treatments:

- Use of alemtuzumab (Campath®) ≤ 6 months prior to screening and post-transplantation during the study
- Use of basiliximab (Simulect®) induction therapy during the study
- Use of bortezomib (Velcade®) ≤ 3 months prior to screening and post-transplantation during the study. Bortezomib may be used at the discretion of the

principal investigator for salvage therapy of AMR not responsive to first line therapy

- Use of rituximab (Mabthera®) ≤ 3 months prior to screening and post-transplantation during the study. Rituximab may be used at the discretion of the principal investigator for salvage therapy of AMR not responsive to first line therapy
- Use of Immunoadsorption therapy at any time (in place of plasmapheresis)
- **Use of prophylactic PP or IVIg during the first 9 weeks post-transplantation**

Investigational Product, Dosage and Mode of Administration:
Eculizumab treatment will start during the transplantation procedure and continue per the following regimen:

- Eculizumab 1200 mg (4 vials) administered intravenously (IV) over 25 to 45 minutes approximately 1 hour prior to kidney allograft reperfusion (Day 0)
- Eculizumab 900 mg (3 vials) administered IV over 25 to 45 minutes on the following post-transplantation days:
  - Day 1
  - Day 7
  - Day 14 (± 2 days)
  - Day 21 (± 2 days)
  - Day 28 (± 2 days)
- Eculizumab 1200 mg (4 vials) administered IV over 25 to 45 minutes at:
  - Week 5 (± 2 days)
  - Week 7 (± 2 days)
  - Week 9 (± 2 days)

PP and/or IVIg may be used only to treat biopsy proven AMR. In this setting the study drug should continue to be administered per the guidelines below in the sections on **Treatment of AMR During the Treatment Period** or **Treatment of AMR after the Week 9 Treatment Period.**

Duration of Treatment:
Patients will be screened and enrolled within 24 hours prior to transplantation and will be followed for primary and secondary endpoints to Month 12 post-transplantation, and for DSA, kidney function and patient and graft survival up to Month 36 post-transplantation.

All patients will receive study drug for 9 weeks post-transplantation.

Post-transplantation Immunosuppression and Concomitant Medications:
Induction Therapy:

- Thymoglobulin (1.5 mg/kg x 4 doses [6 mg/kg recommended, may use up to 7.5 mg/kg])

Maintenance Immunosuppression:

- Tacrolimus
  - Maintain trough levels at 4 to11 ng/ml for Months 1 through 12
  - No calcineurin inhibitor avoidance or withdrawal protocols allowed
- Mycophenolate mofetil (MMF; Cellcept®)/Enteric-coated mycophenolic acid (EC-MPA; Myfortic®)
  - MMF: 1 gram BID (may titrate down or alter dosing schedule for patient intolerance)
  - EC-MPA: 720 mg BID (may titrate down or alter dosing schedule for patient intolerance)
  - Generic formulations of the above are acceptable for purposes of the study
- Prednisone initially per SOC at the transplant center and tapered to 5 mg daily by 3 months post-transplantation
  - No steroid avoidance or withdrawal protocols allowed

Concomitant and Prophylactic Medications: All concomitant medications should be administered to all patients according to standard institutional protocols and applied uniformly to all patients. Examples of these medications include but are not restricted to:

- Cytomegalovirus (CMV) prophylaxis
- Pneumocystis *carinii/jiroveci* pneumonia (PCP) prophylaxis
- Antifungal prophylaxis

Induction, maintenance immunosuppressive, and prophylactic therapies should be used uniformly across all centers.

DSA and Cell-based Crossmatch Evaluations:
Patients will undergo routine post-transplantation monitoring for circulating DSA and cell-based cross match (XM) as follows:

- Routine monitoring of DSA (Luminex LabScreen) and cell-based XM's which include BFXM and TFXM tests will be performed by the Central Laboratory at Days 0, 1, 7, 14, 21, 28, Week 9, and Months 3, 6 and 12
  - DSA, BFXM and TFXM tests will also be collected at Month 36, but are not to be included in the primary efficacy analysis. They will be sent to the Central Laboratory and used for purposes of long term follow up only
- Duplicate samples will be sent to the transplant center's Local Laboratory for DSA and/or cell-based XMs to facilitate patient management. **The Central Laboratory data will not be used for patient management**
- Interim samples for patient management will be analyzed at the transplant center's HLA Local Laboratory and may include any of the following tests: DSA, CDC, BFXM, and TFXM. **Duplicate samples are not required for the Central**

Laboratory
Kidney Allograft Biopsy Evaluations: All protocol and "for cause" kidney biopsies will be processed and analyzed by the site's Local Pathology Laboratory. Processed slides and two paraffin embedded unstained slides will also be forwarded to the Central Pathology imaging center for review by independent pathologists. Additional details about processing and review of the slides for the Central Pathology Laboratory can be found in the Pathology Laboratory Manual. Kidney biopsies will be obtained under the following scenarios: 1. For-Cause Allograft Biopsy: Biopsy will be performed if there are clinical signs of allograft dysfunction based upon at least one of the following criteria, with or without elevation of DSA from baseline (day of transplant): a. A decrease in serum creatinine less than 10% per day in three consecutive days in the first week post-transplantation compared to the Day 0 immediate post-transplantation creatinine b. An increase in serum creatinine of ≥ 30% from nadir. Nadir is defined as the lowest serum creatinine within the first week post-transplantation c. Oliguria d. Clinical suspicion of AMR 2. Protocol Biopsy: Mandated biopsies will be performed: a. Post reperfusion (intra-operative) b. Day 14 post-transplantation c. Month 3 post-transplantation d. Month 12 post-transplantation e. Month 36 post-transplantation (for long term follow up only; will not be included in primary efficacy analysis)
Treatment of AMR During the Treatment Period Post-Transplantation: If the patient has a biopsy-proven diagnosis (from local pathologist) of clinically significant (elevated creatinine) AMR during the first 9 weeks post-transplantation, the patient will be considered a treatment failure (See Criteria for Evaluation Section below for biopsy criteria). AMR episodes will be treated according to local SOC protocols and at the Principal Investigators' discretion (with the exception of prohibited medications). If the patient receives PP for the treatment of AMR, then supplemental doses of eculizumab should be used as follows: • Eculizumab 600 mg (2 vials) will be given within 1 hour after the end of **each** PP session o This is in order to maintain levels between 50 and 100 μg/mL of eculizumab, as has been predicted based on empirical experience and pharmacokinetic-pharmacodynamic (PK-PD) modeling calculations for eculizumab under conditions of PP

- Doses will be given IV over 25-45 minutes
- AMR may be treated with eculizumab for at least 5 weeks or until the serum creatinine returns to within 10% of their pre-rejection baseline creatinine or until they achieve a new stable baseline serum creatinine defined as less than a 20% variation on three successive tests taken at least 24 hours apart. The maximum number of weeks that the patient will be treated with eculizumab for acute AMR is 9.

Treatment of AMR Occurring After the Week 9 Treatment Period:
AMR episodes occurring after Week 9 will be treated according to local SOC protocols and at the Principal Investigators' discretion (with the exception of prohibited medications). Eculizumab may be used to treat AMR.

If eculizumab is used to treat AMR, dosing will be **(weeks are calculated from the day of first dose of eculizumab after AMR diagnosis)**:

- Initial dose 900 mg (Day 1), if dosed within 7 days of last dose of eculizumab
- Initial dose 1200 mg (Day 1), if dosed after 7 days of last dose of eculizumab
- 900 mg weekly for 4 doses (Weeks 1, 2, 3, 4; ± 2 days), then;
- 1200 mg every other week at weeks 5, 7, and 9 (±2 days)
- AMR may be treated with eculizumab for at least 5 weeks or until the serum creatinine returns to within 10% of their pre-rejection baseline creatinine or until they achieve a new stable baseline serum creatinine defined as less than a 20% variation on three successive tests taken at least 24 hours apart. The maximum number of weeks that the patient will be treated with eculizumab for acute AMR is 9.

Treatment of Persistent DSA:
DSA will be analyzed both by central and local laboratory during treatment, at the end of the treatment period (Week 9) and at Months 3, 6, 12 and 36. Central Laboratory results at week 9 only will be provided to the local centers. If the recipient maintains a positive DSA and a positive BFXM and/or TFXM as measured by the central laboratory (week 9 result) then PP and/or IVIg may be used to lower the DSA as follows:

- PP and/or IVIg will be administered per the clinical judgment of the principal investigator.
- Supplementary eculizumab following PP may be administered during weeks 9 and10 only.
- Other medications such as rituximab and bortezomib are not allowed to treat persistent DSA.
- Serum samples will be submitted to the central lab for DSA and B/TFXM testing. Serum samples will be obtained prior to beginning PP, then weekly during PP (pre-PP sample) and one month following the conclusion of PP therapy.

Note: Eculizumab supplementation will not be allowed for treatment of persistent DSA that extends beyond the 10th postoperative week.

Treatment with Fresh Frozen Plasma:

If a patient receives FFP not associated with PP then the patients receiving eculizumab should receive a supplemental dose of eculizumab (600 mg) 1 hour prior to FFP administration.

Criteria for Evaluation:

Primary Analysis of Data

The primary analysis of all endpoints will occur after all patients have reached Month 12 post-transplantation. Patients will continue to be followed on Months 18, 24 and 36 for collection of additional follow up data on patient and graft survival, kidney disease and disease status.

Efficacy

Primary Endpoint:

The primary composite endpoint is the Week 9 post-transplantation treatment failure rate defined as the occurrence of 1) biopsy-proven AMR, 2) graft loss, 3) patient death, or 4) loss to follow up.

The diagnosis of AMR will be based on kidney allograft dysfunction and biopsy performed "for cause." The histological diagnosis will be based on Banff 2007 criteria for AMR as determined by the Central Pathology Laboratory. For this study only level II and level III AMR will be accepted as defined below:

Presence of circulating anti-donor specific antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):

- Banff 2007 Level II - Capillary and/or glomerular inflammation (ptc/g > 0) and/or thromboses
- Banff 2007 Level III - Arterial—v3

Secondary Endpoints:

1. Cumulative incidence of AMR between Week 9 and Month 12 post-transplantation (AMR of any grade that meets Banff 2007 criteria)
2. Treatment failure rate defined as the occurrence of 1) biopsy-proven AMR, 2) graft loss, 3) patient death, or 4) loss to follow-up at Month 12 post-transplantation
3. Graft and patient survival at Months 6 and 12 post-transplantation
4. Histological evidence of AMR on protocol biopsies without other clinical findings at Day 14, and Months 3 and 12 post-transplantation
5. Overall pathological changes, including chronic AMR, on protocol biopsies at Day 14, and Months 3 and 12 post-transplantation
6. Cumulative number of PP treatments at 12 months post-transplantation
7. Cumulative incidence of patients requiring splenectomy at 12 months post-transplantation

8. Incidence of delayed graft function (DGF) post-transplantation (defined as the requirement for dialysis within the first post-transplantation week for reasons other than post-operative hyperkalemia, acute pulmonary edema or fluid overload due to comorbid conditions)
9. Cumulative incidence and duration of dialysis between 7 days and 12 months post-transplantation
10. Number of days the serum creatinine is more than 30% above nadir following the diagnosis of AMR.
11. Proportion of patients with stable renal function between Week 4 and Month 12 post-transplantation as measured by:
    a. Estimated Glomerular Filtration Rate (calculated) by Modification of Diet in Renal Disease 7 (MDRD7) on at least 3 consecutive measurements taken at least 2 days apart while not on PP or dialysis that vary ≤ 20%
    b. Serum creatinine defined as the value on at least 3 consecutive measurements taken at least 2 days apart while not on PP or dialysis that vary ≤ 20%

Safety:
Safety endpoints will be evaluated at Week 9 and Month 12 post-transplantation and will include the following:

1. Adverse events (AEs) will be assigned Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and tabulated as the number and percent of patients experiencing an adverse event
2. Safety evaluations will consist of monitoring and recording all AEs, including serious adverse events (SAEs), the regular monitoring of hematology, blood chemistry and urine results, regular monitoring of vital signs, physical condition and body weight measurements
3. In addition to the above, the following specific safety evaluations will be performed:
    - Cumulative incidence of clinically significant infection (confirmed by culture, biopsy, genomic or serologic findings) that requires hospitalization or anti-infective treatment, or is otherwise deemed significant by the Principal Investigator
    - Cumulative incidence of CMV disease
    - Cumulative incidence of BK virus disease
    - Cumulative incidence of encapsulated bacterial infection
4. Cumulative incidence of PTLD (post-transplantation lymphoproliferative disease)
5. Cumulative incidence of malignancy
6. Cumulative incidence of biopsy-proven acute cellular rejection of any grade that meets Banff 2007 criteria
7. Proportion of patients that develop severe acute cellular rejection that do not respond to thymoglobulin or other lymphocyte depleting agents
8. Cumulative incidence of allograft loss for reasons other than AMR

9. Overall patient survival

Study Assessments:
The study protocol mandated visits subsequent to hospital discharge will be followed unless there is evidence of rejection, or other significant clinical events (serious adverse event [SAE] or meaningful changes in laboratory parameters).

- See below schedule of assessments in Tables 7, 8, 9, and 10.

Patients who discontinue from study drug will:

- Be monitored every 2 weeks for at least 2 months (total of 4 visits) following the final dose;
- Receive an abbreviated physical examination and routine blood draws for the standard care of their kidney transplant allograft every two weeks for at least 2 months.

Subsequent to the patient discontinuing and the above follow up visits for 2 months being completed the same events outlined for Month 12 in the Schedule of Assessment will be performed on the patient's last visit.

Statistical Methods:

Sample Size and Power Considerations:

Sample size and power considerations were based on the primary efficacy variable and a single-arm study with the following assumptions:

1. Composite endpoint true treatment failure rate at Week 9 post-transplantation with standard of care in the study population is, $\pi_0 = 40\%$
10. Composite endpoint treatment failure rate at Week 9 post-transplantation with eculizumab is, $\pi_1 = 20\%$
11. Null hypothesis, H_0: $\pi_1 = 40\%$
12. Alternative hypothesis, H_1: $\pi_1 \neq 40\%$
13. Type I error, $\alpha = 0.05$ (two-sided significance test)
14. Statistical test = Exact binomial test

An exact binomial test with a nominal 0.050 two-sided significance level will have >90% power to detect a difference between the null hypothesis proportion, π_1 of 0.400 and the alternative proportion, π_1, of 0.200 when the sample size is 80.

The primary efficacy variable is a binary outcome variable where patients meeting the composite endpoint definition will be considered treatment failures and all others will be considered treatment successes. The rate of treatment failure at 9 weeks post-transplantation in the eculizumab treated group will be calculated along with an exact 95% confidence interval (CI). Although this is a single-arm, phase II clinical study, test of the null hypothesis (the true rate of treatment failure with eculizumab is 40%) will be performed using the exact binomial

test. Results will be used to inform the design of a Phase III study.

Safety data will be summarized with frequency tables and will include hematology, coagulation, urinalysis, serum chemistry, vital signs, ECG, and AEs. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory data will be presented as shift tables with numerical values and toxicity grade.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ABO	A, B and O Blood Glycoproteins (Blood Type)
AE	Adverse Event
aHUS	Atypical Hemolytic Uremic Syndrome
ALT	Alanine aminotransferase (SGPT)
AMR	Antibody-Mediated Rejection
AP	Alkaline Phosphatase
AST	Aspartate aminotransferase (SGOT)
BFXM	B-Cell Cytometric Flow Crossmatch
BE	Bioequivalence
BID	Twice Daily
BK	BK Virus
BUN	Blood Urea Nitrogen
°C	Degrees Celsius
CBC	Complete Blood Count
CI	Confidence Interval
CDC	Complement-Dependent Cytotoxicity
CDRs	Complementarity Determining Regions
CMV	Cytomegalovirus
CRF	Case Report Form
CsA	Cyclosporine
CyP	Cyclophosphamide
DD	Deceased Donor
DGF	Delayed Graft Function
DMC	Data Monitoring Committee
DSA	Donor Specific Antibody
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease
°F	Degrees Fahrenheit
FCXM	Flow Cytometric Crossmatch
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
β-HCG	Beta-Human Chorionic Gonadotrophic Hormone
HBV	Hepatitis B Virus
HCT	Hematocrit
HCV	Hepatitis C Virus
HEENT	Head, Ears, Eyes, Nose, Throat
Hgb	Hemoglobin

HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IVIG	Intravenous Immune Globulin
kDa	Kilodalton
LD	Live Donor
LDH	Lactate Dehydrogenase
LF	Leflunomide
mAb	Monoclonal Antibody
MAC	Membrane Attack Complex
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCS	Mean Channel Shift
MCV	Mean Corpuscular Volume
MDRD7	Modification of Diet in Renal Disease 7
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean Fluorescence Intensity
MHC	Major Histocompatibility Complex
MMF	Mycophenolate Mofetil
PCP	Pneumocystis *carinii*/Pneumocystis *jiroveci* Pneumonia
PD	Pharmacodynamics
PK	Pharmacokinetics
Plts	Platelets
PP	Plasmapheresis
POD	Post-operative Day
PNH	Paroxysmal Nocturnal Hemoglobinuria
PRA	Percent Reactive Antibody
PT	Prothrombin Time
PTT/aPTT	Partial Thromboplastin Time/activated Partial Thromboplastin Time
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAB	Single-bead Antigen
SCr	Serum Creatinine
SOC	Standard of Care
TAC	Tacrolimus
TEAE	Treatment Emergent Adverse Event
TFXM	T-Cell Cytometric Flow Crossmatch
XM	Crossmatch
WBC	White Blood Cells

5. INTRODUCTION

5.1. Background Information and Scientific Rationale

5.1.1. Antibody Mediated Rejection

Over the past three decades, improvements in solid organ transplantation have paralleled advances in medical management, tissue typing, organ preservation and immunosuppression. During this time, the use of calcineurin inhibitors has focused attention on the role of T cells in allograft rejection; a form of rejection known as acute cellular rejection. More recently, antibody mediated rejection (AMR), a rejection reaction that results from the action of antibodies on the allograft has gained attention as a significant obstacle to successful kidney transplantation. This form of rejection causes severe and rapid dysfunction and loss of allografts.[1-4]

The most common mechanism underlying AMR is an anamnestic response that originates from previous antigenic exposure. These donor specific antibody (DSA) responses are usually robust and result in the rapid production of high levels of DSA and acute allograft dysfunction.[5] The mechanism of injury in AMR involves antigens that initiate the production of DSAs resulting in antigen-antibody interactions, complement activation and inflammation, and the resultant donor tissue damage.[6]

The main target of DSA's is endothelial cells within the microcirculation of the donor organ. This leads to activation of the complement cascade which initiates injury to the capillaries. Complement activation leads to C4d deposition in the peritubular capillaries of the renal allograft.[7, 8] This C4d deposition is an important diagnostic criterion for the development of AMR.

The impact of AMR on graft survival is dramatic and continues long after the initial inflammatory condition has resolved as was recently demonstrated in a study by LeFaucheur and Glotz. In this single center study of a large cohort of sensitized recipients, the investigators compared allograft survival for recipients successfully treated for AMR versus those that never experienced AMR.[9]

The effect of AMR on allograft survival, in spite of successful AMR treatment, is demonstrated by the data in Table 3 below. The data in this single center study of deceased donor kidney recipients, who were sensitized to their donors, compared the survival of the transplanted kidneys for those who experienced AMR to those who did not. The outcomes were independent of whether the recipients continued to have persistent DSA. The results strongly support the concept that prevention of the inflammatory lesion of AMR, rather than treatment intervention once AMR develops, is the key factor to transplantation across the humoral immune barrier.[9] All but two episodes of AMR occurred within six weeks, with most occurring within four weeks of transplantation, which is consistent with multiple reports in the literature by numerous investigators describing AMR as a very early clinical event.[10-12]

Table 3: Allograft Survival for DSA+ DD Kidney Transplant Recipients With and Without AMR

Time Point	Recipient Allograft Survival with and without AMR	
	AMR+ N=29	**AMR- N=54**
1 year	79.3%	88.6%
3 years	68.9%	88.6%
8 years	41.7%	71.8%

The key results from these additional reports are summarized in Table 4. Stegall, *et al.* described a series of 19 kidney transplant recipients who received kidney transplants following desensitization and who developed AMR. All occurrences of AMR occurred within the first six weeks and most within four weeks post-transplantation.[13] Montgomery and colleagues described another series of 62 patients in whom all instances of AMR occurred within the first 10 days post-transplantation.[10] Regardless of the clinical setting, a common theme is that most instances of AMR are reported to occur very early following transplantation.

Table 4: Publications on AMR in Kidney Transplantation

Author/year (reference)	Number of Patients	Time to Diagnosis of AMR
Stegall (2006)[13]	19	< 6 weeks
Montgomery (2004)[10]	62 (pediatric population)	< 10 days
Rostaing (2009)[14]	22	Mean 21 days
Faguer (2007)[15]	8	< 6weeks
Crespo (2001)[16]	18	< 22 days
White (2004)[17]	9	< 28 days
Braun (2004)[18]	1	Day 7
Han (2008)[19]	13	< 10 days
Muro (2005)[20]	1	Day 2
LeFaucheur (2010)[9]	29	< 6 weeks
Higgins (2009)[21]	36	< 40 days

Taken together, this clinical experience demonstrates that AMR is a lesion that occurs early after transplantation and points to the importance of prevention of the acute inflammatory lesion of AMR during the first month post-transplantation.

5.1.2. Role of Complement in AMR

AMR can result from uncontrolled complement mediated injury that is initiated when DSA binds to receptors on the donor organ blood vessel endothelium. This antibody-antigen interaction results in activation of the complement cascade with the resultant production of complement split products C5a and C5b. C5a is a potent anaphylotoxin and inflammatory mediator while C5b is a necessary component for formation of the C5b-9 terminal complement complex, also known as

the membrane attack complex. C5b-9 is an activator of leukocytes and vascular cells and stimulates the secretion of mediators from storage granules and the translocation of P-selectin from platelet α-granules to the plasma membrane. P-selectin initiates adhesion of monocytes and platelets to the vascular endothelium and serves as a co-stimulatory molecule for the production of inflammatory mediators. In addition, C5b-9-activated endothelial cells synthesize IL-8, tissue factor and monocyte chemotactic protein 1 (MCP-1), which is an important chemotactic factor in macrophage recruitment to sites of tissue injury.

Complement activation can be documented by measuring complement protein by-products. While some complement components bind to the antibody-antigen complex, others can be found in the local environment. For example, C4d, a stable complement component of the proximal portion of the complement cascade, can be localized by immunohistologic techniques in tissue specimens near sites of inflammation and is used as a marker for complement activation in allograft biopsy specimens.

5.2. Desensitization Protocols, Prophylaxis and Treatment for AMR

DSA reduction techniques (desensitization) are used to facilitate kidney transplantation for recipients who are sensitized to their donor organs by lowering the amount of circulating DSA. Extensive review of the literature reveals an array of techniques that include direct antibody removal by plasmapheresis (PP), immune modulation using intravenous immune globulins (IVIg), and attempts to deplete B cells using a variety of immunosuppressive agents. Of all of these modalities only PP assures immediate removal of DSA. However, PP does not result in long-term reduction in HLA antibody. Unless a transplant is received within several days of 'desensitization' DSA typically return to pre-desensitization levels. As there is no way to predict when a deceased donor organ will become available, PP is rarely part of the desensitization protocol for patients on the organ donor waiting list.[22]

There is no general consensus with regard to quantitative levels of DSA that adequately define the risk of developing AMR for any given patient but experience has demonstrated that increasing levels of DSA correlated directly with the risk to develop AMR. Lefaucher and Glotz recently reported their single center experience transplanting DSA positive, CDC crossmatch negative recipients. In that study they examined the relationship between the levels of DSA as detected by the Luminex single antigen bead technique and development of AMR. These investigators found that in recipients with MFI < 3000 the prevalence of AMR was 18.7% and while it was 36.4% and 51.3% respectively for those patients with MFI between 3000 and 6000 and > 6000. They also observed that kidneys having AMR had significantly shorter graft survival than did those which did not experience AMR (9).

Recently Stegall and colleagues reported the Mayo Clinic experience using eculizumab to prevent AMR in living kidney donor recipients who were sensitized to their donor kidneys. They found that eculizumab reduced the occurrence of AMR in a cohort of sensitized living donors to 7.7% compared to 41.2% in a historical control group which had a similar degree of immunologic risk. In the proposed trial eculizumab will be used to prevent AMR in a cohort of sensitized recipients of deceased donor kidneys who have a similar degree of immunologic risk to their donor organs as described in the Mayo Clinic study.[23]

When AMR occurs it must be treated as early as possible to avoid irreversible damage to or loss of the transplant. Today the standard of care for AMR is plasmapheresis (PP) with or without IVIg.(57,58,59)

If AMR occurs in the proposed study group it will be treated initially using the SOC therapy, PP and/or IVIg. If in the judgment of the Principal Investigator SOC therapy fails to successfully treat the AMR episode then the PI may elect to also use eculizumab or other putative therapy.

5.3. Unmet Clinical Need

Solid organ transplantation remains the most effective form of therapy for treatment of patients with end-stage kidney disease.[24] In 2009, there were over 50,000 patients in Europe on the waiting list for kidney transplant; only 1/3 of these patients received a transplant.[25] While the demand for kidneys has continued to rise, the availability of organs has remained roughly the same over the last decade. Two major impediments to successful kidney transplantation are the shortage of available organs and the number of sensitized recipients.

Nearly a third of potential recipients on the Organ Procurement and Transplantation Network – UNOS renal transplant waiting-list are considered sensitized (defined as a Panel Reactive Antibody [PRA] score > 10%).[25] These patients have pre-formed antibodies against an array of donor-specific human leukocyte antigens (HLA) or DSAs. Sensitization can occur from previous exposure to donor antigens through blood transfusions, pregnancy, and/or prior organ transplantation.[5] The presence of DSAs can lead to AMR and three types have been reported:

- Hyperacute rejection which presents within minutes of revascularization;
- AMR which presents within days to weeks after transplantation;[26], [11]
- Chronic antibody mediated rejection which occurs following the “de novo” generation of donor-specific antibodies and generally occurs several months to years from the time of transplant.[7]

The success rate for sensitized renal transplant recipients treated with newer desensitization approaches including IVIg and plasmapheresis have reported early success rates over 90% at one year following transplant in several centers.[10, 11, 27] However, AMR remains an important issue. Published data suggests that in patients who developed AMR, long-term allograft function and survival are impaired.[5] For example, Lederer, *et al*. showed that when AMR occurred early in the post-transplantation period, there was a reduction in the half-life of the allograft of up to 50% compared to recipients who did not experience an early AMR.[28] This was substantiated in other clinical studies which showed that positive crossmatch patients developed AMR had more histological evidence of transplant glomerulopathy at 1 year than those who had no AMR.[29] Hence, the prevention of AMR is critically important in attaining the best possible long-term results in sensitized renal transplant patients.

To date, there are no approved therapeutic agents indicated for the prevention of AMR. This development program is specifically designed to assess the efficacy and safety of eculizumab for prevention of AMR in recipients who are pre-sensitized to their deceased donor kidneys.

5.4. Description of Eculizumab

Eculizumab (h5G1.1-mAb solution for infusion) is a humanized monoclonal antibody with binding specificity uniquely specific for the human complement C5 protein. Comprised of 1324 amino acids with a molecular mass of approximately 148 kDa, eculizumab was derived from a murine monoclonal antibody (m5G1.1-mAb) that recognizes the human complement component C5.

Humanization of the antibody was achieved by grafting the murine antibody's complementarity determining regions (CDRs) into human antibody-derived variable heavy and light chain framework regions. The constant regions of h5G1.1-mAb include the human kappa light chain and a hybrid IgG human heavy chain. The heavy chain CH1 domain, hinge region and the first 29 amino acids of the CH2 domain were derived from human IgG2, while the remainder of the CH2 domain and the CH3 domain originated from human IgG4.

Approved by the FDA and European Medicines Agency (EMA) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), eculizumab is also being studied in other complement-mediated disorders.[30-32]

5.5. Summary of Pre-Clinical Experience

Eculizumab is uniquely specific for human C5 and does not cross-react with C5 from any other species. Therefore, in order to evaluate anti-C5 treatment in a mouse allotransplant model, the anti-mouse C5 monoclonal antibody BB5.1 was used. The ability of anti-C5 mAb in preventing allograft rejection, either alone or in combination with other immunosuppressants, was evaluated using major histocompatability complex (MHC)-mismatched C3H-to-BALB/c transplant mouse models in which allografts develop typical features of AMR, characterized by substantial intragraft deposition of antibodies and complement, and high circulating anti-donor antibodies.[33-35]

Three different studies were performed to assess graft survival:

- hearts from C3H mice transplanted heterotopically into non-presensitized BALB/c mice;[35]
- hearts from C3H mice transplanted heterotopically into BALB/c mice that were presensitized by receiving a skin graft from C3H mice one week prior to transplant;[34] and
- kidneys from C3H mice transplanted into BALB/c mice that were presensitized by receiving a skin graft from C3H mice one week prior to kidney transplant[33]

Graft survival time was assessed and histopathological and immunohistochemical analyses were performed to characterize graft rejection when present. Table 5 summarizes the results of these experiments.

Table 5: Summary of Murine Transplant Experiments

Study	Treatment	N	Mean Graft Survival Days ± SD	Type of Rejection
1. Non-presensitized	Untreated	8	8.0 ± 0.6	AMR

MHC-mismatched cardiac allograft	Control mAb	8	8.2 ± 0.8	AMR
	CsA	8	15.5 ± 1.1	AMR
	Control mAb + CsA	4	16.3 ± 1.0	AMR
	Anti-C5 mAb	8	8.3 ± 0.5	ACR
	CsA + Anti-C5 mAb (BB5.1)	8	> 100*	na
2. Presensitized MHC-mismatched cardiac allograft	Untreated	8	3.1 ± 0.4	AMR
	CsA	8	3.0 ± 0.0	AMR
	CyP	8	3.3 ± 0.5	AMR
	CsA + CyP	8	3.5 ± 0.6	AMR
	Anti-C5mAb	8	3.5 ± 0.5	AMR
	Anti-C5mAb + CsA	8	11.9 ± 1.8	AMR
	Anti-C5mAb + CyP	9	3.2 ± 0.4	AMR
	Anti-C5mAb + CsA + CyP	8	> 100*	na
3. Presensitized MHC-mismatched kidney allograft	Untreated	5	8.5 ± 1.3	AMR + CMR
	CsA	5	9.3 ± 2.5	AMR + CMR
	LF	5	6 ± 1.0	AMR + CMR
	CsA + LF	5	11.7 ± 2.1	AMR + CMR
	Anti-C5mAb	5	7.0 ± 1.0	AMR + CMR
	Anti-C5mAb + CsA	5	7.0 ± 1.0	AMR + CMR
	Anti-C5mAb + LF	5	8.3 ± 3.2	AMR + CMR
	Anti-C5 mAb + CsA + LF	5	> 100*	na

na = not applicable; mAb = monoclonal antibody; ACR = acute cellular rejection; CMR = cell mediated-rejection

*P < 0.01 relative to all other groups

In both the non-presensitized and presensitized allotransplant models, anti-C5 mAb treatment, in combination with other immunosuppressants, prevented humoral and cellular rejection, thereby achieving indefinite allograft survival in all animals.

In presensitized animals, anti-C5 mAb therapy in conjunction with cellular immunosuppression appeared to induce long term graft acceptance through a process of graft accommodation.

These data suggest that inhibition of terminal complement using anti-C5 mAb therapy may reduce the occurrence of AMR in clinical allotransplantation.

5.6. Summary of *In Vitro* Functional Characterization

Preclinical studies with the humanized h5G1.1-mAb, eculizumab, or a G4 isotype, h5G1.1 G4-mAb, showed that the variable regions of m5G1.1 used to make the eculizumab antibody have a high affinity and specific action for preventing complement activation.[36] The antibody only binds to human C5, and does not appreciably react with C5 from any other species. Eculizumab does not react non-specifically with normal human tissue.[37] The sites required for binding the human C5 molecule have been identified as a discontinuous clustered epitope.[38] A single chain form of eculizumab was shown to have the same epitope as the parental m5G1.1.[38] Eculizumab also has the same variable regions as the m5G1.1 antibody, thus should maintain specificity for the same epitope as the parental m5G1.1 antibody. Humanization of m5G1.1-mAb by CDR grafting did not alter the capacity of the antibody to inhibit complement activation.[39] Both the h5G1.1-mAb and G4 versions maintained functional activity of the

m5G1.1/.[40] Eculizumab inhibits the formation of C5a and assembly of C5b-9 complement complex/membrane attack complex (MAC) following complement activation. The G4 isotypic version was used in animal modeling.[41] The G2/G4 version, eculizumab has been developed as a human therapeutic.

5.7. Summary of Clinical Experience

The clinical experience with eculizumab in transplant recipients consists of several published case reports, the results of a pilot study of eculizumab prophylaxis from the Mayo Clinic and an ongoing Alexion Pharmaceuticals sponsored, investigator initiated prospective study of eculizumab to prevent AMR in kidney transplant recipients who are sensitized to their prospective donors.[42] Preliminary findings from the experience to date suggest that eculizumab may reduce the risk of AMR and preserve graft function.

In one report of a highly sensitized patient with severe AMR following a second kidney transplant, eculizumab combined with IVIg, PP and rituximab resulted in a marked reduction in MAC deposition in the kidney with no effect on DSA levels.[43] Four months later, the patient (who had previously received an autologous bone marrow transplant for Hodgkin's lymphoma that developed following kidney transplantation) succumbed to hemoptysis and pulmonary failure caused by marrow transplant-related pulmonary venoocclusive disease. The renal allograft was reported to be functioning well at the time of death.

Two additional case reports describe eculizumab treatment in cross-match positive patients. Both patients experienced severe AMR following a second and fourth transplant, respectively. In the first patient, urine output increased and serum creatinine improved after two courses of treatment with eculizumab. In the second patient, rejection resolved following treatment with both eculizumab and anti-thymocyte globulin. The patient did experience cytomegalovirus (CMV) infection and bacterial pneumonia. Serum creatinine was 2.6 mg/dL (228 μmol/L) at latest follow up.

Earlier studies performed at the Mayo Clinic were the basis on which their group designed the pilot study that examined eculizumab as prophylaxis for AMR in sensitized kidney transplant recipients.[27, 44] The results obtained in these earlier studies demonstrated that for 71 sensitized recipients the incidence of AMR correlated with the strength of anti HLA antibody as measured by B cell (BFXM) and/or T cell flow cytometry (TFXM). Sensitized candidates were those patients having baseline positive BFXM and/or TFXM $\geq$ 200 and $\leq$ 450 mcs to their donors. The incidence of AMR for recipients with +BTFXM < 300 mcs was 31% (9/29) and 39% (16/41) for recipients with positive B or TFXM > 300 mcs. Patients having baseline BFXM and/or TFXM < 300 mcs did not undergo antibody depletion prior to transplant. Patients having baseline BFXM and/or TFXM > 300 mcs underwent desensitization prior to transplantation.

The ongoing Alexion supported investigator initiated study at the Mayo Clinic designed to assess the efficacy of eculizumab to reduce AMR in living donor kidney transplant recipients who are sensitized to their donors accrued its first patient on 6/1/2008 and 26 sensitized patients have been transplanted to date.[45, 46] Patients having baseline B/TFXM $\geq$ 300 underwent pre-transplant desensitization with PP/IVIG until their pre-transplant B/TFXM was < 200. Patients with baseline B/TFXM < 300 were not treated with PP/IVIg prior to transplantation. For the 16 transplant recipients who reached 1 year of follow-up, eculizumab was discontinued at 4 weeks

for 8 patients, 8 weeks for 6 patients and 1 year for 2 patients. No cases of acute AMR occurred after eculizumab was discontinued.

Data from the 26 eculizumab-treated patients were compared to data for 26 standard of care (SOC)-treated control patients who were matched for DSA level, age and sex. When outcomes were compared for acute AMR, the number of patients that received post-transplant plasmapheresis and the number of patients that required splenectomy (surgical removal of the spleen) all were significantly less for the eculizumab-treated group than for the SOC-treated group, 2/26 (7.7%) vs. 14/26 (54%, p 0.0006), 3/26 (12%) vs. 20/26 (77% $p < 0.0001$), and 0/26 (0%) vs. 8/26 (31% $p > 0.0042$) respectively.[46]

In addition, in patients with very high levels of donor specific antibodies (B/TFXM > 300) within the first 3 months, AMR occurred in only 15% of eculizumab-treated patients, compared to 100% of control patients.

C4d, a stable complement split product that is used as a bio-marker for complement activation was present in the biopsies from 100% of recipients with high DSA in both the eculizumab and control groups. Since eculizumab inhibits C5, a component of the complement cascade that occurs distal to the production of the C4d split product, this finding combined with the low incidence of AMR even when high levels of DSA were present, supports the hypothesis that eculizumab prevents AMR through inhibition of terminal complement activation.

In a separate abstract from this study, further evaluation of biopsy specimens from eculizumab-treated patients revealed that the C5 complement inhibitor may prevent endothelial cell activation in the early post-transplantation period.[47]

5.8. Clinical Studies: Pharmacokinetics/Pharmacodynamics

Serum eculizumab concentrations higher than 50 ug/mL are expected to inhibit C5 activity. As concentrations of eculizumab decline from 50 ug/mL, a higher frequency of complement activity will be encountered.

A pharmacokinetics (PK) model of eculizumab has been developed from these data that fits all the diseases studied and is useful for the prediction of eculizumab concentrations. The PK behavior of eculizumab is well described with a simple one-compartmental model. PK parameter estimates predict an average $T_{1/2}$ of approximately 261-271 hours and average clearance of approximately 0.33 mL/h/kg with the PNH dose regimen.[48]

Pharmacodynamics in PNH Patients:

Eculizumab (Soliris®) was approved by the FDA for use in patients with PNH in March 2007. In the placebo-controlled clinical study, when administered as recommended, eculizumab treatment resulted in reduced hemolysis as shown by the reduction of serum LDH levels from 2200 ± 1034 U/L (mean ± SD) at baseline to 700 ± 388 U/L. The effect was evident by week one following treatment initiation and was maintained through the end of follow up at week 26 (327 ± 433 U/L). In the single arm clinical study, eculizumab maintained this effect through 52 weeks.[49]

Pharmacokinetics in PNH Patients:

A population PK analysis with a standard 1-compartmental model was conducted on the multiple dose PK data from 40 PNH patients receiving the recommended eculizumab regimen. In this model, the clearance of eculizumab for a typical PNH patient weighing 70 kg was 22 mL/hr and the volume of distribution was 7.7 L. The half-life was 272 ± 82 hrs (mean ± SD). The mean observed peak and trough serum concentrations of eculizumab by week 26 were 194 ± 76 mcg/mL and 97 ± 60 mcg/mL, respectively. Studies have not been conducted to evaluate the PK of eculizumab in special patient populations identified by gender, race, age (pediatric or geriatric), or the presence of renal or hepatic impairment.[49]

5.8.1. Clinical Studies: Safety

Clinical Study Experience in PNH:

Meningococcal infections are the most important adverse reactions experienced by patients receiving eculizumab therapy. In PNH clinical studies, two patients experienced meningococcal sepsis, but subsequently recovered without sequelae. Both patients had previously received a meningococcal vaccine. In clinical studies among patients without PNH, meningococcal meningitis occurred in an unvaccinated patient.

The data described below are from 196 adult patients who received eculizumab for PNH, age 18-85, of whom 55% were female. All had signs or symptoms of intravascular hemolysis. Eculizumab was studied in a placebo-controlled clinical study (in which 43 patients received eculizumab and 44, placebo); a single arm clinical study and a long term extension study. One hundred eighty-two (182) patients were treated for more than one year. All patients received the recommended eculizumab dose regimen.

Results of the eculizumab clinical studies performed in PNH patients and presented here cannot be directly translated to experience in transplant recipients. Nevertheless, certain trends can be described.

Among 193 patients with PNH treated with eculizumab in placebo-controlled, single-arm and long-term extension studies, serious adverse reactions occurred at an incidence of 16%. The most common serious adverse reactions were viral infection (2%), headache (2%), anemia (2%) and pyrexia (2%). In the placebo-controlled clinical study, serious adverse reactions including infections and progression of PNH occurred among 4 (9%) patients receiving eculizumab and 9 (21%) patients receiving placebo. No deaths were recorded over the course of the study.

Infection with herpes simplex virus, sinusitis, respiratory tract infections, myalgia and flu-like illness all affected a higher proportion of eculizumab-treated patients compared to those who received placebo. Headache, nasopharyngitis, back pain and nausea also occurred at numerically higher incidence in patients treated with eculizumab. Post-marketing adverse event experience has been consistent with the product labeling.

Immunogenicity:

The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to eculizumab in an enzyme linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay. Low titers of antibodies to

eculizumab were detected in 3/196 (2%) of all PNH patients treated with eculizumab. No apparent correlation of antibody development to clinical response was observed.

5.8.2. Drug Interaction Studies

No detailed drug interaction studies have been completed for the approved indication of PNH.[49]

The Mayo Clinic investigator-initiated study provides preliminary data suggesting that eculizumab is safe and well-tolerated when used concomitantly with other immunosuppressive therapies. No evidence of drug contraindications has been reported in the 26 patients treated with eculizumab when combined with other agents used for immunosuppression in transplant recipients.

The observation that eculizumab can be used in conjunction with traditional immunosuppressants for transplantation is also supported by a recent report by Schrezenmeier and colleagues in patients with PNH who have been administered both eculizumab and immunosuppressive agents.[50] These authors reviewed the safety and efficacy of eculizumab in a population of 17 of 195 PNH patients listed in the international PNH registry who received eculizumab to reduce their ongoing hemolysis as well as concomitant immunosuppressive therapy for bone marrow suppression. Results of the experience suggested that eculizumab was well tolerated with no apparent adverse effects when the drug was combined with cyclosporine (CsA) alone, or with CsA plus anti-lymphocyte/antithymocyte globulin, alemtuzumab or azathioprine. Equally important, there was no evidence that the immunosuppressive agents block the complement-inhibiting activity of eculizumab.

The interaction between eculizumab and commonly prescribed immunosuppressants was also examined in the standard hemolytic assay commonly used to determine the inhibition of hemolysis by eculizumab. Three concentrations of eculizumab, two of which inhibit complement-mediated hemolysis were tested in combination with peak concentrations of 11 immunosuppressive drugs (cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus (rapamycin), azathioprine, rituximab, daclizumab, basiliximab, CTLA4-Ig and two commercial forms of IVIG). No immunosuppressive drugs affected the hemolysis profile of eculizumab. Results of these preliminary experiments together with the initial clinical experience in kidney transplant patients indicate that commonly prescribed transplant drugs will not likely alter the pharmacodynamic (PD) or pharmacokinetic (PK) profile of eculizumab.

5.9. Basis for Eculizumab Dose Selection

5.9.1. Eculizumab Dose Selection, Treatment Regimen and Route of Administration

The dosages and treatment regimen selected for this current transplant study are based on aggregate findings from PK and pharmacodynamic (PD) evaluations in patients with PNH, initial data from the ongoing transplant study at the Mayo Clinic, emerging PK/PD data in patients with aHUS, and the recognized importance of achieving complete and sustained complement suppression in both the plasma and in the kidney allograft.

Eculizumab will be administered by intravenous (IV) infusion over 25-45 minutes in a fixed regimen consisting of:

- 1200 mg of eculizumab approximately 1 hour prior to reperfusion of the allograft
- 900 mg of eculizumab on post-transplantation days
    - 1, 7, and
    - 14, 21 and 28 (± 2 days)
- 1200 mg of eculizumab on Weeks 5, 7 and 9 (± 2 days)
- For cases of proven AMR within the first 9 weeks post-transplantation that are treated using PP, eculizumab (600mg) will be administered within 1 hour after the end of **each** PP.

5.10. Summary of Known or Potential Risks and Benefits to Human Patients

5.10.1. Risks

The known and potential risks, as assessed by adverse events in PNH and aHUS studies to human patients, are outlined in the current package insert and investigator brochure.[48, 49]

5.10.2. Benefits

Based on preliminary data in a small series of patients and published case study experience, eculizumab treatment should limit the occurrence of AMR in highly sensitized recipients of deceased donor kidneys. The antibody is not expected to appreciably alter the levels of DSA found in these patients or to interact pharmacodynamically with standard induction or maintenance immunosuppressive agents. The principal clinical benefit of eculizumab is to realize transplantation in a previously excluded subpopulation of patients or in those at elevated risk for early graft loss.[48]

6. STUDY OBJECTIVES AND PURPOSE

Eculizumab, an inhibitor of terminal complement activation, has been shown in hypothesis-generating clinical studies to successfully reduce the incidence of AMR following kidney transplantation of sensitized living donor recipients. This phase II study is designed to assess the effect of eculizumab on the incidence of AMR, patient survival, graft survival, or loss to follow-up, in kidney transplant recipients who are sensitized to their deceased donors.

6.1. Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of eculizumab to prevent AMR in sensitized recipients of deceased donor kidney transplants.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

The current eculizumab study is an open-label, single-arm, multicenter, phase II study (See Section 7.9, Figure 1). After appropriately screened patients have been cleared for transplant by the Principal Investigator, they will be enrolled in the study and undergo eculizumab therapy. Patients will receive eculizumab (study drug) for 9 weeks post-transplantation. All patients will receive standard immunosuppression, prophylactic medications and post-transplantation care. The diagnosis of AMR for the determination of the primary end point will be based on "for cause" kidney biopsies. In addition, protocol biopsies will be performed on all patients at predetermined time points. All patients will be screened for standard laboratory values, DSA titers, TFXM, BFXM, complement-dependent cytotoxicity (CDC), estimated glomerular filtration rate (eGFR) and other clinical and laboratory parameters for evaluation of primary and secondary endpoints as well as safety (See Section 7.10, Tables 7, 8, 9, and 10). The primary analysis of the data will occur after all patients have reached Month 12 post-transplantation. However, patients will have additional follow up at Months 18, 24 and 36 post-transplantation to assess patient and graft survival, kidney disease and disease status.

7.1.1. Study Period (Years)

This study is estimated to require approximately 4 years for completion. The following are the expected major timelines for this study:

- Estimated date first patient enrolled: 2nd Q2012
- Estimated date last patient, first visit: 2nd Q2014
- Estimated date last patient last visit: 2nd Q2015
- Estimated date of last patient completing 3 year follow up data collection: 2nd Q2017

It is estimated that approximately 20 kidney transplant centers in Europe and Australia will be required in order to fully enroll this study. Additional sites/countries will be considered if necessary.

7.1.2. Pre-screening, Screening and Enrollment

Pre-screening:

Investigator will pre-screen highly sensitized patients on their transplant waiting list in order to identify those patients that may be suitable for this protocol.

Screening/Enrollment:

Patients who are considered candidates to receive a deceased donor kidney transplant by the investigative sites' selection criteria and who are sensitized to their deceased donor as defined below will be considered for enrollment in this study. Candidates for enrollment will sign an informed consent form (ICF) and will undergo the baseline HLA screening at the investigative site's Local Laboratory with duplicate specimens being sent to the Central Laboratory for

confirmation. The Local Laboratory specimen values will be utilized for verification that the candidates meet enrollment criteria for study entry. If all inclusion criteria and none of the exclusion criteria are met, patients will be vaccinated against *N. meningitidis*. Furthermore, all patients that were not already vaccinated within the time period of active coverage specified by the vaccine manufacturer, must be re-vaccinated 30 days after initial vaccination. Tetravalent conjugated vaccines for *N. meningitidis* must be used. If patients were not already vaccinated at least 14 days prior to receiving the first dose of eculizumab, they will receive prophylactic treatment with an appropriate antibiotic for 14 days after the vaccination.

Baseline parameters to determine if patients are "sensitized" include the following:

1. Sensitizing event (history of prior exposure to HLA):
    a. Prior solid organ or tissue allograft
    b. Pregnancy
    c. Blood transfusion
    d. Prior exposure to specific donor's HLA

If history is consistent with DSA exposure then the following blood draws will be performed to confirm candidacy:

2 Patients must have
- Had an historical positive complement-dependent cytotoxicity (CDC). **Patient must be CDC negative at time of transplant.**

and/or
- Current B cell flow cytometric cross match (BFXM) or T cell flow cytometric cross match (TFXM) ≥ 300 and ≤ 500 mean channel shift (mcs). **No patient may have either a BFXM or TFXM > 500 mcs.**

and/or
- DSA identified by single antigen bead (SAB) assay (Luminex Labscreen assay) with a single MFI > 3000

c. **The local Laboratory specimens can be used to select patients for study entry**
d. A duplicate set of samples will be analyzed at the Central HLA laboratory.

7.1.3. Primary Endpoint

The primary composite endpoint is the Week 9 post-transplantation treatment failure rate defined as the occurrence of 1) biopsy-proven AMR, 2) graft loss, 3) patient death, or 4) loss to follow-up.

Diagnosis of AMR will be based on kidney allograft dysfunction and biopsy performed "for cause." The histological diagnosis will be based on Banff 2007 criteria (Appendix 20.1) for AMR as determined by the Central Pathology Laboratory. For this study only level II and level III AMR will be accepted as defined below:

Presence of circulating anti-donor specific antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):

- Banff 2007 level II - Capillary and/or glomerular inflammation (ptc/g > 0) and/or thromboses
- Banff 2007 level III - Arterial—v3

7.1.4. Secondary Endpoints

Secondary endpoints for this study include the following:

1. Cumulative incidence of AMR that occurs between Week 9 and Month 12 post-transplantation (AMR of any grade that meets Banff 2007 criteria)
2. Treatment failure rate defined as the occurrence of 1) biopsy proven AMR, 2) graft loss, 3) patient death, 4) loss to follow up at Month 12 post transplantation
3. Graft and patient survival at Months 6 and 12 post-transplantation
4. Histological evidence of AMR on protocol biopsies without other clinical findings at Day 14, and Months 3 and 12 post-transplantation
5. Overall pathological changes, including chronic AMR, on protocol biopsies at Day 14 and Months 3 and 12 post-transplantation
6. Cumulative number of PP treatments at 12 months post-transplantation
7. Cumulative incidence of patients requiring splenectomy at 12 months post-transplantation
8. Incidence of delayed graft function (DGF) post-transplantation (defined as the requirement for dialysis within the first post-transplantation week for reasons other than post-operative hyperkalemia, acute pulmonary edema or fluid overload due to comorbid conditions)
9. Cumulative incidence and duration of dialysis between 7 days and 12 months post-transplantation
10. Number of days the serum creatinine is more than 30% above nadir following the diagnosis of AMR.
11. Stable renal function between Week 4 and Month 12 post-transplantation as measured by:
    a. Estimated Glomerular Filtration Rate (calculated) by Modification of Diet in Renal Disease 7 (MDRD7) on at least 3 consecutive measurements taken at least 2 days apart while not on PP or dialysis that vary ≤ 20%
    b. Serum creatinine defined as the value on at least 3 consecutive measurements taken at least 2 days apart while not on PP or dialysis that vary ≤ 20%

7.2. Number of Patients

An estimated 80 patients will be enrolled into this single-arm study. This is based on a single-arm exact binomial test for the primary efficacy endpoint variable. See Statistics and Data Analysis section for additional details.

7.3. Treatment Assignment and Duration of Treatment

Patients who are CDC negative, and are cleared for transplantation by the Principal Investigator will be enrolled and receive eculizumab treatment. Patients will be followed for primary and secondary endpoints to Month 12 post-transplantation, and for DSA, kidney function and patient and graft survival up to Month 36 post-transplantation.

Patients that are diagnosed with biopsy proven AMR during the first 9 weeks of treatment are considered treatment failures. Investigators will be allowed to continue treatment of the AMR with eculizumab in addition to other agents. In addition, for biopsy proven AMR that is diagnosed after 9 weeks, investigators may also use eculizumab as part of the AMR treatment regimen. Please see Section 10 for dosing instructions for eculizumab.

7.3.1. Eculizumab Treatment

All doses of eculizumab will be IV as a continuous infusion **over 25-45 minutes**. See Section 10.0 for procedures pertaining to the preparation and administration of eculizumab.

Patients must have a negative CDC cross match prior to transplantation. Treatment will start during the transplantation procedure and continue as follows:

- Eculizumab 1200 mg (4 vials) administered in the operating room approximately 1 hour prior to kidney allograft reperfusion (Day 0)
- Eculizumab 900 mg (3 vials) on the following post-transplantation days:
    - Day 1
    - Day 7
    - Day 14 (± 2 days)
    - Day 21 (± 2 days)
    - Day 28 (± 2 days)

- Eculizumab 1200 mg (4 vials) given on the following post-transplantation weeks:
    - Week 5 (± 2 days)
    - Week 7 (± 2 days)
    - Week 9 (± 2 days)

PP and/or IVIg may be used only to treat biopsy proven AMR. In this setting the study drug should continue to be administered per the guidelines below in the Sections 11.2.1 or 11.2.2

7.4. Dose Adjustment Criteria

Eculizumab is administered intravenously as a fixed dose depending upon the time relative to the transplant as listed above in Section 7.3.1.

7.4.1. Safety Criteria for Adjustment or Stopping Doses

If an adverse reaction occurs during the administration of eculizumab, the infusion may be slowed or stopped at the discretion of the Principal Investigator. If the infusion is slowed, the total infusion time should not exceed two hours. The adverse reaction must be recorded on the AE page of the CRF.

Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

7.4.1.1. Infusion Reactions

As with all protein products, administration of eculizumab may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. Eculizumab administration should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy administered. The infusion reaction must be recorded on the AE page of the CRF.

7.5. Criteria for Study Termination

Alexion Pharmaceuticals may terminate this study at any time for safety or administrative reasons. Alexion Pharmaceuticals will terminate the study if the occurrence of adverse events (AEs) or other findings suggests an unacceptable risk to the health of the patients.

The Data Monitoring Committee (DMC) is in charge of monitoring the risk-benefit ratio for the patients and can make the following recommendation to Sponsor:

- Continued enrollment and dosing of eculizumab treatment
- Enroll at a reduced dose of eculizumab treatment
- Increase monitoring of patients of eculizumab treatment

Further information can be found in the DMC Study Charter.

7.6. Study Procedures

7.6.1. General Information

Transplant recipients will be cared for according to the investigative site's SOC protocols employed for post-transplantation follow-up. The Principal Investigator at each site will be directly responsible for supervising the care of these recipients during the length of the study.

7.6.2. Laboratory Information

Sites will utilize Local Laboratories for the following tests:

- Hematology Panel
- Chemistry Panel
- Urinalysis
- Spot urine for urine protein/creatinine ratio
- Tacrolimus Troughs

- Activated Partial Prothromplastin Time (aPTT), PT (Prothrombin Time), and International Normalized Ratio (INR)
- eGFR (MDRD 7)
- Serum Pregnancy Test for Women of Childbearing Potential (See Section 7.6.6 for exemptions)
- BFXM and TFXM for routine management (Local [optional] and Central Laboratories [mandatory])
- CDC (Local and Central Laboratories)
- The DSA by Luminex LabScreen (Local and Central Laboratories)

7.6.3. Central Laboratory Information

A Central Laboratory will be responsible for BFXM, TFXM, CDC and DSA by Luminex LabScreen taken at predetermined times (See Schedule of Assessments in Tables 7, 8, 9, and 10).

PK/PD samples will be forwarded by the sites to the Central Laboratory for accessioning and storage until the end of the study at which time all samples will be forwarded to Alexion for analysis.

Additional Central Laboratory information pertaining to processing of samples can be found in the Study Manual.

7.6.4. Central Pathology Information

All protocol and "for cause" kidney biopsies will be processed and analyzed by the site's Local Pathology Laboratory. Processed slides and two paraffin embedded unstained slides will also be forwarded to the Central Pathology imaging center for review by a panel of independent pathologists.

Additional details about processing and review of the slides for the Central Pathology Laboratory can be found in the Pathology Laboratory Manual.

7.6.5. Clinical Assessments

Clinical assessments will be conducted routinely during the post-operative period according to the transplant site protocol and also at various time points throughout the study. These assessments will include an assessment of the patient's health status, renal function and new diagnoses.

7.6.6. Female Patients of Child-Bearing Potential

Female candidates who are of child-bearing potential must have a negative pregnancy test (serum beta-hCG) and practice a medically approved contraceptive regimen during the post-transplantation period for at least 5 months following discontinuation of eculizumab.

Female patients are exempt from contraception requirement if they are post-menopausal for at least 1 year before dosing or are surgically sterile (i.e., no uterus or no ovaries). Females who have their fallopian tubes banded, tied or cut are not considered surgically sterile without FSH

level confirmation. Of note, females with end stage renal disease (ESRD) can be amenorrheic prior to transplantation.

7.6.6.1. Timing of Visits and Missed Visits

The schedule for clinical assessments during the Pre-Transplant, Immediate Post-Transplant, Extended Post-Transplant, and Long Term Outcome Phases are located in Tables 7, 8, 9, and 10 in Section 7.10. For practical logistical reasons the assigned visit windows are designed to allow more flexibility after the initial 9 weeks of the study.

In all cases, if a study visit is missed it is expected that a protocol deviation will be documented on the appropriate forms.

7.6.7. Screening/Enrollment Phase

The following procedures will be performed during the screening period:

Pre-Transplant Day -1 to Day 0 Prior to Transplant

- Informed consent
- Demographics
- Medical history (including current medications)
- Complete physical exam including vital signs, height and weight
- Determination of eligibility based on inclusion/exclusion criteria
- 12-lead electrocardiogram (ECG)
- Hematology panel
- Chemistry panel
- Urinalysis
- aPTT, PT and INR
- Serum pregnancy test for women of childbearing potential (See Section 7.6.6 for exemptions)
- Vaccination against *N. meningitidis.* Patients must be vaccinated at least 14 days prior to receiving the first dose of eculizumab or be vaccinated and receive prophylactic treatment with an appropriate antibiotic for 14 days after the vaccination. Furthermore, all patients that were not already vaccinated within the time period of active coverage specified by the vaccine manufacturer, must be re-vaccinated 30 days after initial vaccination.
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- CDC (samples to Local and Central Laboratories)

- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Record concomitant medications
- Assessment of AEs
- Instruct the patient on the signs and symptoms of *N. meningitidis*. Provide Identification Card to the patient explaining that the patient is participating in a clinical trial with a description of the Investigational Product and emergency contact information.
- Enrollment

NOTE: Entry criteria for the study can be determined by Local Laboratory data for DSA, CDC, BFXM, and/or TFXM at Screening.

All patients must be CDC negative at the time of transplant.

7.6.8. Immediate Post-Transplant Phase

The Local Laboratory specimen data for BFXM, TFXM, and/or DSA will used for patient management.

During the study, patients must carry a detailed card describing the "alert" symptoms for *Neisseria meningitides* at all times. Development of the "alert" symptoms card will be the responsibility of Alexion or its designee. The triggers for seeking immediate medical attention are any of the following symptoms:

- Headache with nausea or vomiting
- Headache with fever
- Headache with a stiff neck or back
- Fever of 103°F (39.4°C) or higher
- Fever and a rash
- Confusion
- Severe myalgia with flu-like symptoms
- Sensitivity to light

Week 0 (On Transplant Day 0)

For all patients, the following will be completed on the day of the transplant following the transplant:

- Kidney transplant procedure
- Complete physical exam including vital signs and weight
- Hematology panel

- Chemistry panel
- Urinalysis
- aPTT, PT and INR
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Assess renal function/need for dialysis
- Kidney allograft biopsy (post-reperfusion; send duplicate slides to Central Pathology)
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs
- Administer eculizumab, 1200 mg (4 vials), **approximately one hour prior** to reperfusion of kidney allograft
- Baseline and peak PK and PD collection (baseline samples should be taken 5-90 minutes prior to study drug infusion; peak samples are to be taken 60 minutes after the completion of the study drug infusion)

Post-Transplant Day 1

For all patients, the following should be completed one day post-transplantation:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- aPTT, PT and INR
- Tacrolimus trough
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Assess renal function/need for dialysis
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs
- Administer eculizumab, 900 mg (3 vials)

- Trough and peak PK and PD collection (trough samples should be taken 5-90 minutes prior to study drug infusion; peak samples are to be taken 60 minutes after the completion of the study drug infusion)

Post-Transplant Days 2-6

For all patients the following should be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- aPTT, PT and INR
- Tacrolimus trough
- Assess renal function/need for dialysis
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs

Post-Transplant Day 7

For all patients the following should be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- Urinalysis
- Spot urine for urine protein/creatinine ratio
- aPTT, PT and INR
- Tacrolimus trough
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Assess renal function/need for dialysis
- Record concomitant medications

- Record immunosuppressive medications
- Assessment of AEs
- Administer eculizumab, 900 mg (3 vials)
- Trough and peak PK and PD collection (trough samples should be taken 5-90 minutes prior to study drug infusion; peak samples are to be taken 60 minutes after the completion of the study drug infusion)

7.6.9. Extended Post-Transplant Phase

All patients will continue to be seen for study visits at regular intervals Post-Transplant Day 14 through Month 12 (primary efficacy analysis).

The Local Laboratory specimen data for BFXM, TFXM, and/or DSA will used for patient management.

Post-Transplant Day 14/Week 2

For all patients, the following will be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- aPTT, PT and INR
- Tacrolimus trough
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Assess renal function/need for dialysis
- Kidney allograft biopsy (send duplicate slides to Central Pathology)
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs
- Administer eculizumab, 900 mg (3 vials)
- Trough and peak PK and PD collection (trough samples should be taken 5-90 minutes prior to study drug infusion; peak samples are to be taken 60 minutes after the completion of the study drug infusion)

Post-Transplant Day 21/Week 3

For all patients, the following will be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- aPTT, PT and INR
- Tacrolimus trough
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Assess renal function/need for dialysis
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs
- Administer eculizumab, 900 mg (3 vials) – No PK/PD assessments required for this dose

Post-Transplant Day 28/Week 4

For all patients, the following will be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- Urinalysis
- Spot urine for urine protein/creatinine ratio
- aPTT, PT and INR
- Tacrolimus trough
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)

- Vaccination against *N. meningitidis*. Only for patients that were not already vaccinated within the time period of active coverage specified by the vaccine manufacturer
- Assess renal function/need for dialysis
- eGFR (MDRD 7)
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs
- Administer eculizumab, 900 mg (3 vials)
- Trough and peak PK and PD collection (trough samples should be taken 5-90 minutes prior to study drug infusion; peak samples are to be taken 60 minutes after the completion of the study drug infusion)

Post-Transplant Days 35 and 49/Weeks 5 and 7

For all patients, the following will be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- SCr and BUN
- Tacrolimus trough
- Assess renal function/need for dialysis
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs
- Administer eculizumab, 1200 mg (4 vials)
- Trough and peak PK and PD collection (trough samples should be taken 5-90 minutes prior to study drug infusion; peak samples are to be taken 60 minutes after the completion of the study drug infusion)

Post Transplant Day 56/Week 8

For all patients, the following will be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel

- Chemistry panel
- aPTT, PT and INR
- Tacrolimus trough
- Assess renal function/need for dialysis
- eGFR (MDRD 7)
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs

Post Transplant Day 63/Week 9

For all patients, the following will be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- Urinalysis
- Spot urine for urine protein/creatinine ratio
- aPTT, PT and INR
- Tacrolimus trough
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Assess renal function/need for dialysis
- eGFR (MDRD 7)
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs
- Administer eculizumab, 1200 mg (4 vials)
- Trough and peak PK and PD collection (trough samples should be taken 5-90 minutes prior to study drug infusion; peak samples are to be taken 60 minutes after the completion of the study drug infusion)

Post Transplant Week 12/Month 3

For all patients, the following will be completed:

- Complete physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- Urinalysis
- Spot urine for urine protein/creatinine ratio
- aPTT, PT and INR
- Tacrolimus trough
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Assess renal function/need for dialysis
- eGFR (MDRD 7)
- Kidney allograft biopsy (send duplicate slides to Central Pathology)
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs

Post Transplant Weeks 17 & 21/Months 4 & 5

For all patients the following will be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- SCr and BUN
- Tacrolimus trough
- Assess renal function/need for dialysis
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs

Post Transplant Week 26/Month 6

For all patients, the following will be completed:

- Complete physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- Urinalysis
- Spot urine for urine protein/creatinine ratio
- aPTT, PT and INR
- Tacrolimus trough
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Assess renal function/need for dialysis
- eGFR (MDRD 7)
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs

Post Transplant Weeks 30 & 34/Months 7 & 8

For all patients, the following will be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- SCr and BUN
- Tacrolimus trough
- Assess renal function/need for dialysis
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs

Post Transplant Week 38/Month 9

For all patients, the following will be completed:

- Abbreviated physical exam including vital signs and weight

- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- aPTT, PT and INR
- Tacrolimus trough
- Assess renal function/need for dialysis
- eGFR (MDRD 7)
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs

Post Transplant Weeks 44 & 48/Months 10 & 11

For all patients, the following will be completed:

- Abbreviated physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- SCr and BUN
- Tacrolimus trough
- Assess renal function/need for dialysis
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs

Post Transplant Week 52/Month 12 - Study Primary Analysis Time Point

For all patients, the following will be completed:

- Complete physical exam including vital signs and weight
- Clinical assessment including evaluation for rejection
- Hematology panel
- Chemistry panel
- Urinalysis
- Spot urine for urine protein/creatinine ratio
- aPTT, PT and INR

- Tacrolimus trough
- BFXM and TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (samples to Local and Central Laboratories)
- Assess renal function/need for dialysis
- eGFR (MDRD 7)
- Kidney allograft biopsy (send duplicate slides to Central Pathology)
- Record concomitant medications
- Record immunosuppressive medications
- Assessment of AEs

7.6.10. Long Term Outcomes Phase

Additional study visits will occur at Months 18, 24 and 36 for long term follow up data. This data will not be used for purposes of the primary efficacy analysis.

Post Transplant Months 18 and 24

For all patients, the following will be completed:

- Assessment of rejection episodes in interim from last visit, patient survival, graft survival and kidney disease and disease status
- Chemistry panel
- Tacrolimus trough
- Other immunosuppressant levels

Post Transplant Month 36

For all patients, the following will be completed:

- Assessment of rejection episodes in interim from last visit, patient survival, graft survival and kidney disease and disease status
- Chemistry panel
- Tacrolimus trough
- Other immunosuppressant levels
- BFXM, TFXM for routine management (samples to Local [optional] and Central Laboratories [mandatory])
- DSA by Luminex LabScreen (sample to Central Laboratory only)
- Kidney allograft biopsy (duplicate slides to Central Pathology Laboratory)

7.7. Treatment of Persistent DSA Levels

DSA will be analyzed both by central and local laboratory during treatment, at the end of the treatment period (Week 9) and at Months 3, 6, 12 and 36. Central Laboratory results at week 9 only will be provided to the local centers. If the recipient maintains a positive DSA and a positive BFXM and/or TFXM as measured by the central laboratory (week 9 result) then PP and/or IVIg may be used to lower the DSA as follows:

- PP and/or IVIg will be administered per the clinical judgment of the principal investigator.
- Supplementary eculizumab as a booster following PP/before FFP may be administered during weeks 9-10 only.
- Other medications such as rituximab and bortezomib are not allowed to treat persistent DSA.
- Serum samples will be submitted to the central lab for DSA and B/TFXM testing. Serum samples will be obtained prior to beginning PP, then weekly during PP (pre-PP sample) and one month following the conclusion of PP therapy.

Note: Eculizumab supplementation will not be allowed for treatment of persistent DSA that extends beyond the 10th postoperative week.

7.8. Treatment with Fresh Frozen Plasma

If a patient receives FFP not associated with PP then the patients receiving eculizumab should receive a supplemental dose of eculizumab (600 mg) 1 hour prior to FFP administration.

7.9. Early Discontinuations

7.9.1. Screen Failure

Patients who do not meet the study criteria during the screening/enrollment phase will be considered screen failures. These patients will be discontinued from the study without follow-up. A discontinuation CRF form that documents the reason for the screening failure will be completed

7.9.2. Premature Discontinuations and Withdrawals

Early Termination Withdrawals or Discontinuations:

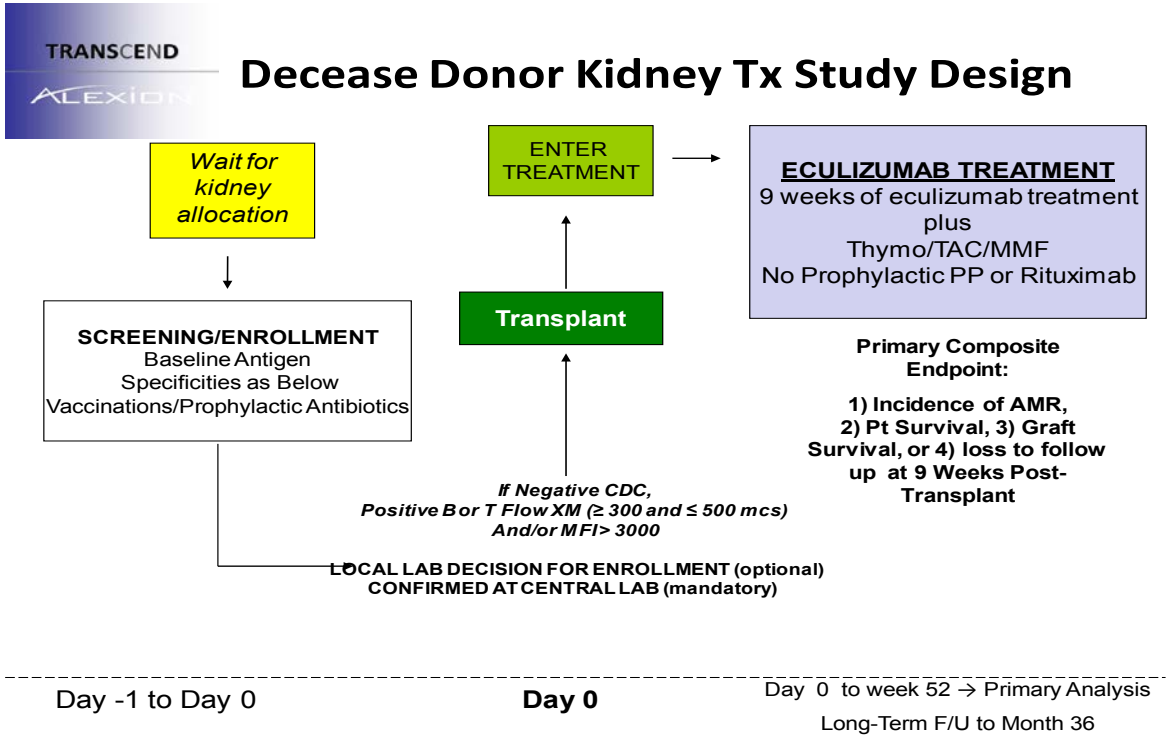
Reasons for early discontinuation or withdrawal should be documented completely in the appropriate CRF.

If a patient discontinues the eculizumab study drug at any time during the study, the patient will have additional study visits to ensure safety follow-up every 2 weeks for 2 months (maximum of 4 visits) following the final dose. These visits may coincide with routine follow-up visits for maintenance of their kidney transplant per the transplant center. The last visit should include all assessments listed for the Month 12 visit in the Schedule of Assessments (Table 9).

- Abbreviated Physical Exam including vitals and weight
- Evaluation to assess transplant which may include collection of blood samples
    - Review of any changes in the patients' health
    - Appropriate study procedures if the patient is diagnosed with AMR during evaluation

7.10. Study Design Diagram

Figure 1: Study Design



7.11. Schedules of Assessments

Table 6: Schedule of Assessment - Pre-Transplant Phase	
Pre-Transplant Study Visit	Screening and Enrollment
Study Week	Day -1 to Day 0 Prior to Transplant
Visit Window	N/A
Procedure	
Informed Consent	X
Demographics	X
Medical History	X
Physical Exam including Vital Signs, Height and Weight	X
Assessment of Inclusion/Exclusion Conformity	X
ECG	X
Vaccination against *N. meningitidis*[b]	X
Provide Patient Safety Card for *N. meningitidis*	X
Chemistry Panel including SCr and BUN	X
Hematology Panel including WBC diff., Plts, Hgb	X
Urinalysis	X
aPTT, PT and INR	X
Serum Pregnancy Test for Women of Childbearing Potential	X
BFXM and TFXM	X[c]
CDC	X[d]
DSA by Luminex LabScreen	X[d]
Enrollment	X
Concomitant Medications	X
Adverse Event Assessment	X

a. Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms.
b. Patients must be vaccinated at least 14 days prior to receiving the first dose of eculizumab or be vaccinated and receive prophylactic treatment with an appropriate antibiotic for 14 days after the vaccination. Furthermore, all patients not already vaccinated within the time period of active coverage specified by the vaccine manufacturer, must be re-vaccinated 30 days after initial vaccination.
c. BFXM and TFXM levels may be run at the Local Laboratory (optional). Duplicate samples will be sent to the Central Laboratory for the Screening and Day -1 samples. **The Local Laboratory specimens can be used to select patients for study eligibility and determine if the patient can proceed to transplantation. Duplicate samples will be sent to the Central Laboratory for confirmation.** At all other interim time points selected by the Investigative Site for patient management, the Local Laboratory will be used for processing of specimens. These interim samples do not need to be sent to the Central Laboratory. See Study Manual for sample processing information.
d. CDC and/or DSA levels are to be run at the Local Laboratory. Duplicate samples will be sent to the Central Laboratory for the Screening and Day -1 samples. **The Local Laboratory specimens will be used to select patients for study eligibility and determine if the patient can proceed to transplantation. Duplicate samples will be sent to the Central Laboratory for confirmation.** At all other interim time points selected by the Investigative Site for patient management, the Local Laboratory will be used for processing of specimens. These interim samples do not need to be sent to the Central Laboratory. See Study Manual for sample processing information.

Table 7: Schedule of Assessment - Immediate Post Transplant Phase								
Transplant Study Visit	Transplant, Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Study Week	Week 0	Week 0						Week 1
Visit Window	0	0	0	0	0	0	0	0
Procedure								
Kidney Transplantation	X							
Physical Exam including Vital Signs and Weight	X							
Abbreviated Physical Exam including Vital Signs and Weight[a]		X	X	X	X	X	X	X
Clinical Assessment including Evaluation for Rejection		X	X	X	X	X	X	X
Administer Eculizumab[b]	X[c]	X[d]						X[d]
Hematology Panel including WBC diff., Plts, Hgb	X	X	X	X	X	X	X	X
Chemistry Panel including SCr and BUN	X	X	X	X	X	X	X	X
PK, PT and PD[e]	B/P	T/P						T/P
Urinalysis	X							X
Spot Urine for Urine Protein/Creatinine Ratio								X
aPTT and INR	X	X	X	X	X	X	X	X
Tacrolimus trough		X	X	X	X	X	X	X
BFXM and TFXM[f]	X	X						X
DSA by Luminex LabScreen[g]	X	X						X
Assess renal function/ need for dialysis	X	X	X	X	X	X	X	X
Kidney Allograft Biopsy (post reperfusion)	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Immunosuppressive Medications	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X

a. Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms.
b. No PP or IVIg may be administered during first 9 weeks unless biopsy-proven AMR
c. Administer eculizumab 1200 mg (4 vials) IV over 25-45 minutes one hour prior to re-perfusion of kidney
d. Administer eculizumab 900 mg (3 vials) IV on Days 1 and 7 post-transplantation over 25-45 minutes
e. B = Baseline sample; T = Trough sample; P = Peak sample. Baseline and trough samples for PK/PD are to be taken 5-90 minutes before the study drug infusion. Peak samples for PK/PD testing are to be taken 60 minutes after the completion of the study drug infusion. See Study Manual for sample processing information.
f. BFXM and TFXM levels are to be draw on Days 0, 1, and 7 and may be run at the Local Laboratory (optional). Duplicate samples are to be sent to the Central Laboratory. At all other interim time points selected by the Investigative Site for patient management, the Local Laboratory will be used for processing of specimens. These interim samples do not need to be sent to the Central Laboratory. See Study Manual for sample processing information. Local Laboratory specimen data will be used for all patient management. See Study Manual for sample processing information.
g. DSA levels are to be draw on Days 0, 1, and 7 and run at the Local Laboratory. Duplicate samples are to be sent to the Central Laboratory. At all other interim time points selected by the Investigative Site for patient management, the Local Laboratory will be used for processing of specimens. These interim samples do not need to be sent to the Central Laboratory. See Study Manual for sample processing information. Local Laboratory specimen data will be used for all patient management. See Study Manual for sample processing information.

Table 8: Schedule of Assessment - Extended Post Transplant Phase													
Transplant Study Visit	Day 14	Day 21	Day 28	Days 35 & 49	Day 56	Day 63	Mo. 3	Mo. 4 & 5	Mo. 6	Mo. 7 & 8	Mo. 9	Mo. 10 & 11	Mo. 12
Study Week	Week 2	Week 3	Week 4	Week5 & 7	Week 8	Week 9	Week 12	Week17 & 21	Week 26	Week30 & 34	Week 38	Week44 & 48	Week 52
Visit Window	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Procedure													
Physical Exam Including Vital Signs and Weight							X		X				X
Abbreviated Physical Exam Including Vital Signs and Weight[a]	X	X	X	X	X	X		X		X	X	X	
Clinical Assessment including Evaluation for Rejection	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer Eculizumab[b]	X[c]	X[c]	X[c]	X[d]		X[d]							
Hematology Panel including WBC diff, Plts, Hgb	X	X	X		X	X	X		X		X		X
Chemistry Panel including SCr and BUN	X	X	X	X[e]	X	X	X	X[e]	X	X[e]	X	X[e]	X
PK and PD[f]	T/P		T/P	T/P		T/P							
Urinalysis			X			X	X		X				X
Spot Urine for Urine Protein/Creatinine Ratio			X			X	X		X				X
aPTT, PT and INR	X	X	X		X	X	X		X		X		X
Tacrolimus trough	X	X	X	X	X	X	X	X	X	X	X	X	X
BFXM and TFXM[g]	X	X	X			X	X		X				X
DSA by Luminex LabScreen[f]	X	X	X			X	X		X				X
Assess Renal Function / need for dialysis	X	X	X	X	X	X	X	X	X	X	X	X	X
eGFR (MDRD 7)			X		X	X	X		X		X		X
Kidney Allograft Biopsy	X						X						X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

Immunosuppressive Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms.
b. No prophylactic PP or IVIg may be administered during first 9 weeks unless biopsy-proven AMR
c. Administer eculizumab 900 mg (3 vials) IV on Days 14, 21, 28 over 25-45 minutes
d. Administer eculizumab 1200 mg (4 vials) IV at Weeks 5, 7, 9 over 25-45 minutes
e. SCr and BUN only.
f. T = Trough sample; P = Peak sample. Trough samples for PK/PD are to be taken 5-90 minutes before the study drug infusion. Peak samples for PK/PD testing are to be taken 60 minutes after the completion of the study drug infusion. See Study Manual for sample processing information.
g. BFXM and TFXM levels are monitored on Days 14, 21, 28, Week 9 and Months 3, 6 and 12 and may be run at the Local Laboratory (optional). Duplicate samples are to be sent to Central Laboratory. At all other interim time points selected by the Investigative Site for patient management, the Local Laboratory will be used for processing of specimens. These interim samples do not need to be sent to the Central Laboratory. See Study Manual for sample processing information. Local Laboratory specimen data will be used for all patient management. See Study Manual for sample processing information.
f. DSA levels are monitored on Days 14, 21, 28, Week 9 and Months 3, 6 and 12 at the Local Laboratory. Duplicate samples are to be sent to Central Laboratory. At all other interim time points selected by the Investigative Site for patient management, the Local Laboratory will be used for processing of specimens. These interim samples do not need to be sent to the Central Laboratory. See Study Manual for sample processing information. Local Laboratory specimen data will be used for all patient management. See Study Manual for sample processing information.

Table 9: Schedule of Assessment - Long Term Outcome Data Collection

Post- Transplant Study Visit	Month 18	Month 24	Month 36
Study Week	Week 78	Week 104	Week 156
Visit Window	± 14 days	± 14 days	± 14 days
Procedure			
Assessments for Interim Rejection Episodes, Graft Loss, Patient Survival, Kidney Disease and Disease Status[a]	X	X	X
Chemistry Panel including SCr and BUN	X	X	X
Tacrolimus Trough	X	X	X
Other Immunosuppresant Levels	X	X	X
BFXM and TFXM[b]			X
DSA by Luminex LabScreen[b]			X
Kidney Allograft Biospy[c]			X

a. Interim rejection episodes will be recorded from previous visit through subsequent visit.
b. BFXM, TFXM, and DSA specimens to be sent to the Central Laboratory only. See Study Manual for sample processing information.
c. Duplicate slides will be sent to Central Pathology Laboratory.

8. SELECTION AND WITHDRAWAL OF PATIENTS

All patients must adhere to the following inclusion/exclusion criteria.

8.1. Patient Inclusion Criteria

1. Male or female patients ≥ 18 years old
15. Patients with Stage V chronic kidney disease who will receive a kidney transplant from a deceased donor to whom they are sensitized
16. History of prior exposure to HLA:
    a. Prior solid organ or tissue allograft
    b. Pregnancy
    c. Blood transfusion
    d. Prior exposure to specific donor's HLA
17. Historical positive CDC cross match **and/or** BFXM or TFXM ≥ 300 and ≤ 500mcs (no patient may have a BFXM or TFXM > 500mcs) **and/or** DSA identified by single antigen bead (SAB) assay (Luminex Labscreen assay) with a single MFI > 3000.
18. Negative CDC at time of transplantation
19. Able to understand the ICF and willing to comply with study procedures
20. Female patients of child-bearing potential must have a negative pregnancy test (serum beta-hCG) and must be practicing an effective, reliable and medically approved contraceptive regimen while on eculizumab treatment and for up to 5 months following discontinuation of treatment

8.2. Patient Exclusion Criteria

1. Has received treatment with eculizumab at any time prior to enrolling in this study
21. ABO incompatible with deceased donor
22. History of severe cardiac disease (e.g. New York Heart Association [NYHA] Functional Class III or IV, myocardial infarction ≤ 6 months of enrollment, ventricular tachyarrhythmias requiring ongoing treatment, unstable angina or other significant cardiovascular diseases)
23. Prior splenectomy
24. Has a known bleeding disorder
25. Has any active bacterial or other infection which is clinically significant in the opinion of the Investigator and is a contraindication to transplantation
26. Has participated in any other investigational drug study or was exposed to an investigational drug or device within 30 days of screening
27. Has received rituximab (Mabthera®) ≤ 3 months prior to screening

28. Has received bortezomib (Velcade®) ≤ 3 months prior to screening
29. Has received alemtuzumab (Campath®) ≤ 6 months prior to screening
30. Hypersensitivity to murine proteins or to one of the product excipients
31. History of illicit drug use or alcohol abuse within the previous year
32. Unresolved meningococcal disease
33. Pregnancy or Lactation
34. Current cancer or a history of cancer within the 5 years prior to screening, with the exception of patients who have successfully treated nonmetastatic basal or squamous cell carcinoma of the skin; carcinoma in situ of the cervix; or breast carcinoma in situ
35. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the study, poses an added risk for the patient, or confounds the assessment of the patient
36. Active infection with Hepatitis B (HBV), Hepatitis C (HCV) or Human Immunodeficiency Virus (HIV)

8.3. Patient Withdrawal Criteria

Patients will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care.

Patients must be withdrawn from the study for any of the following reasons:

- Patient request
- Patient is unwilling or unable to comply with the protocol
- Medical reason, at the discretion of the Investigator and/or the Medical Monitor

The reasons for patient study drug and/or patient withdrawal must be recorded in the patient's CRF and in the source records. The Investigator must notify Alexion Pharmaceuticals and the Medical Monitor immediately when a patient has been discontinued/withdrawn due to an AE. All patients who are withdrawn from the study should complete the tests and evaluations scheduled for the final visit of the study.

If a patient is discontinued due to an adverse event (AE), the event will be followed until it is resolved or in the opinion of the Principal Investigator the patient is determined to be medically stable. Every effort will be made to undertake protocol-specified safety follow-up procedures.

Patients who fail to return for final assessments will be contacted by the site study staff in an attempt to have them comply with the protocol. As it is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE, follow-up due diligence documentation will consist of 2 phone calls followed by 1 registered letter to the patient's last known address. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures.

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

Eculizumab is a recombinant humanized monoclonal IgG2/4κ antibody produced by murine myeloma cell culture and purified by standard bioprocess technology. Eculizumab contains human constant regions from human IgG2 sequences and human IgG4 sequences and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

9.2. Post-transplant Immunosuppression and Concomitant Medications

Patients who are enrolled and receive their kidney transplants are required to take immunosuppressive and prophylactic medications to maintain allograft function and protect them from infection. In addition, medications will be used to manage co-morbid conditions such as hypertension, hyperlipidemia, diabetes, and pain. These conditions will be managed according to the SOC practices at the individual investigative sites.

Among the medications that will be given to transplant recipients will be:

Induction Therapy:

- Thymoglobulin (1.5 mg/kg x4 doses [6 mg/kg recommended, may use up to 7.5 mg/kg])

Maintenance Immunosuppression:

- Tacrolimus
  - Maintain trough levels at 4 to11 ng/mL for Months 1 through 12
  - No calcineurin inhibitor avoidance or withdrawal protocols are allowed
- Mycophenolate mofetil (MMF; Cellcept®)/Enteric-coated mycophenolic acid (EC-MPA; Myfortic®)
  - MMF: 1 gram BID (may titrate down or alter dosing schedule for patient intolerance)
  - EC-MPA: 720 mg BID (may titrate down or alter dosing schedule for patient intolerance)
  - Generic formulations of the above are acceptable for purposes of the study
- Prednisone initially per SOC at the transplant center and tapered to 5 mg daily by 3 months post-transplantation
  - No steroid avoidance or withdrawal protocols allowed

Concomitant and Prophylactic Medications: All concomitant medications should be administered to all patients according to standard institutional protocols and applied uniformly to all patients. Examples of these medications include but are not restricted to:

- CMV prophylaxis
- Pneumocystis *carinii/jiroveci* Pneumonia (PCP) prophylaxis
- Antifungal prophylaxis

Induction, maintenance immunosuppression, and prophylactic therapies should be used uniformly across all centers in the study and recorded in the CRF's.

9.2.1. Prohibited Medications/Treatments

The following medications/treatments are prohibited as their use may compromise the findings or interact with eculizumab:

- Use of alemtuzumab (Campath®) ≤ 6 months prior to screening and post-transplantation during the study
- Use of basiliximab (Simulect®) induction therapy during the study
- Use of bortezomib (Velcade®) ≤ 3 months prior to screening and post-transplantation during the study. Bortezomib may be used at the discretion of the principal investigator for salvage therapy of AMR not responsive to first line therapy.
- Use of rituximab (Mabthera®) ≤ 3 months prior to screening and post-transplantation during the study. Rituximab may be used at the discretion of the principal investigator for salvage therapy of AMR not responsive to first line therapy.
- Use of immunoadsorption at any time (in place of plasmapheresis)
- Use of prophylactic PP or IVIg during the **first 9 weeks** post-transplantation during eculizumab treatment

9.3. DSA and Cell-based Crossmatch Evaluations

Patients will undergo routine post-transplantation monitoring for circulating DSA and cell-based cross match (XM) evaluations as follows:

- Per protocol clinical monitoring of DSA (Luminex LabScreen) and cell-based cross matches which include BFXM and TFXM will be performed by the Central Laboratory at Days 0, 1, 7, 14, 21, 28, Week 9, and Months 3, 6 and 12
    - DSA, BFXM and TFXM tests will also be collected at Month 36, but are not to be included in the primary efficacy analysis. They will be sent to the Central Laboratory and used for purposes of long term follow up only
- Duplicate samples will be sent to the transplant center's Local Laboratory for DSA and/or cell-based XMs to facilitate patient management. **The Central Laboratory data will not be used for patient management**
- Interim samples for patient management will be analyzed at the transplant center's HLA Local Laboratory and may include any of the following tests: DSA, CDC,

BFXM, and TFXM. **Duplicate samples are not required for the Central Laboratory**

9.4. Treatment Compliance

Patients will be administered eculizumab IV in a controlled setting such as a hospital, outpatient clinic or short-stay care unit, thereby ensuring compliance with study drug administration under the supervision of the Investigator. Study coordinators at the investigative sites will ensure that all study participants are adequately informed on the specific treatment regimens required for compliance with the study protocol.

Alexion Pharmaceuticals or its designee will periodically monitor study sites to ensure compliance with the protocol and communicate with sites on a regular basis regarding study protocol deviations. All protocol deviations will be appropriately documented by the Investigator and study monitors.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Eculizumab is supplied in 30 mL vials with a solution concentration of 10 mg/mL. Each single entry 30 mL vial will contain a solution concentration of 10 mg/mL and has enough solution to withdraw the indicated 30 mL.

10.2. Study Drug Packaging and Labeling

The study drug eculizumab will be released to the site upon receipt of all required essential documents based upon federal, state, and local regulations. Each kit will have a single panel label describing the contents and a place for the pharmacist to record the patient number and initials. The pharmacy should immediately notify the distributor if vials are damaged. Eculizumab must be stored in a secure, limited-access storage area.

10.3. Study Drug Storage

The study drug (eculizumab) vials must be stored in the original carton until time of use under refrigerated conditions at 2-8°C (36-46°F) and protected from light. Do not use beyond the expiration date stamped on the carton. Refer to Section 10.5 below for stability and storage of diluted solutions of eculizumab. ***DO NOT FREEZE AND DO NOT SHAKE.***

10.4. Study Drug Preparation

Infusions of the study drug should be prepared using aseptic technique. Each vial of eculizumab contains 300 mg of active ingredient in 30 mL of product solution. Eculizumab must be diluted to a final admixture concentration of 5 mg/mL using the following steps:

- Withdraw the required amount of eculizumab from the vial into a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute eculizumab to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume of diluent to drug volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP to the infusion bag.

The final admixed eculizumab 5 mg/mL infusion volume is 120 mL for 600 mg doses, 180 mL for 900 mg doses or 240 mL for 1200 mg doses.

Table 10: Eculizumab and Diluent Volumes

Eculizumab Dose	Volume of Eculizumab	Volume of Diluent [1]	Total Volume of Administration
600 mg	60 mL (2 vials)	60 mL	120 mL
900 mg	90 mL (3 vials)	90 mL	180 mL
1200 mg	120 mL (4 vials)	120 mL	240 mL

1) Choose one of the following diluents: a. 0.9% sodium chloride; b. 0.45% sodium chloride; c. 5% dextrose in water; d. Ringer's injection.

Gently invert the infusion bag containing the diluted eculizumab solution to ensure thorough mixing of the product and diluent. Empty vials and vials with residual materials should be kept for inspection by the study monitor prior to their destruction, or handled per local site pharmacy standard operating procedures for clinical study drugs.

Prior to administration, the admixture should be allowed to adjust to room temperature (18-25° C, 64-77°F).

The admixture must not be heated in a microwave or with any heat source other than ambient air temperature.

The eculizumab admixture should be inspected visually for particulate matter and discoloration prior to administration.

10.5. Administration and Stability of Solution

Do Not Administer As an Intravenous Push or Bolus Injection.

The eculizumab admixture should be administered by IV infusion over 35 minutes (range 25-45 minutes). It is not necessary to protect the infusion bags from light while study drug is being administered to the patient. At the site's discretion, the diluted study drug may be administered via gravity feed, a syringe-type pump, or an infusion pump. The patients will be monitored for 1 hour following infusion.

Admixed solutions of eculizumab are stable for 24 hours at 2-8°C (36-46°F) and at room temperature. If the eculizumab is prepared more than 4 hours in advance of a patient's visit, the diluted material should be stored at 2°C to 8°C.

If an AE occurs during the administration of the study drug, the infusion may be slowed or stopped at the discretion of the Investigator, depending upon the nature and severity of the event. The adverse event must be captured in the patient's source document and CRF.

10.6. Study Drug Accountability

The current International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines requires the Principal Investigator to ensure that study drug deliveries from the Sponsor are received by a responsible person (e.g. pharmacist). In addition, the following guidelines should also be adhered to:

- Study drug deliveries need to be recorded
- Study drug is handled and stored safely and properly
- Study drug is only dispensed to patients in accordance with the protocol
- Unused study drug is returned to the Sponsor or standard procedures for the alternative disposition of unused study drug are followed
- When a study drug shipment is received at the site, the pharmacist should verify the contents, sign the packing invoice provided with the shipment, and maintain the original copy for review by the study monitor. A signed copy should be faxed to the

contact provided on the packing list and the duplicate copy kept in the pharmacy binder

Accountability logs and Inventory logs will be provided to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing, and disposition of the study drug. During the study, the following information must be noted in the accountability log: the patient number(s), initials of patient(s) to whom drug is dispensed, kit number, the date(s) and time that the study drug is prepared and dispensed, and the initials of the pharmacist or designee who prepared the study drug. Sites should keep a running total of their drug supply. Empty vials and vials with residual materials should be kept for inspection by the study monitor prior to their destruction, or handled per local site pharmacy standard operating procedures for clinical study drugs.

The study monitor will examine the inventory during the study. Additionally, the inventory records must be readily available and may be subject to regulatory authorities, the local regulatory agency, or an independent auditor's inspection at any time.

10.7. Study Drug Handling and Disposal

Drug inventory and accountability records for the study drug will be kept by the Investigator/Pharmacist. Study drug accountability throughout the study must be documented. The following guidelines should be followed:

- The Investigator agrees not to supply study drugs to any person except the patients of the study.
- The Investigator/Pharmacist will keep the study drug in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the Investigator to dispense the investigative drug.
- A study drug inventory will be maintained by the Investigator/Pharmacist. The inventory will include details of material received and a clear record of when they were dispensed and to which patient.
- At the conclusion or termination of this study, the Investigator/Pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record. Delivery records and records of used or returned study drug must be reconcilable. Appropriate forms of deliveries and returns must be signed by the person responsible at the investigative site.
- Used or unused study drug may be destroyed at the study center according to standard institutional procedures after drug accountability has been conducted by the Sponsor or designee. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor or designee upon request.
- Unused study drug not destroyed at the site must be returned to the Sponsor or designee at the end of the study or upon expiration.

10.8. Warnings and Precautions

The safety and effectiveness of eculizumab in pediatric patients, pregnant women, and lactating women have not been established.

Patients who develop adverse events of rash, hives, itching, and/or dysphagia of mild to moderate severity during their infusions while receiving study drug may continue to be infused as deemed to be medically appropriate by the Investigator. Medical intervention may include, but is not limited to: slowing of the infusion rate (with or without treatment). For further information, please refer to the current Investigator's Brochure.

Infusion-related reactions occurred in thirteen patients prior to the recent Phase III PNH studies. In eight cases, eculizumab was discontinued immediately. In the remaining five cases, patients continued to be dosed without experiencing any clinically meaningful event. In the recently completed double blind, placebo-controlled, PNH study (C04-001), a review of adverse events occurring within 24 hours of study drug infusion was done, which determined that headache was the most common adverse event reported in both eculizumab-treated (37%) and placebo-treated (18%) patients. The headaches that occurred during the first infusions were deemed to be related to the mechanism of action of eculizumab in PNH patients. The frequency of headaches was similar between eculizumab-treated and placebo-treated patients after the first few infusions of study drug. No patients discontinued study because of an infusion reaction.

Any acute reaction should be treated according to standard medical practice depending upon clinical signs and symptoms. If a patient requires medical intervention measures, this patient should remain at the investigational site for a minimum one-hour observation period after the completion of the infusion.

Inhibition of the terminal complement complexes predisposes patients to infections with encapsulated bacteria. In particular, patients treated with eculizumab are at increased risk for the development of infection caused by *Neisseria meningitidis*, as infection with this organism is more frequent in patients who have a terminal complement deficiency. Because eculizumab can directly inhibit complement activation, an increased susceptibility to infection is a potential adverse effect of eculizumab. Infection with *Neisseria meningitidis* can be life-threatening or fatal. Therefore, to decrease the risk of such possible infection, all patients must be vaccinated with a meningococcal vaccine according to current medical guidelines for vaccination use at least 14 days before his or her first study drug infusion, or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination. Furthermore, all patients that were not already vaccinated within the time period of active coverage specified by the vaccine manufacturer must be re-vaccinated 30 days after initial vaccination. Tetravalent conjugated vaccines against serotypes A, C, Y, and W135 must be used. Patients with a documented history of vaccination with *Neisseria meningitidis* will be assessed by the Sponsor and Investigator on a case-by-case basis to determine if re-vaccination at day 30 will be required.

There have been reported cases of *Neisseria meningitidis* in patients participating in eculizumab clinical studies and in patients receiving commercial product. The Investigator's Brochure contains the detailed information.

During the study, patients must carry a detailed ID card describing the "alert" symptoms for *Neisseria meningitidis* at all times. Development of the "alert" symptoms card will be the

responsibility of Alexion or its designee. The triggers for seeking immediate medical attention are any of the following symptoms:

- Headache with nausea or vomiting
- Headache with fever
- Headache with a stiff neck or back
- Fever of 103°F (39.4°C) or higher
- Fever and a rash
- Confusion
- Severe myalgia with flu-like symptoms
- Sensitive to light

Any patient experiencing any of the above noted symptoms must be seen by a physician as quickly as possible.

If the Principal Investigator deems that the benefits exceed the risks, dosing with study drug in a patient with systemic infections may be continued with caution once the patient has been evaluated by the Investigator, appropriate cultures have been obtained and antibiotics have begun.

As this is a clinical study, careful observation of the patient is necessary. All adverse events including any serious adverse event (SAE) or AE leading to discontinuation experienced during the study period must be described in detail, fully evaluated by the Investigator and reported on the appropriate CRF.

11. ASSESSMENT OF EFFICACY

11.1. Kidney Allograft Biopsy Evaluations

For-cause kidney biopsies will be required to confirm the diagnosis of AMR. Protocol biopsies will be used to monitor subclinical changes in the allograft. These will be performed to assist in the diagnosis of subclinical instances of AMR that are only evidenced histologically.

1. For Cause Allograft Biopsies - Will be obtained for clinical signs of allograft dysfunction based upon at least one of the following criteria, with or without elevation of DSA from baseline (day of transplant):
    a. A decrease in serum creatinine less than 10% per day in three consecutive days in the first week post transplantation compared to Day 0 immediate post-transplantation creatinine
    b. An increase in serum creatinine of ≥ 30% from nadir. Nadir is defined as the lowest serum creatinine within the first week post-transplantation
    c. Oliguria
    d. Clinical suspicion of AMR

For-cause kidney biopsy slides will be read at the transplant center and used for clinical management. Slides that were read locally will be sent to the Central Pathology Laboratory for review.

37. Protocol Biopsy - Mandated biopsies will be performed:
    a. Post reperfusion (Intra-operative)
    a. Day 14 post-transplantation
    b. Month 3 post-transplantation
    c. Month 12 post-transplantation
    d. Month 36 post-transplantation (for long term follow up only; will not be included in primary efficacy analysis)

Protocol kidney biopsies will be used to evaluate other secondary endpoints and also for evaluation of subclinical cases of AMR that may only be evident on a histological basis. Protocol biopsies will be read at the transplant center and may be used for clinical management. Slides that were read locally will be sent to the Central Pathology Laboratory.

11.2. Treatment of Antibody Mediated Rejection Episodes

The cumulative incidences of AMR at Week 9 and through Month 12 of the study are the primary and secondary endpoints respectively. Should it occur, the following guidelines will be used in the treatment of AMR.

11.2.1. For AMR Occurring During the Treatment Period Post-Transplantation

If the patient has a biopsy-proven diagnosis (from local pathologist) of clinically significant (elevated creatinine) AMR during the first 9 weeks post-transplantation, the patient will be considered a treatment failure. AMR episodes will be treated according to local SOC protocols and at the Principal Investigators' discretion (with the exception of prohibited medications).

If the patient receives PP for the treatment of AMR and it is determined by the Principal Investigator that the patient will remain on eculizumab, then supplemental doses of eculizumab should be used as follows:

- Eculizumab 600 mg (2 vials) will be administered within 1 hour of completing each PP session
    - This is in order to maintain levels between 50 and 100 μg/mL of eculizumab, as has been predicted based on empirical experience and PK-PD modeling calculations for eculizumab under conditions of PP
- Doses will be given IV over 25-45 minutes

AMR may be treated with eculizumab for at least 5 weeks or until the serum creatinine returns to within 10% of their pre-rejection baseline creatinine or until they achieve a new stable baseline serum creatinine defined as less than a 20% variation on three successive tests taken at least 24 hours apart. The maximum number of weeks that the patient will be treated with eculizumab for acute AMR is 9.

11.2.2. For AMR Occurring After the Week 9 Treatment Period

AMR episodes occurring after Week 9 will be treated according to local SOC protocols and at the Principal Investigators' discretion (with the exception of prohibited medications). Eculizumab may be used to treat diagnosed AMR. See Section 10.0 for general administration guidelines.

If eculizumab is used to treat AMR, dosing will be as follows **(weeks are calculated from the day of first dose of eculizumab after AMR diagnosis)**:

- Initial dose 900 mg (Day 1), if dosed within 7 days of last dose of eculizumab;
- Initial dose 1200 mg (Day 1), if dosed after 7 days of last dose of eculizumab;
- 900 mg weekly for 4 doses (Weeks 1, 2, 3 and 4; ± 2 days), then;
- 1200 mg every other week beginning on Week 5 for Weeks 5, 7, and 9 (± 2 days)
- AMR may be treated with eculizumab for at least 5 weeks or until the serum creatinine returns to within 10% of their pre-rejection baseline creatinine or until they achieve a new stable baseline serum creatinine defined as less than a 20% variation on three successive tests taken at least 24 hours apart. The maximum number of weeks that the patient will be treated with eculizumab for acute AMR is 9.

12. ASSESSMENT OF SAFETY

12.1. Data Monitoring Committee

An independent DMC will be comprised of at least 3 clinicians experienced in high risk kidney transplantation. Other members may also have expertise in the following areas: nephrology transplant specialist and/or transplant surgeon, infectious disease, and biostatistics. Since its primary function will be to ensure patient safety, the DMC will have access to all safety data and a data management expert will be part of the DMC to ensure timely delivery of all required data. The DMC will also have access to a statistician and/or an epidemiologist if necessary.

The broad remit of the DMC is to monitor safety and efficacy data as it is accumulated and to make decisions on study conduct and dose regimen to ensure patients' safety. The operational details and responsibilities of the DMC will be specified in a charter.

12.2. Safety Parameters

12.2.1. Demographic/Medical History

The demographic information to be collected includes date of birth, gender, race and/or ethnicity.

Medical history information to be collected includes all ongoing conditions and relevant/significant medical history (including all major hospitalizations and surgeries). Symptoms related to renal transplantation and/or the underlying etiology of the disease should be listed on the medical history form. Worsening of any of these signs or symptoms during the course of this study must be captured as an AE.

12.2.2. Vital Signs

The following vital signs will be collected: body temperature (°C), heart rate (beats/min), respiratory rate (breaths/min), and blood pressure (mmHg).

12.2.3. Weight and Height

Height (cm) and weight (kg) will be collected at screening. Post screening visits will include weight collection only.

12.2.4. Physical Examinations

A complete physical exam consisting of an examination of the following: General Appearance, Skin, Head, Ears, Eyes, Nose and Throat (HEENT), Cardiovascular, Pulmonary, Abdomen/Gastrointestinal, Neurological, Lymph Nodes, Spine, Extremities, and Musculoskeletal. A genitourinary examination should be performed unless a separate examination was performed within 1 year by another physician and is documented in the patient record.

Abbreviated physical exams will be completed at the time points specified on the Schedule of Assessments. The body systems included in these exams will be based on Investigator judgment and/or patient symptoms.

12.2.5. Electrocardiogram

A 12-lead ECG will be performed. The data to be collected include includes heart rate, PR, QRS and QT intervals (uncorrected) and any abnormalities.

12.2.6. Laboratory Assessments

12.2.6.1. Hematology

The hematology panel will include complete blood count (CBC), with differential and platelet counts. CBC includes red blood cells (RBCs), white blood cells (WBCs), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC).

12.2.6.2. Blood Chemistry Panel

The blood chemistries will include: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), lactic dehydrogenase (LDH), total and direct bilirubin, total protein, albumin, uric acid, and total cholesterol.

12.2.6.3. Coagulation

The coagulation testing will include an activated partial thromboplastin time (aPTT), prothrombin time (PT) and international normalized ratio (INR).

12.2.6.4. Urinalysis

Urinalysis testing will include protein, glucose, ketones, occult blood, and WBCs by dipstick, with microscopic examination and spot urine for urine protein/creatinine ratio.

12.2.6.5. Pregnancy Screen

At screening, a pregnancy test (serum beta-hCG) will be completed for all females of child bearing potential (See Section 7.6.6 for exemptions).

12.3. Adverse and Serious Adverse Events

12.3.1. Adverse Event

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment. Patients will be instructed to contact the Principal Investigator or Sub-Investigator if any symptoms develop any time after the informed consent and informed assent (if applicable) has been signed. If there is any doubt as to whether or not a clinical observation is an AE, the event should be recorded and reported.

A treatment-emergent AE (TEAE) is defined as any event not present prior to exposure to Investigational Product or any event already present that worsens in either intensity or frequency following exposure to Investigational Product.

Adverse events will be assigned Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and tabulated as incidence rates per treatment group.

Safety evaluations will consist of monitoring and recording all adverse events, including SAEs, the regular monitoring of hematology, blood chemistry and urine results. In addition, regular monitoring of vital signs, physical condition and body weight measurements will be performed.

The safety reference document for this clinical trial will be the Investigator brochure.

12.3.2. Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (i.e., baseline, treatment, or follow-up), and at any dose of the investigational product that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
    - The term "life-threatening" means that the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization or the development of drug dependency or drug abuse.

All SAEs that occur after any patient has been enrolled, before treatment, during treatment, or throughout the duration of the patient follow-up, whether or not they are related to the study, must be recorded on forms provided by Alexion Pharmaceuticals.

12.3.3. Other Adverse Events of Interest

Other adverse events of interest may be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from the study, will be classified as other AEs of interest. For each other adverse event of interest, a narrative may be written and included in the Clinical Study Report.

Other Adverse Events of Interest for this study will include:

- Cumulative incidence of clinically significant infection (confirmed by culture, biopsy, genomic, or serologic findings) that requires hospitalization or anti-infective treatment, or is otherwise deemed significant by the Investigator
- Cumulative incidence of CMV disease
- Cumulative incidence of BK virus disease
- Cumulative incidence of encapsulated bacterial infection
- Cumulative incidence of PTLD (post-transplant lymphoproliferative disease)
- Cumulative incidence of malignancy
- Cumulative incidence of biopsy-proven acute cellular rejection
- Proportion of patients that develop severe acute cellular rejection that do not respond to thymoglobulin or other lymphocyte depleting agents
- Cumulative incidence of allograft loss for reasons other than AMR
- Overall patient survival

12.4. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Unlikely, Possible, Probable, or Definite).

- Unrelated: This relationship suggests that there is no association between the Investigational Product and the reported event.
- Unlikely: This relationship suggests that the clinical picture is highly consistent with a cause other than the Investigational Product but attribution cannot be made with absolute certainty and a relationship between the Investigational Product and AE cannot be excluded with complete confidence.
- Possible: This relationship suggests that treatment with the Investigational Product may have caused or contributed to the AE, i.e. the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the Investigational Product, but could also have been produced by other factors.

  Probable: This relationship suggests that a reasonable temporal sequence of the event with the Investigational Product administration exists and the likely association of the event with the Investigational Product. This will be based upon the known pharmacological action of the Investigational Product, known or previously reported adverse reactions to the Investigational Product or class of drugs, or judgment based on the Principal Investigator's clinical experience.
- Definite: Temporal relationship to the Investigational Product, other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain event, corresponds with the known pharmaceutical profile, improvement on discontinuation, re-appearance on re-challenge

12.5. Recording Adverse Events

Adverse events spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site as per the timetable listed in Tables 7, 8, and 9. Clinically significant changes in laboratory values, blood pressure, and pulse need to be reported as AEs. Abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from the signing of the ICF until the end of the study. SAE information will be collected from signing of ICF until the end of the study. The medical term for the AE should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities and may require systemic drug therapy or other treatment)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.3. An AE of severe intensity may not be considered serious.

If it becomes known during the administration of the study drug that a patient is pregnant, the study drug will be stopped immediately. In addition, for any woman who becomes pregnant at any time during the study, Pharmacovigilance must be notified via the same method as SAE Reporting (See Section 12.6). Pharmacovigilance will supply the Investigator with a copy of a "Pregnancy Reporting and Outcome Form". The patient should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth or congenital abnormality), even if the patient was discontinued from the study. When the outcome of the pregnancy becomes known the form should be completed and returned to Pharmacovigilance. If additional follow-up is required, the Investigator will be requested to provide the information.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.6. Reporting Adverse Events

The Investigator is responsible for reporting all AEs and SAEs observed or reported during the study regardless of their relationship to the study drug or their clinical significance.

All AEs that occur after the patient has given consent must be reported in detail in the patient's source/chart and on the appropriate CRF and followed to satisfactory resolution or until the

Principal Investigator or Sub-Investigator deems the event to be chronic or the patient to be stable. The description of the AE will include the onset date, resolution date, intensity, seriousness, and the likelihood of relationship of the AE to the study drug.

Additional information to be reported includes any required treatment or evaluations, and outcome. All reported AEs will be followed to adequate resolution. Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study and this deterioration is felt to be related to study drug, it should be recorded as an AE.

All SAEs (related and unrelated) will be recorded from the signing of consent form until the end of the study. All SAEs must be reported to Alexion Pharmaceuticals Pharmacovigilance Designee within one business day of the first awareness of the event. Additionally, any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax to Alexion Pharmaceuticals. Contact and fax information will be provided in the Study Manual.

Additional follow-up information, if required or available, should all be faxed to Alexion Pharmaceuticals Pharmacovigilance Designee within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

Alexion Pharmaceuticals is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the institutional review board (IRB) or independent ethics committee (IEC) of all SAEs that occur at his or her site per their local IRB or IEC established guidelines for submission. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

13. STATISTICS AND DATA ANALYSIS

13.1. General Considerations for Data Analysis

Details of the statistical analysis described below will be specified in a separate Statistical Analysis Plan prior to data lock and analysis. Any deviations from the statistical plan will be specified and justified in the Clinical Study Report.

For continuous data, the mean, standard deviation, median, minimum and maximum will be reported. For categorical data, percent and frequency will be reported.

13.1.1. Missing Data

Missing data on demographic, recipient-, donor- and transplant-related information and on laboratory data will be treated as missing; no method for imputation is planned. Missing data on time to event endpoints will have events coded as right censored per the following table:

Table 11: Missing Data Events Coding for Time to Event Data Analyses

Endpoint	Right Censoring
Time to First Biopsy-proven AMR	Patients who did not experience a biopsy-proven AMR at any time during follow-up will be right censored as of the date of last patient contact.
Time to First Biopsy-proven ACR	Patients who did not experience a biopsy-proven ACR at any time during follow-up will be right censored as of the date of last patient contact.
Graft Survival	Patients who are alive with functioning graft will be right censored as of the date of last patient contact.
Patient Survival	Patients who are still alive as of the last known follow-up will be right censored as of the date of last patient contact.

13.1.2. Analysis Datasets

Full Analysis (FA) Set

Patients who are enrolled, receive a deceased donor kidney transplant, and receive at least one dose of eculizumab will be included in the full analysis (FA) set. All efficacy analyses will be performed using the FA set.

Per Protocol Set

Patients who experience a major protocol deviation that is deemed to have affected outcome will be excluded from the FA set to create the Per Protocol analysis set. Efficacy analyses will only be performed using the Per Protocol set if the percent of patients in the Per Protocol set compared to the FA set is less than 80%. The Per Protocol set will be determined and documented prior to database lock.

Safety Set

Patients who are enrolled and receive at least one dose of eculizumab will be included in the Safety set. All safety analyses will be performed using the Safety set.

13.2. Efficacy Analysis

The primary analysis of all endpoints will occur after all patients have reached Month 12 post-transplantation. Patients will continue to be followed on Months 18, 24 and 36 for collection of additional follow up data on patient and graft survival, kidney disease and disease status.

13.2.1. Primary Efficacy Variable and Analysis

The primary efficacy composite endpoint is the Week 9 post-transplantation treatment failure rate defined as the occurrence of 1) biopsy-proven AMR, 2) graft loss, 3) patient death, or 4) loss to follow-up.

The diagnosis of AMR will be based on kidney allograft dysfunction and biopsy performed "for cause." The histological diagnosis will be based on Banff 2007 criteria for AMR as determined by the Central Pathology Laboratory. For this study only level II and level III AMR will be accepted as defined below:

Presence of circulating anti-donor specific antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):

- Banff 2007 Level II - Capillary and/or glomerular inflammation (ptc/g > 0) and/or thromboses
- Banff 2007 Level III - Arterial—v3

The primary efficacy variable is a binary outcome variable where patients meeting the above composite endpoint definition will be considered treatment failures and all others will be considered treatment successes. The point estimate of the incidence of treatment failure at 9 weeks post-transplantation will be calculated along with an exact 95% confidence interval (CI). The null hypothesis that the true rate of treatment failure at 9 weeks post-transplantation is equal to 40% will be tested using the exact binomial test. (See Section 13.6, Sample Size and Power Considerations).

13.2.2. Secondary Efficacy Variables and Analyses

Secondary efficacy endpoints include:

1. Cumulative incidence of AMR that occurs between Week 9 and Month 12 post-transplantation (AMR of any grade that meets Banff 2007 criteria)
2. Treatment failure rate defined as the occurrence of 1) biopsy-proven AMR, 2) graft loss, 3) patient death, 4) loss to follow up at Month 12 post-transplantation
3. Graft and patient survival at Months 6 and 12 post-transplantation

38. Histological evidence of AMR on protocol biopsies without other clinical findings at Day 14, and Months 3 and 12 post-transplantation
39. Overall pathological changes, including chronic AMR, on protocol biopsies at Day 14, and Months 3 and 12 post-transplantation
40. Cumulative number of PP treatments at 12 months post-transplantation

41. Cumulative incidence of patients requiring splenectomy at 12 months post-transplantation
42. Incidence of DGF post-transplantation (defined as the requirement for dialysis within the first post-transplantation week for reasons other than post-operative hyperkalemia, acute pulmonary edema or fluid overload due to comorbid conditions)
43. Cumulative incidence and duration of dialysis between 7 days and 12 months post-transplantation
44. Number of days the serum creatinine is more than 30% above nadir following the diagnosis of AMR.
45. Stable renal function between Week 4 and Month 12 post-transplantation as measured by:
    a. Estimated Glomerular Filtration Rate (calculated) MDRD7 on at least 3 consecutive measurements taken at least 2 days apart while not on PP or dialysis that vary $\leq 20\%$
    b. Serum creatinine defined as the value on at least 3 consecutive measurements taken at least 2 days apart while not on PP or dialysis that vary $\leq 20\%$

Patient and graft survival, the cumulative incidence of delayed AMR, the cumulative incidence of biopsy-proven AMR without other clinical findings, and the cumulative incidence of biopsy-proven acute cellular rejection, each at the times post-transplantation listed above, will be estimated using the product-limit (Kaplan-Meier) method. In addition to point estimates, 95% CIs will be provided.

The cumulative number of PP treatments post-transplantation will be summarized using survival analysis techniques e.g., Nelson-Aalen estimator.

The incidence of treatment of AMR diagnosed solely on histological evidence on protocol biopsies will be provided along with 95% CIs. The actual treatments used will be summarized or listed.

The percentage of patients requiring splenectomy, the incidence of DGF, and the incidence of dialysis beyond 7 days post-transplantation will be provided along with 95% CIs.

The duration of dialysis beyond 7 days post-transplantation, and the number of days that serum creatinine is more than 30% above nadir following the diagnosis of AMR summarized using descriptive statistics.

Overall pathological changes on protocol biopsies at Day 14, and Months 3 and 12, and change in renal function between Week 4 and Month 12, will be summarized using descriptive statistics.

13.3. Safety Analysis

Safety assessments will consist of summarizing all AEs, including SAEs, hematology, blood chemistry and urine results, regular monitoring of vital signs, physical condition and body weight measurements.

All AEs (serious and non-serious), regardless of relationship to study drug, will be classified by system organ class and preferred term using the MedDRA (version 10.1 or higher). Incidence rates will be tabulated for each system organ class and preferred term.

In addition to the above, the following specific safety assessments will be summarized for the study at Week 9 and Month 12 post transplantation:

1. Cumulative incidence of clinically significant infection (confirmed by culture, biopsy, genomic or serologic findings) that requires hospitalization or anti-infective treatment, or is otherwise deemed significant by the Investigator
46. Cumulative incidence of CMV disease (incidence and %)
47. Cumulative incidence of BK virus disease (incidence and %)
48. Cumulative incidence of encapsulated bacterial infections (incidence and %)
49. Cumulative incidence of PTLD
50. Cumulative incidence of malignancy
51. Cumulative incidence of biopsy-proven acute cellular rejection of any grade that meets Banff 2007 criteria
52. Proportion of patients that develop severe acute cellular rejection that do not respond to thymoglobulin or other lymphocyte depleting agents
53. Cumulative incidence of allograft loss for reason other than AMR
54. Overall patient survival

13.4. Interim Analysis

No formal statistical interim analyses of the primary and secondary efficacy variables are planned.

13.5. Long Term Outcomes Data Collection

For purposes of long term follow up data collection to evaluate interim rejection episodes, graft loss, patient survival, kidney disease and disease status, all patients will be seen at Months 18, 24, and 36. The following information will be collected:

1. Chemistry panel (including BUN and sCr)
2. Tacrolimus trough levels
3. Other Immunosuppressive levels
4. DSA, BFXM and TFXM (Month 36 only)
5. Kidney allograft biopsy (Month 36 only)

These data will not be considered as part of the primary efficacy analysis.

13.6. Sample Size and Power Considerations

The primary efficacy composite endpoint is the Week 9 post-transplantation treatment failure rate defined as the occurrence of 1) biopsy-proven AMR, 2) graft loss, 3) patient death, or 4) loss to follow-up. Sample size and power considerations were based on the primary efficacy variable and a single-arm study with the following assumptions:

1. Composite endpoint true treatment failure rate at Week 9 post-transplantation with standard of care in the study population is, $\pi_0 = 40\%$
55. Composite endpoint treatment failure rate at Week 9 post-transplantation with eculizumab is, $\pi_1 = 20\%$
56. Null hypothesis, H_0: $\pi_1 = 40\%$
57. Alternative hypothesis, H_1: : $\pi_1 \neq 40\%$
58. Type I error, $\alpha = 0.05$ (two-sided significance test)
59. Statistical test = Exact binomial test

An exact binomial test with a nominal 0.050 two-sided significance level will have >90% power to detect a difference between the null hypothesis proportion, π_1 of 0.400 and the alternative proportion, π_1, of 0.200 when the sample size is 80.

14. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Alexion Pharmaceuticals will visit the investigational study site to:

Determine the adequacy of the facilities

Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Alexion Pharmaceuticals or its representatives. This will be documented in a Clinical Study Agreement between Alexion Pharmaceuticals and the Investigator.

During the study, a monitor from Alexion Pharmaceuticals or representative will have regular contacts with the investigational site, for the following purposes:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts)
- Record and report any protocol deviations not previously sent to Alexion Pharmaceuticals
- Confirm AEs and SAEs have been properly documented on CRFs and confirm SAEs have been forwarded to Alexion Pharmaceuticals and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of Alexion Pharmaceuticals, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of an Alexion Pharmaceuticals audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Alexion Pharmaceuticals immediately if contacted by a regulatory authority about an inspection.

14.3. Institutional Review Boards and Independent Ethics Committees

The Principal Investigator must obtain IRB or IEC approval for the investigation. Initial and continuing IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Alexion Pharmaceuticals may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

Alexion Pharmaceuticals, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local, federal and regulatory agency regulations.

16.1. Potential Ethical Considerations

The reproductive toxicity of eculizumab in humans is unknown. Women of childbearing potential must use contraception while on treatment until 5 months following discontinuation of eculizumab and must be informed that there are potential hazards to the fetus should pregnancy occur during treatment.

Eculizumab has been approved by the FDA and EMA for the treatment of PNH and aHUS. In addition, a small investigator-initiated study in kidney transplant patients is currently underway at the Mayo Clinic. Thus, there may be unforeseen or unknown risks for this patient population either from administration of eculizumab alone or in combination with other medications the patient may be receiving to maintain their kidney transplant.

The ICF identifies procedures that may pose a risk to the patient beyond the potential systemic effects of administering eculizumab. Needle biopsies of the transplanted kidney are commonly performed as part of patient management. Risks associated with a percutaneous biopsy of the transplanted kidney include pain at the biopsy site, bleeding, and rarely graft loss.[51] Risks due to phlebotomy or IV catheter placement may include bruising, localized bleeding or swelling, infection, syncope, and pain associated with the procedure. Risks associated with IV injection of study drug may include pain, erythema, swelling, tenderness, inflammation, extravasations and/or bruising at the site of the IV catheter.

16.2. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Alexion Pharmaceuticals before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study and any materials provided to the patient. The protocol must be re-approved by the IRB or IEC upon receipt of amendments.

The Principal Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Alexion Pharmaceuticals will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.3. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the Alexion Pharmaceutical's policy on Bioethics.

16.4. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed and dated ICF must be given to the patient.

Informed written consent is required from each patient prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the clinical site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50 and other regulatory agency guidance.

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the patients. It is the responsibility of the Investigator to obtain consent and to provide the patient with a copy of the signed and dated ICF. Confirmation of a patient's informed consent must also be documented in the patient's medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB/IEC and by Alexion Pharmaceuticals or its designee. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and Alexion Pharmaceuticals or its designee.

16.5. Patient Data Protection

Prior to any testing under this protocol, including screening tests and evaluations, patients must authorize the release and use of protected health information, as required by local, federal and regulatory agency law.

The patient will not be identified by name in the CRF or in any study reports. These reports will be used for research purposes only. Alexion Pharmaceuticals, its designee, and various government health agencies may inspect the records of this study. Every reasonable effort will be made to keep the patient's personal medical data confidential.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Alexion Pharmaceuticals or their designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Alexion Pharmaceuticals or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

The Sponsor, Alexion Pharmaceuticals, has no objection to publication or public disclosure for non-commercial purposes by the Institution or Investigator of the study data in accordance the guidelines outlined within study specific agreements between the Sponsor and the investigative sites. The terms for publication are outlined in the Clinical Study Agreement, Statement of Agreement or the Master Clinical Study Agreement. Refer to these documents for further details and information.

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20. APPENDICES

20.1. Banff Criteria 2007 Update[52]

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Table 3: Banff 97 diagnostic categories for renal allograft biopsies—Banff'07 update [1,2]

1. **Normal**
2. **Antibody-mediated changes** (may coincide with categories 3, 4 and 5 and 6)
   Due to documentation of circulating antidonor antibody, and C4d[3] or allograft pathology
   C4d deposition without morphologic evidence of active rejection
   C4d+, presence of circulating antidonor antibodies, no signs of acute or chronic TCMR or ABMR (i.e. g0, cg0, ptc0, no ptc lamination). Cases with simultaneous borderline changes or ATN are considered as indeterminate
   Acute antibody-mediated rejection[4]
   C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):
   I. ATN-like minimal inflammation
   II. Capillary and or glomerular inflammation (ptc/g >0) and/or thromboses
   III. Arterial—v3
   Chronic active antibody-mediated rejection[4]
   C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries
3. **Borderline changes:** 'Suspicious' for acute T-cell-mediated rejection (may coincide with categories 2 and 5 and 6)
   This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2 or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis
4. **T-cell-mediated rejection** (TCMR, may coincide with categories 2 and 5 and 6)
   Acute T-cell-mediated rejection (Type/Grade:)
   IA. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
   IB. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
   IIA. Cases with mild-to-moderate intimal arteritis (v1)
   IIB. Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
   III. Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
   Chronic active T-cell-mediated rejection
   'chronic allograft arteriopathy' (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)
5. **Interstitial fibrosis and tubular atrophy**, no evidence of any specific etiology
   (may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointerstitial features)
   Grade
   I. Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
   II. Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)
   III. Severe interstitial fibrosis and tubular atrophy/ loss (>50% of cortical area)
6. **Other:** Changes not considered to be due to rejection—acute and/or chronic (for diagnoses see Table 14 in (42); may include isolated g, cg or cv lesions and coincide with categories 2, 3, 4 and 5)

[1]The 2007 updates are underlined.
[2]All existing scoring categories (g, t, v, i, cg, ct, ci, cv, ah, mm) remain unchanged (42)
[3]Please refer to Table 2 and Figure 1.
[4]Suspicious for antibody-mediated rejection if C4d (in the presence of antibody) or alloantibody (C4d+) not demonstrated in the presence of morphologic evidence of tissue injury.

20.2. MDRD 7 (Estimated GFR)

Modification of Diet in Renal Disease (MDRD) 7 Calculation [53]:

MDRD 7 equation (MDRD7) = 170 × [serum creatinine(mg/dL)]−0.999 × [age]−0.176 × [0.762 if patient is female] × [1.18 if patient is black] × [serum urea nitrogen concentration (mg/dL)]−0.170 × [serum albumin concentration (g/dL)]0.318

20.3. List of Laboratory Tests

Chemistry, Coagulation, Hematology, Urinalysis, Pregnancy, and HLA Tests:

Chemistry			
Sodium	Carbon Dioxide	Total Cholesterol	AST
Potassium	Albumin	Total Protein	ALT
Chloride	BUN	Creatinine	Alkaline Phosphatase
Calcium	Magnesium	Phosphorus	Glucose
Uric Acid	LDH	GGT	Total and Direct Bilirubin
Coagulation			
aPTT	PT	INR	
Complete Blood Count with Differential and Platelet Count			
Hemoglobin	Hematocrit	RBC	WBC
MCV (mean corpuscular volume)	Mean Corpuscular Hemoglobin (MCH)	Mean Corpuscular Hemoglobin Concentration (MCHC)	Platelets
Urinalysis with Microscopy			
Protein	Ketones	WBC's by dipstick	
Glucose	Occult Blood	Microscopy	
Spot Urine for Urine Protein/Creatinine Ratio			
Pregnancy Testing (if applicable)			
Serum beta-hCG			

HLA Laboratory Testing:
Donor Specific Antibody Test - DSA
Complement Dependent Cytotoxicity - CDC
B-cell Flow Cross Match - BFXM
T-cell Flow Cross Match - TFXM