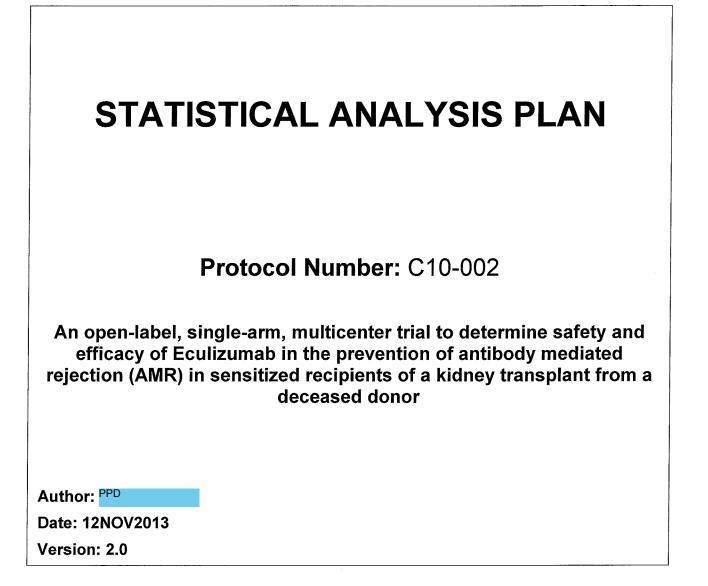
An Open-Label, Single-Arm, Multicenter Trial to Determine Safety and Efficacy of Eculizumab in the Prevention of Antibody Mediated rejection (AMR) in Sensitized Recipients of a Kidney Transplant from a Deceased Donor

Unique Protocol ID:	C10-002
NCT Number:	NCT01567085
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Date of Statistical Analysis Plan:	12 November 2013

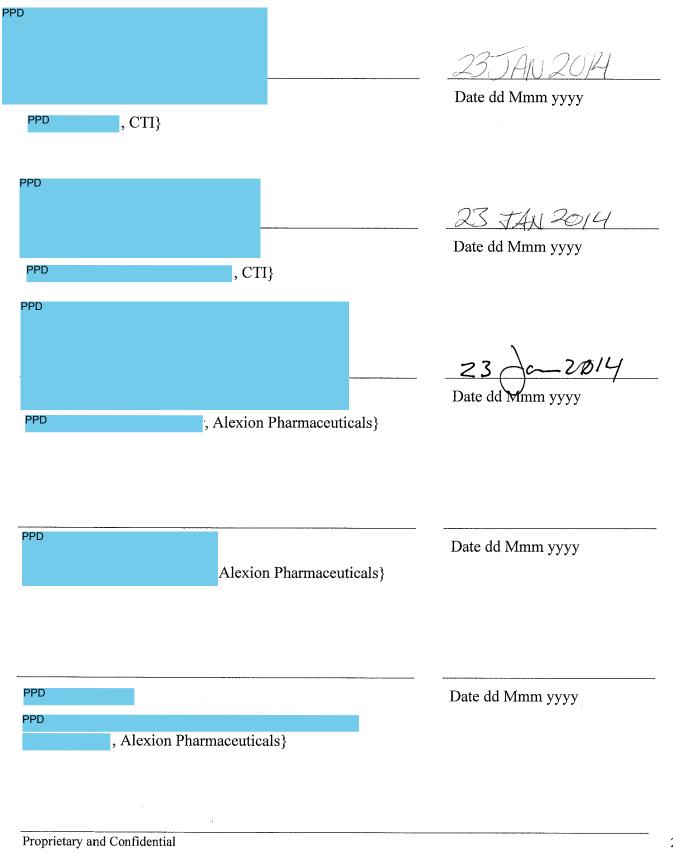
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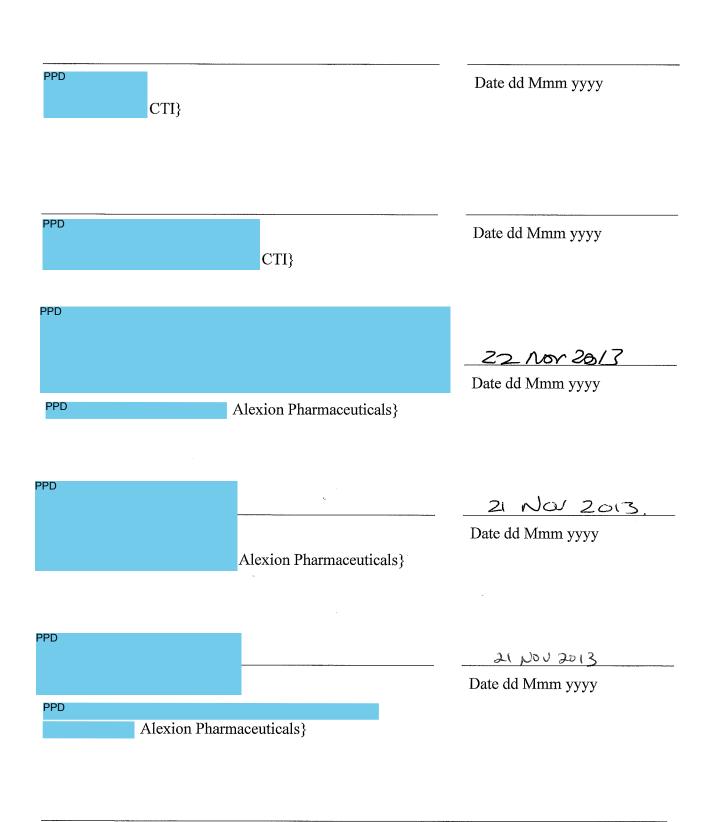


Alexion Pharmaceuticals {Protocol Number: C10-002 08OCT2013 (Final Version 2.0)}

1 APPROVAL SIGNATURES



1 APPROVAL SIGNATURES



Alexion Pharmaceuticals {Protocol Number: C10-002 08OCT2013 (Final Version 2.0)}

2			TABLE OF CONTENTS	
1	Al	PPRO	VAL SIGNATURES	2
2	TA	ABLE	OF CONTENTS	3
3	Al	BBRE	EVIATIONS AND ACRONYMS USED IN THIS DOCUMENT	6
4	DI	ESCR	IPTION OF THE PROTOCOL	7
	4.1	Ove	erview of Study design	7
	4.2	Stu	dy Objective	8
	4.3	Stu	dy Population	8
	4.3	3.1	Main Criteria for Inclusion	9
	4.3	3.2	Exclusion Criteria	9
	4.4	Cha	nges from Analyses Specified in the Protocol	10
	4.5	Cha	nges from Analyses Specified in the Previous Version of the SAP	11
5	Dł	EFINI	TIONS	11
	5.1	Effi	cacy	12
	5.1	1.1	Primary Endpoint(s)	12
	5.1	1.2	Secondary Endpoints	12
	5.1	1.3	Tertiary Endpoints:	13
	5.2	Safe	ety	13
	5.2	2.1	Adverse Events (AEs)	14
	5.2	2.2	Vital Signs	15
	5.2	2.3	Physical Examination	15
	5.2	2.4	Electrocardiogram (ECG)	15
	5.2	2.5	Clinical Laboratory Assessments	15
	5.2	2.6	Other Safety Events of Special Interest	16

Alexion Pharmaceuticals {Protocol Number: C10-002 08OCT2013 (Final Version 2.0)}

6	DA	ATA SETS ANAYLYZED (STUDY POPULATIONS)	1	17
1	6.1	Full Analysis (FA) Set	17	
4	6.2	Per Protocol Set	17	
	5.3	Safety Set	17	
7	ST	ATISTICAL ANALYSIS	1	17
,	7.1	General Considerations	17	
,	7.2	Assessment Windows	18	
,	7.3	Study Patients	19	
	7.3.	.1 Disposition of Patients	19	
	7.3.	.2 Protocol Deviations	19	
	7.3.	.3 Demographics, Disease Characteristics, and History	19	
	7.3.	.4 Concomitant Medications / Therapies	21	
	7.4	Efficacy Analyses	22	
	7.4.	.1 Primary Analysis	22	
	7.4.	.2 Secondary Analyses	24	
	7.4.	.3 Tertiary Analyses	26	
	7.4.	.4 Other Efficacy Analyses	26	
	7.4.	.5 Pharmacokinetic and Pharmacodynamic Analyses	26	
-	7.5	Safety Analyses	26	
	7.5.	.1 Study Duration, Treatment Compliance, and Exposure	26	
	7.5.	.2 Adverse Events (AEs)	27	
	7.5.	.3 Other Safety	29	
8	REI	FERENCES		1
9	API	PENDICIES	3	2

	Pharmaceuticals 1 Number: C10-002 08OCT2013 (Final Version 2.0)}	Statistical Analysis Plan {12NOV2013, Version 2.0}
9.1	Protocol Schedule of events	
9.2	Sample Size and Power	
9.3	Technical Specifications for Derived Variables	
9.4	Listing of Potential Tables and Listings	

3

ABBREVIATIONS AND ACRONYMS USED IN THIS DOCUMENT

The following abbreviations and acronyms are used in this Statistical Analysis Plan (SAP).

ACR	Acute Cellular Rejection	HLA	Human Leukocyte Antigen
AE	Adverse event	INR	International Normalized Ratio
ALT	Alanine aminotransferase (SGPT)	IVIg	Intravenous immunoglobulin
AMR	Antibody-Mediated Rejection	IV	Intravenous
AST	Aspartate aminotransferase (SGOT)	kg	Kilogram
ATC	Anatomical, Therapeutic, and Chemical	LDH	Lactate Dehydrogenase
BFXM	B-Cell Cytometric Flow Crossmatch	MCH	Mean Corpuscular Hemoglobin
BK	BK Virus	MCHC	Mean Corpuscular Hemoglobin Concentration
BUN	Blood Urea Nitrogen	MCV	Mean Corpuscular Volume
CBC	Complete Blood Count	MDRD7	Modification of Diet in Renal Disease 7 variable equation
CDC	Complement-Dependent Cytoxicity	MedDRA	Medical Dictionary for Regulatory Activities
CI	Confidence Interval	Min	Minute
cm	Centimeters	mL	Milliliter
CMV	Cytomegalovirus	mg	Milligrams
DCD	Donor After Cardiac Death	MMF	Mycophenolate Mofetil
DGF	Delayed Graft Function	mmHg	Millimeters of Mercury
dL	Deciliter	PP	Plasmapheresis
DMC	Data Monitoring Committee	РТ	Preferred Term (MedDRA)
DSA	Donor Specific Antibody	PTLD	Post transplant lymphoproliferative disease
EBV	Epstein-Barr Virus	PTT/aPTT	Partial Thromboplastin Time/activated Partial Thromboplastin Time
ECD	Expanded Criteria Donor	RBC	Red Blood Cells
ECG	Electrocardiogram	SAB	Single-bead Antigen
EC-MPS	Enteric Coated Mycophenolate Sodium	SAE	Serious Adverse Event
eGFR	Estimated Glomerular Filtration Rate	SAP	Statistical Analysis Plan
FA	Full Analysis	SAS®	Statistical Analysis Software®
FFP	Fresh Frozen Plasma	SCD	Standard Criteria Donor
GGT	Gamma-Glutamyltransferase	SOC	System Organ Class (MedDRA)
HBV cAb	Hepatitis B Virus Core Antibody	TEAEs	Treatment-Emergent Adverse Events
HBV sAg	Hepatitis B Virus Surface Antigen	TFXM	T-Cell Cytometric Flow Crossmatch
HCV cAb	Hepatitis C Virus Core Antibody	WBC	White Blood Cells
HIV	Human Immunodeficiency Virus		

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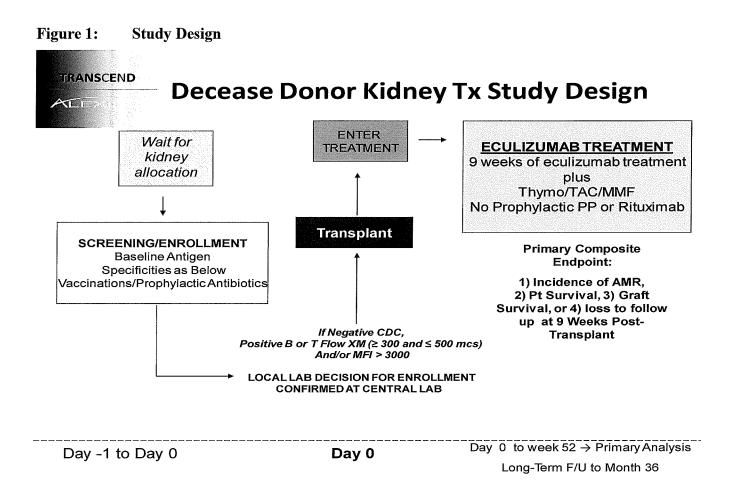
4 DESCRIPTION OF THE PROTOCOL

4.1 Overview of Study design

Eculizumab, an inhibitor of C5, has been shown in clinical studies to successfully reduce the incidence of antibody mediated rejection (AMR) following kidney transplantation of sensitized living donor recipients. This phase II study is designed to assess the safety and potential efficacy of eculizumab on reducing the incidence of AMR in kidney transplant recipients who are sensitized to their deceased donors.

This is an open-label, single-arm, multicenter, phase II study. A schematic representation of the study design is presented in Figure 1. Schedule of Events are provided in Appendix 9.1. Briefly, appropriately screened patients will be enrolled in the study and undergo eculizumab therapy. Patients will receive study drug one hour prior to transplantation to 9 weeks post-transplantation. All patients will receive standard immunosuppression, prophylactic medications and posttransplantation care. The primary efficacy variable is a composite endpoint defined as the occurrence of AMR, graft loss, patient death, or loss to follow-up at Week 9 (Figure 1). The diagnosis of AMR for the determination of the primary efficacy endpoint will be based on "forcause" 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, donor specific antibody (DSA) titers, T-cell flow cross match (TFXM), B-cell flow cross match (BFXM), complement dependent cytotoxicity (CDC), estimated glomerular filtration rate (eGFR), and other clinical and laboratory parameters for evaluation of efficacy and safety. The primary analysis of the data will occur after all patients have reached Month 12 posttransplantation. However, patients will have additional follow up at Months 18, 24, and 36 posttransplantation to assess patient and graft survival, kidney disease, and disease status.

Refer to protocol number C10-002 for further study details.



4.2 Study Objective

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

4.3 Study Population

Approximately 80 adult (at least 18 years of age) male or female deceased donor kidney transplant recipients who meet inclusion/exclusion criteria will be enrolled in the study.

Participating centers will include approximately 20 renal transplant centers in the Europe and Australia with the appropriate patient population.

4.3.1 Main Criteria for Inclusion

- 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
- Historical positive CDC cross match and/or BFXM or TFXM ≥ 300 and ≤ 500mcs (no patient may have > 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.

4.3.2 Exclusion Criteria

- 1. Has received treatment with eculizumab at any time prior to enrolling in this study
- 2. ABO incompatible with deceased donor
- 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®) \leq 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 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
- 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)

4.4 Changes from Analyses Specified in the Protocol

Competing risk analysis will be used to estimate the cumulative risk function (e.g., for delayed AMR between Week 9 and Month 12 and other secondary endpoints) rather than using the Kaplan-Meier estimator. The Kaplan-Meier method has a tendency to overestimate the event probability of interest in the presence of competing risk events (e.g., death or graft loss).

A Full Analysis set will be used for the analysis of the efficacy data. It is defined in Section 6.1.

A Per Protocol analysis set will be created and used for analyses if criteria defined in Section 6.2 are met.

4.5 Changes from Analyses Specified in the Previous Version of the SAP

Sample size was updated to reflect Version 2.0 of the C10-002 protocol.

The derivation of the primary endpoint was clarified to add that biopsies taken for the reason 'proteinuria' or 'increased creatinine' or 'acute tubular necrosis' would also be considered to be biopsies performed 'for cause'. In addition, biopsies performed for the reason 'other, specify' will be reviewed by the Medical Monitor to determine if they should also be included as a biopsy performed 'for cause'. Previously, only biopsies performed for the reason 'suspected rejection' were to be considered biopsies performed 'for cause'.

Two additional exploratory (tertiary) endpoints have been added to be analyzed: DSA and B- and T-cell cross match levels.

Additional displays of exposure (from the first dose to 2 weeks after the last dose of eculizumab) vs. non-exposure (after 2 weeks post the last dose of eculizumab) adverse events have been added.

Two additional adverse events of special interest have been added to be analyzed:

- 1. Cumulative incidence of aspergillus infections by Month 12
- 2. Cumulative incidence of fungal infections by Month 12

5 **DEFINITIONS**

The primary analysis of all endpoints will occur after all patients have reached Month 12 posttransplantation. An interim analysis may be performed after all patients have reached Week 9. All data collected up to Month 12 will be cleaned and the database locked prior to the primary analysis. Methods presented herein pertain to the analysis of all data collected up to Month 12. Patients will be continued to be followed on Months 18, 24, and 36 for collection of additional follow-up data on patient and graft survival, kidney function, and disease status. Methods used to analyze this data will be provided under a separate document.

5.1 Efficacy

5.1.1 **Primary Endpoint(s)**

The primary efficacy endpoint is a composite endpoint defined as the occurrence of 1) biopsyproven AMR, 2) graft loss, 3) patient death, or 4) loss to follow-up by Week 9 posttransplantation. The diagnosis of AMR will be based on kidney allograft dysfunction and biopsy performed "for cause". A biopsy performed due to suspected rejection, proteinuria, increased creatinine, or acute tubular necrosis will be considered performed "for cause". In addition, the Medical Monitor will review biopsies performed due to "other" reasons to determine if any of these should be considered "for cause". The histological diagnosis will be based on Banff 2007 criteria for AMR (Level II or Level III) as determined by the Central Pathology Laboratory. An event that is considered AMR by a local pathologist will not be considered diagnostic for AMR (and meet the primary endpoint definition) unless confirmed by Central Pathology.

The primary efficacy endpoint variable is a binary outcome where patients meeting any one of the above composite endpoints at Week 9 post-transplantation will be considered treatment failures and all others will be considered treatment successes.

5.1.2 Secondary Endpoints

Secondary efficacy endpoints include:

- i. Cumulative incidence of AMR between Week 9 and Month 12 post-transplantation.This includes AMR of any level (grade I, II, or III) that meets Banff 2007 criteria.
- Cumulative incidence of treatment failure, defined as the occurrence of 1) biopsy-proven AMR, 2) graft loss, 3) patient death, or 4) loss to follow-up by Month 12 post-transplantation. Biopsy-proven AMR is defined the same way as in the primary endpoint.
- iii. Graft and patient survival at Month 6 and at Month 12 post-transplantation.
- iv. Histological evidence of AMR on protocol biopsies without other clinical findings at Day 14 and at Month 3 and Month 12 post-transplantation.
- v. Overall pathological changes including chronic AMR on protocol biopsies at Day 14 and at Months 3 and 12 post-transplantation.

- vi. Cumulative number of plasmapheresis (PP) treatments at 12 months posttransplantation.
- vii. Cumulative incidence of patients requiring splenectomy at 12 months posttransplantation.
- viii. Incidence of delayed graft function (DGF) post-transplantation. DGF is defined as the requirement for dialysis within the first week post-transplantation for reasons other than post-operative hyperkalemia, acute pulmonary edema or fluid overload due to comorbid conditions.
- ix. Cumulative incidence and duration of dialysis between Day 7 and Month 12 posttransplantation.
- Number of days the serum creatinine is more than 30% above nadir following the diagnosis of AMR, which follows the same definition of the biopsy-proven AMR as for the primary efficacy endpoint
- xi. Stable renal function between Week 4 and Month 12 post-transplantation as measured by:
 - a. Estimated glomerular filtration rate (calculated) MDRD7 (See Appendix 9.3) 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 $\leq 20\%$.

5.1.3 Tertiary Endpoints:

The following tertiary endpoints will be summarized over time:

- i. DSA levels.
- ii. B- and T-cell cross match levels.

5.2 Safety

Safety assessments will include incidences of adverse events (AEs), serious adverse events (SAEs), predefined abnormal laboratory values, infections (CMV, BK, bacterial, fungal), malignancies, post-transplant lymphoproliferative disorder (PTLD), biopsy-proven acute cellular

rejection, and premature discontinuation for any reason. Safety assessments will also include vital signs, physical examinations, electrocardiogram, hematology, blood chemistry, coagulation, and urinalysis.

5.2.1 Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a patient enrolled in this study regardless of its causal relationship to study treatment.

A treatment-emergent AE (TEAE) is defined as any event not present prior to exposure of study drug or an event already present that worsens in either intensity or frequency following exposure. Any AE that is missing an onset date will be considered treatment-emergent.

All adverse events will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 or higher.

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

- Results in death.
- It is immediately life-threatening.
- 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 on 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.

"Exposure" adverse events will be considered those that have a start date from the first dose of eculizumab to 2 weeks after the last dose of eculizumab . "Non-exposure" adverse events will be considered those that have a start date 2 weeks after the last dose of eculizumab.

5.2.2 Vital Signs

Vital signs including blood pressure (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), and body temperature (⁰C) will be measured as specified in the Schedules of Assessments (See Appendix 9.1). Height (cm) and body weight (kg) will also be collected; however, height will only be measured at the screening visit.

5.2.3 Physical Examination

A complete physical exam will be conducted at the screening visit. Abbreviated physical exams will be performed as specified in the Schedule of Assessments (See Appendix 9.1). The body systems included in these abbreviated exams will be based on Investigator judgment and/or patient symptoms.

5.2.4 Electrocardiogram (ECG)

A 12-lead ECG will be performed at the screening visit (See Appendix 9.1). The data to be collected includes heart rate, PR, QRS, and QT intervals (uncorrected and corrected) and any abnormalities.

5.2.5 Clinical Laboratory Assessments

Blood and urine samples will be collected for laboratory safety tests as specified in the Schedules of Assessments (See Appendix 9.1). Laboratory testing is described below.

Chemistry and Renal Profile:

 Creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR; MDRD7), glucose, total protein, uric acid, total cholesterol, lactic dehydrogenase (LDH) and electrolytes (including sodium, potassium, chloride, calcium, magnesium, and phosphorus)

Hepatic Profile:

• Albumin, total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and gamma glutamyl transferase (GGT)

Complete Blood Count (CBC):

• Hemoglobin, hematocrit, platelets, red blood cell (RBC) count, white blood cell (WBC) count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)

Urinalysis:

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

Coagulation:

• Coagulation testing will include an activated partial thromboplastin time (aPTT), Prothrombin Time (PT), international normalized ratio (INR), and fibrinogen and/or fibrinogen split products.

5.2.6 Other Safety Events of Special Interest

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 by Month 12
- 4. Cumulative incidence of CMV disease by Month 12
- 5. Cumulative incidence of BK virus disease by Month 12
- 6. Cumulative incidence of encapsulated bacterial infections by Month 12
- 7. Cumulative incidence of aspergillus infections by Month 12
- 8. Cumulative incidence of fungal infections by Month 12
- 9. Cumulative incidence of PTLD (post transplant lymphoproliferative disease) by Month 12
- 10. Cumulative incidence of any malignancy by Month 12
- Cumulative incidence of biopsy-proven acute cellular rejection that meets Banff 2007 criteria of any grade by Month 12
- 12. Proportion of patients that develop severe acute cellular rejection that do not respond to thymoglobulin or other lymphocyte depleting agents by Month 12
- 13. Cumulative incidence of allograft loss for reasons other than AMR by Month 12

6

DATA SETS ANAYLYZED (STUDY POPULATIONS)

6.1 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.

6.2 Per Protocol Set

Patients who experience a major protocol deviation as defined in Section 7.3.2 or any other 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.

6.3 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.

7 STATISTICAL ANALYSIS

7.1 General Considerations

Due to the small number of patients expected to enroll at each center, all summaries, and analyses will be performed using data pooled across centers. Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations, mean, standard deviation, median, inter-quartile range, minimum and maximum. Categorical variables will be summarized by presenting the number of patients and percentage for each category.

Analyses will be performed using SAS for Windows statistical software (SAS, Cary, NC) version 9.2, except where other software may be deemed more appropriate (e.g., R).

Patient data will be listed, sorted by investigative center, patient number, and chronological order (where appropriate). Deviations from the statistical analysis plan will be documented in the clinical trial report.

7.2 Assessment Windows

For the purpose of listing and summarizing data, the time-in-study for each patient observation will be defined using study days. Such days will be measured relative to day of transplantation (Day 0). Because protocol-specified visits (e.g., Days 14 and 63) will not necessarily occur on the same study day for all patients, study visits will be defined through the use of windows. Analyses that summarize data for a specific visit will exclude data that is collected outside of the visit window. If a patient has multiple values of the same data within a window, the closest value to the protocol-specified visit will be used. If there is a tie in determining the closest value, then the data value just prior to the protocol-specified visit will be used. All Study Visits will be assigned per the following schema (Table 1):

Study Visit	Visit and Laboratory Testing Window	Study Visit Window (Study Visit Start – Study Visit End)				
Day -1 to Day 0 prior to transplant	Screening/Enrollment	-				
Day 0	Day of transplantation (defined by time of graft reperfusion in the recipient)	-				
Days 1,2,3,4,5, and 6	No windows	-				
Day 7	- 0 / + 3 days	Day 7 – 10				
Day 14 (Week 2)	± 3 days	Day 11 – 17				
Day 21 (Week 3)	± 3 days	Day 18-24				
Day 28 (Week 4)	± 3 days	Day 25 – 31				
Day 35 (Week 5)	- 3 / + 6 days	Day 32 – 41				
Day 49 (Week 7)	- 7 / + 3 days	Day 42 – 52				
Day 56 (Week 8)	± 3 days	Day 53 – 59				
Day 63 (Week 9)	- 3 / + 10 days	Day 60 – 73				
Month 3 (Week 12, Day 84)	- 10 / + 17 days	Day 74 – 101				
Month 4 (Week 17, Day 119)	- 17 / + 13 days	Day 102 – 132				
Month 5 (Week 21, Day 147)	- 14 / + 17 days	Day 133 – 164				
Month 6 (Week 26, Day 182)	- 17 / + 13 days	Day 165 – 195				
Month 7 (Week 30, Day 210)	- 14 / + 13 days	Day 196 – 223				
Month 8 (Week 34, Day 238)	- 14 / + 13 days	Day 224 – 251				
Month 9 (Week 38, Day 266)	- 14 / + 20 days	Day 252 – 286				

Table 1:Definition of Study Visit Windows

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Study Visit	Visit and Laboratory Testing Window	Study Visit Window (Study Visit Start – Study Visit End)
Month 10 (Week 44, Day 308)	- 21 / + 13 days	Day 287 – 321
Month 11 (Week 48, Day 336)	- 14 / + 13 days	Day 322 – 349
Month 12 (Week 52, Day 364)	- 14 / + 45 days	Day 350 – 409

7.3 Study Patients

7.3.1 Disposition of Patients

The number and percent of patients completing the study will be described for all patients. For patients who discontinued the study, the reason for discontinuation will be summarized. In addition, the number of patients who discontinued treatment due to an adverse event will be summarized.

7.3.2 Protocol Deviations

The number and percent of patients with specific major protocol deviations will be summarized using all patients in the FA. The following major protocol deviations will be determined programmatically from the database:

- Patients who violated any inclusion/exclusion criteria.
- Patients who took prohibited medications.
- Patients who received less than 8 of 9 IV infusions of study drug.
- Patients who had major deviations with study drug administration receiving < 80% or > 125% of the recommended total dose in the first 9 weeks.

Protocol deviations from monitoring reports and other relevant sources will also be reviewed, and any important deviations will be included in the list that is summarized and reported.

7.3.3 Demographics, Disease Characteristics, and History

All demographic and baseline characteristics information is summarized using the FA set. Appropriate summary statistics will be presented.

7.3.3.1 Recipient Demographic

The following demographic variables for the recipient will be summarized:

- Sex, race/ethnicity, age (years) at time of transplantation
- Weight (kg) and height (cm)
- Primary cause of chronic kidney disease

7.3.3.2 Donor Demographic

The following demographic variables for the donor will be summarized:

- Sex, race/ethnicity, age (years) at time of death/transplantation
- Donor type (ECD, SCD, DCD)

7.3.3.3 Kidney Disease Information

The following renal failure information will be summarized.

• Duration of chronic renal failure prior to transplantation (months)

7.3.3.4 Dialysis History

The following information on dialysis prior to transplantation will be summarized.

- Was patient on dialysis at time of transplantation
- Duration of dialysis (months)

7.3.3.5 Medical / Surgical History

The number and percent of patients with previous and active medical or surgical conditions at screening will be summarized and presented by MedDRA SOC and PT.

7.3.3.6 Transplant Related Information

The following transplant-related information will be summarized:

- Number and percent of previous kidney transplants
- Type of transplant and reason for allograft loss
- Donor and recipient viral serology status (CMV, EBV, HCV cAb, HBV cAb, HBV sAg, HIV)
- ABO compatibility

- Panel reactive antibody (%)
- Number of HLA mismatches at the A, B, and DR loci (See Appendix 9.3 for details on calculation of HLA mismatches)
- Cold and warm ischemia times (minutes)
- Organ storage method (pump, static, or other)

7.3.3.7 Immunology Information

The following immunologic information will be summarized:

- B- and T-cell cross match levels (mcs)
- Donor specific antibody Class I and Class II status (number and levels)
 - Class I includes the following:
 - HLA A Antigens 1 & 2
 - HLA B Antigens 1 & 2
 - HLA C Antigens 1 & 2
 - Class II includes the following:
 - HLA DR Antigens 1 & 2
 - HLA DRB 3, 4, 5 Antigens 1 & 2
 - HLA DQB1 Antigen 1
 - HLA DQ Antigen 2
 - HLA DPB1 Antigens 1 & 2
 - HLA DQA1 Antigens 1 & 2
 - HLA DPA1 Antigens 1 & 2
- Total DSA level, highest single DSA level, and number of DSA

7.3.3.8 Baseline Electrocardiogram (ECG)

A listing of the screening ECG results (including PR, QRS, QT intervals, and abnormalities) will be presented by patient.

7.3.4 Concomitant Medications / Therapies

Concomitant medications will be coded using the World Health Organization (WHO) drug classifications (WHO-DD 01MAR2010). Tables and listings will show all concomitant medications and therapies used during the study including post-transplant immunosuppression.

The number and percent of patients using all non-immunosuppression concomitant and prophylactic medications/therapies will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class and by preferred term. Maintenance immunosuppression medications including Tacrolimus (total daily dose [mg] and levels [ng/mL]), mycophenolic acid (MMF, EC-MPS, or generic total daily dose [mg]), and corticosteroids usage (total daily dose [mg]) will be summarized at each visit using descriptive statistics. Induction therapy, Thymoglobulin (total daily dose [mg]), will also be summarized at each visit using descriptive statistics.

All concomitant medication data will be listed, sorted by investigative site and patient number, start and stop date. Information listed will include medication, indication, dose, frequency and route of administration.

7.4 Efficacy Analyses

The primary analysis of all endpoints will occur after all patients have reached Month 12 (Day 364) post-transplantation.

All efficacy analyses will be performed using the FA set. A two-sided Type I error rate of 0.05 will be used to define statistical significance for all endpoints without adjusting for multiplicity.

7.4.1 Primary Analysis

The primary efficacy variable is a binary outcome variable where patients meeting the composite endpoint definition defined in Section 5.1.1 will be considered either treatment failures or treatment successes. The point estimate of the incidence of treatment failure at Week 9 (Day 63) will be presented along with an exact 95% confidence interval (CI). Test of the null hypothesis that the true treatment failure rate is equal to 40% will be performed using the exact binomial test.

7.4.1.1 Handling of Dropouts or Missing Data

For the primary efficacy endpoint analysis, all patients will be categorized as either treatment failures or treatment successes at Week 9 given that the primary endpoint definition is a composite that includes loss to follow-up. Therefore, no patient should have missing data for the primary endpoint.

Missing data on time to event endpoints will have events coded as right censored per the Table 2.

Table 2: 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. Competing risk methods will be used to account for competing events (eg, death, allograft loss).
Time to delayed AMR between Week 9 and Month 12	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. Competing risk methods will be used to account for competing events (eg, death, allograft loss).
Time to first biopsy-proven ACR, clinically significant infection, CMV and BK virus disease, PTLD, malignancy, treatment-resistant severe ACR, and allograft loss for reasons other than AMR	Patients who did not experience the events of interest during follow-up will be right censored as of the date of last patient contact. Competing risk methods will be used to account for competing events (eg, death, allograft loss).
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.

7.4.1.2 Subgroup Analysis

No predefined subgroup analyses will be performed. If data permit, subgroups will be explored ad hoc.

7.4.1.3 Multicenter Studies

The primary endpoint will be presented pooled across centers and by highest enrolling centers (centers enrolling 5 or more patients). All other analyses will be performed using data pooled across centers.

7.4.1.4 Hypothesis Testing and Significance Level

A two-sided Type I error rate of 0.05 will be used to define statistical significance for all endpoints without adjusting for multiplicity.

7.4.1.5 Sensitivity Analyses

A sensitivity analysis of Per Protocol treatment efficacy will be performed given that the criteria in Section 6.2 are met and a Per Protocol analysis set is created. All efficacy analyses will be repeated as described using the Per Protocol set.

A sensitivity analysis is planned to explore the effects of local vs. central pathology results on the primary efficacy endpoint (Section 5.1.1). The analysis in Section 7.4.1 will be repeated using the same composite endpoint defined as the occurrence of 1) biopsy-proven AMR, 2) graft loss, 3) patient death, or 4) loss to follow-up by Week 9 post-transplantation. However, the histological diagnosis will be based on Banff 2007 criteria for AMR (Level II or Level III) as determined by local pathology rather than central pathology.

7.4.2 Secondary Analyses

Secondary efficacy endpoints for analysis are listed in Section 5.1.2. The corresponding method of statistical analysis is provided below:

- i. The cumulative incidence function of AMR between Week 9 (Day 63) and Month 12 (Day 364) will be estimated using competing risk survival analysis methods. Estimation will be performed utilizing the SAS macro %CIF (<u>http://support.sas.com/kb/45/997.html</u>).
 Point estimates and corresponding 95% CIs will be provided. Patients alive with functioning graft and no evidence of AMR of any grade at Week 9 will be included in the analysis.
- ii. Treatment failure rate at Month 12 post-transplantation will be analyzed using similar methods as described in Section 7.4.1 for the primary efficacy endpoint. Test of the null hypothesis that the true treatment failure rate is equal to 40% will be performed using the exact binomial test.
- iii. Patient and graft survival at Month 6 and at Month 12 will be estimated by the Kaplan-Meier product-limit method. Point estimates for both time points and corresponding 95% CIs will be provided. Greenwood's formula (Greenwood, 1926) will be used to calculate the standard error for the 95% CIs.
- iv. Histological evidence of AMR will be defined as a biopsy performed for a reason of per protocol with a finding of antibody mediated rejection. The number and percent of

patients with AMR diagnosed solely on histological evidence from protocol biopsies at Day 14 and Months 3 and 12 will be provided.

- v. Pathological changes will come from the results of a per protocol biopsy. Findings to be summarized include AMR type: Acute AMR Banff grade I, II, III, Chronic AMR; T-Cell Mediated Rejection (TCR) type: Acute TCR Banff grade IA, IB, IIA, IIB, III, Chronic TCR. The number and percent of patients with each pathological finding at Day 14, and Months 3 and 12 will be provided. The summary of these findings over time will constitute the 'overall pathological changes'.
- vi. Cumulative number of PP treatments observed at Week 9 and Month 12 posttransplantation will be summarized using descriptive statistics. The mean cumulative function of the number of PP treatments over time will be estimated using recurrent events data analysis methods (Lawless and Nadeau, 1995). A point estimate for each time point and corresponding 95% CIs will be provided.
- vii. Cumulative incidence of patients requiring a surgical procedure of a splenectomy at Week 9 and Month 12 post-transplantation will be estimated using methods described in bullet (i) for delayed AMR. However, all patients will be included in the analysis.
- viii. Incidence of delayed graft function will be provided along with a 95% CI.
- ix. Cumulative incidence function of the need for dialysis between Day 7 and Month 12 posttransplantation will be estimated using methods described in bullet (i). The duration of dialysis (last dialysis date – first dialysis date) beyond 7 days post-transplantation will be summarized using descriptive statistics. Patients who have delayed graft function will be excluded from the analysis.
- x. The number of days at Month 12 post-transplantation that serum creatinine is more than 30% above nadir following the diagnosis of AMR will be summarized using descriptive statistics.
- xi. Renal function will be measured by serum creatinine and estimated glomerular filtration rate (eGFR) using the MDRD7 equation. Summary statistics of the change in renal function between Week 4 (Day 28) and Month 12 (Day 364) post-transplantation will be provided at Days 28, 35, 49, 56, 63, 84, 119, 147, 182, 210, 238, 266, 308, 336 and 364 (week 52). The time from Week 4 to stable renal function as defined in Section 5.1.2 (xi.a) and (xi.b) will be summarized using descriptive statistics. The date of when stable

renal function begins will be determined through medical review. To facilitate the medical review, listings of a patient's renal function over time will be provided for those who have serum creatinine or eGFR which does not vary more than 20% over 3 consecutive measurements taken at least 2 days apart while not on PP or dialysis.

7.4.3 Tertiary Analyses

- Total DSA level, highest single DSA level, percentage of patients with class I and class II DSA, and number of DSA over time will be summarized using descriptive statistics.
- B- and T-cell cross match levels over time will be summarized using descriptive statistics.

7.4.4 Other Efficacy Analyses

Not applicable.

7.4.5 Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic analyses are being performed by Alexion and the methods utilized will be detailed in a separate analysis plan.

7.5 Safety Analyses

Safety assessments will consist of summarizing all AEs, including SAEs, infections (CMV, BK, bacterial, fungal infection), biopsy-proven acute cellular rejection, and malignancies, and laboratory values including, hematology, blood chemistry, coagulation, and urine results. Study drug exposure, and regular monitoring of vital signs, physical condition and body weight measurements will also be summarized.

All safety analyses will be conducted on the Safety set.

7.5.1 Study Duration, Treatment Compliance, and Exposure

Eculizumab is administered intravenously as a fixed dose (over a 25 to 45 minute interval) depending upon the time relative to transplantation. Treatment will start during the transplantation procedure (Day 0) and continue as displayed in Table 3.

Dose	Time				
1200 mg Day 0 – Administered in the operating room ~1 hour prior to kidney allograft reperfusion					
900 mg	Post-transplantation – Days 1, 7, 14 (\pm 2 days), 21 (\pm 2 days), 28 ((\pm 2 days))				
1200 mg	Post-transplantation - Week 5 (Day 35 +/- 2 days), Week 7 (Day 49 +/- 2 days), Week 9 (Day 63 +/- 2 days)				

Table 3: Dose of Eculizumab

A total of nine IV infusions are planned. Eculizumab infusion may be slowed or stopped due to the occurrence of adverse events and/or at the discretion of the PI. Summary statistics (non-missing observations, mean, median, standard deviation, minimum and maximum values) of eculizumab dose actually received (mg) and duration of infusion by time of treatment post-transplantation will be tabulated. Reason(s) for slowing or stopping eculizumab infusion will also be tabulated.

7.5.2 Adverse Events (AEs)

All AEs (serious and non serious) occurring after completion of the informed consent process and before the end of study, regardless of relationship to study drug, will be included and classified by SOC and PT. All adverse events will be summarized for the whole study duration and also by the exposure and non-exposure study periods defined as: (1) first dose of eculizumab -2 weeks after the last dose of eculizumab, and (2) > 2 weeks after the last dose of eculizumab.

All AEs and SAEs will be presented in individual listings. The listing will contain the following information: verbatim term, SOC, PT, intensity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE, whether it led to withdrawal and whether it is a TEAE. Listings will be sorted by patient identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

7.5.2.1 Treatment-Emergent Adverse Events (TEAEs)

An overall summary of all TEAEs defined in Section 5.2.1 will be presented and will include the following:

- the number and percentage of patients experiencing a TEAE
- the number and percentage of patients experiencing a TEAE by strongest relationship to study medication
- the number and percentage of patients experiencing a TEAE by greatest intensity
- the number and percentage of patients experiencing a TEAE leading to treatment withdrawal
- the number and percentage of patients experiencing a treatment emergent SAE (TESAE)

In the overall summary of TEAEs table, besides tabulating the number and percentage of patients, the total number of TEAE episodes will also be provided. If a patient has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

The number of TEAEs and the number and percentage of patients with TEAEs that led to permanent discontinuation of study drug will be summarized by SOC and PT.

7.5.2.2 TEAEs by System Organ Class (SOC) and Preferred Term (PT)

The number of TEAEs, and the number and percentage of patients with treatment-emergent AEs will be summarized by SOC and PT. The incidence of TEAEs will be calculated by dividing the number of patients who have experienced the event by the total number of patients in the Safety set. Thus, the incidence of TEAEs is shown in terms of the total number of patients and not in terms of the total number of episodes. If a patient has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to study drug, will be counted in the summary tables.

A patient with more than one type of TEAE in a particular SOC will be counted only once in the total of patients experiencing TEAEs in that particular SOC. Since a patient could have more than one type of TEAE within a particular SOC, the sum of patients experiencing different TEAEs within the SOC could appear larger than the total number of patients experiencing TEAEs in that SOC. Similarly, a patient who has experienced a TEAE in more than one SOC will be counted only once in the total number of patients experiencing AEs in all SOCs.

7.5.2.3 TEAEs by SOC, PT, and Relationship

The number of TEAEs and the number and percentage of patients with TEAEs will be summarized as described in Section 7.5.2.2 but by SOC, PT, and relationship to study drug (unrelated, unlikely, possible, probable, or definite). In addition, the same summary will be repeated for grouped relationship to study drug (related, unrelated), where possible, probable, and definite relationships are grouped as related and unrelated and unlikely as unrelated.

7.5.2.4 TEAEs by SOC, PT, and Intensity

The number of TEAEs and the number and percentage of patients with TEAEs will be summarized as described in Section 7.5.2.2 but by SOC, PT, and intensity (mild, moderate, or severe).

7.5.2.5 Deaths, Other SAEs, and Other Significant Adverse Events

Patient listings of all deaths and their causes as well as all allograft failures and their causes will be provided.

7.5.3 Other Safety

7.5.3.1 Analyses for Laboratory Tests

Descriptive statistics by time of assessment will be presented for each laboratory parameter. Changes from baseline (screening) as well as shift tables will be presented. All laboratory values will be classified as low, normal, or high based on normal ranges supplied by each local laboratory. For purposes of analyses, laboratory results based upon standardized units will be used.

For each summary, the number of non-missing observations, mean, median, standard deviation, inter-quartile range, minimum, and maximum values will be presented.

7.5.3.2 Vital Signs

Vital sign measurements will be summarized at baseline (screening) and at post-transplantation Study Day visits. In addition, at each post-transplantation visit, changes from baseline will be summarized. If a screening vital sign measurement value is missing, change from baseline will be missing as well. For each summary, the number of non-missing observations, mean, median, standard deviation, inter-quartile range, minimum, and maximum will be presented.

7.5.3.3 Physical Examination

The number and percentage of patients with physical examination abnormalities at each visit will be summarized and presented for each body system. A listing of abnormalities will also be provided.

7.5.3.4 Pregnancy Test

A by patient listing of all pregnancy tests will be provided.

7.5.3.5 Other Safety Parameters of Special Interest

Cumulative incidence functions for clinically significant infection, CMV and BK virus disease, encapsulated bacterial infections, fungal infections, PTLD, malignancy, biopsy-proven ACR, treatment-resistant severe ACR, and allograft loss for reasons other than AMR will be estimated using competing risk survival analysis techniques utilizing the SAS %CIF macro. Cumulative incidence rates at Week 9 and at Month 12 post-transplantation will be provided.

8 **REFERENCES**

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Greenwood M. The natural duration of cancer. Reports of Public Health and Medical Subjects. 1926; 33:London: Her Majesty's Stationary Office.

Lawless, J. F. and Nadeau, C. (1995). Some Simple Robust Methods for the Analysis of Recurrent Events. Technometrics, 37, 158–168.

SAS macro %CIF. http://support.sas.com/kb/45/997.html

9 APPENDICIES

9.1 Protocol Schedule of events

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

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 revaccinated 30 days after initial vaccination.

c. BFXM, TFXM, 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 2:Schedule	of Assessme	nt - Immed	liate Post '	Transplan	t 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	Х							
Abbreviated Physical Exam including Vital Signs and Weight ^a		Х	Х	Х	Х	Х	Х	X
Clinical Assessment including Evaluation for Rejection		Х	Х	Х	Х	Х	Х	X
Administer Eculizumab ^b	X°	X ^d						X ^d
Hematology Panel including WBC diff., Plts, Hgb	Х	Х	Х	Х	Х	Х	Х	X
Chemistry Panel including SCr and BUN	Х	Х	Х	Х	Х	Х	Х	X
PK, PT and PD ^e	B/P	T/P						T/P
Urinalysis	Х							Х
Spot Urine for Urine Protein/Creatinine Ratio								Х
aPTT and INR	Х	Х	X	Х	X	Х	Х	Х
Tacrolimus trough		Х	X	Х	Х	Х	Х	Х
BFXM and TFXM ^f	Х	Х						Х
DSA by Luminex LabScreen ^f	Х	Х						Х
Assess renal function/ need for dialysis	Х	Х	X	X	X	Х	Х	Х
Kidney Allograft Biopsy (post reperfusion)	Х							
Concomitant Medications	X	X	X	Х	Х	Х	Х	Х
Immunosuppressive Medications	Х	Х	Х	X	X	X	Х	Х
Adverse Event Assessment	Х	X	X	X	X	X	X	Х

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 35-45 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 35-45 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, TFXM and/or 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.

Transplant Study Visit	Day	Day	Day	Day	Day	Day	Mo.	Mo.	Mo.	Mo.	Mo.	Mo.	Mo.
	14	21	28	s 35 & 49	56	63	3	4 & 5	6	7& 8	9	10 & 11	12
Study Week	Wee	Wee	Wee	Wee	Wee	Wee	Wee	Wee	Wee	Wee	Wee	Wee	Wee
-	k 2	k 3	k 4	k5 & 7	k 8	k 9	k 12	k17 & 21	k 26	k30 & 34	k 38	k44 & 48	k 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							Х		Х				x
Abbreviated Physical Exam Including Vital Signs and Weight ^a	Х	Х	Х	Х	Х	Х		Х		х	Х	Х	
Clinical Assessment including Evaluation for Rejection	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Administer Eculizumab ^b	X°	X°	X°	X ^d		X ^d							
Hematology Panel including WBC diff, Plts, Hgb	Х	Х	Х		Х	Х	Х		Х		Х		Х
Chemistry Panel including SCr and BUN	х	Х	Х	X ^e	Х	Х	Х	X ^e	Х	Xe	Х	X ^e	X
PK and PD ^f	T/P		T/P	T/P		T/P							
Urinalysis			Х			Х	Х		Х				Х
Spot Urine for Urine Protein/Creatinine Ratio			Х			X	Х		X				Х
aPTT, PT and INR	Х	X	Х		Х	Х	X		X		Х		Х
Tacrolimus trough	X	Х	Х	X	X	X	Х	Х	X	Х	Х	Х	X
BFXM and TFXM ^g	Х	Х	X			Х	Х		Х				Х
DSA by Luminex LabScreen ^g	X	X	Х			Х	Х		Х				Х
Assess Renal Function / need for dialysis	Х	X	Х	X	Х	Х	Х	X	X	X	X	X	Х
eGFR (MDRD 7)			X		Х	Х	X		Х		X		Х
Kidney Allograft Biopsy	Х				,		Х						X
Concomitant Medications	Х	X	X	Х	Х	X	X	Х	X	X	X	X	Х
Immunosuppressive Medications	Х	X	Х	Х	Х	Х	Х	X	Х	X	X	x	X
Adverse Event Assessment	X	X	X	X	X	X	X	x	x	X	X	X	Х

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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 35-45 minutes

d. Administer eculizumab 1200 mg (4 vials) IV at Weeks 5, 7, 9 over 35-45 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, TFXM and/or 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.

9.2 Sample Size and Power

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 followup (Section 5.1.1). Sample size and power considerations are based on the primary efficacy variable and a single arm study with the following conditions/assumptions:

- 1) Composite endpoint true treatment failure rate at Week 9 post-transplantation with standard of care in the study population is, $\pi_0 = 40\%$
- 2) Composite endpoint treatment failure rate at Week 9 post-transplantation with eculizumab is, $\pi_1=20\%$
- 3) Null hypothesis, $H_0: \pi_1 = 40\%$
- 4) Alternative hypothesis, $H_1: \pi_1 \neq 40\%$
- 5) Type I error, $\alpha = 0.05$ (two-sided significance test)
- 6) 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 background treatment failure rate of 40% was derived from a pooled analysis of AMR incidence obtained from the literature (See Table 14, p. 106 of Protocol C10-011).

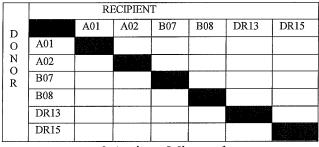
9.3 Technical Specifications for Derived Variables

Estimated GFR

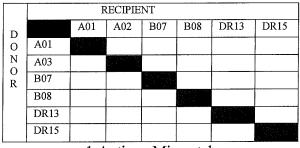
Estimated GFR (mL/min/ $1.73m^2$) at study day visits will be calculated using the MDRD 7-variable equation:

170 X [serum creatinine (mg/dL)]^{-0.999} X [age(years)]^{-0.176} X [0.762 if patient is female] X [1.18 if patient is black] X [serum urea nitrogen concentration (mg/dL)]^{-0.170} X [serum albumin concentration (g/dL)]^{0.318}

Example HLA Mismatch Calculations

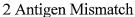


HLA: Mismatched Antigens



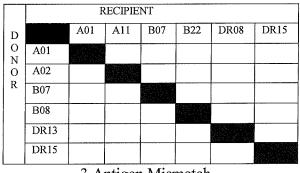
0 Antigen Mismatch

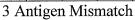
		R	ECIPIEN	Т			
D		A01	A02	B07	B08	DR13	DR09
O N	A01						
0	A02						
R	B44						
	B08						
	DR13						
	DR15						
	2 Antigon Migmotoh						



		R	ECIPIEN	Т			
D		A01	A02	B07	B08	DR13	DR15
O N	A03						
0	A02						
R	B60						
	B51						
	DR13						
	DR14						

1 Antigen Mismatch





		R	ECIPIE	NT			
D		A01	A02	B27	B08	DR11	DR15
0	A24			-			
N O	A33						
R	B07						
	B08						
	DR13						
	DR17						

4 Antigen Mismatch

RECIPIENT A02 DR13 **DR15** B07 B08 A01 D 0 A24 Ν A33 0 R B27 B56 **DR17 DR18**

5 Antigen Mismatch



6 Antigen Mismatch

Homozygosity: Instances in which antigens are not defined are typically a result of homozygosity. Homozygosity is defined as the condition of having identical genes at one or more loci (A, B, DR). As HLA genes are inherited from the mother and the father, if the mother and father share an antigen or multiple antigens, it is possible for a child to inherit the same A and/or B and/or DR antigen from both parents. When this occurs, antigens suspected to be duplicated are termed "blank", and the results will appear as shown below.

		I	RECIPIE	ENT		
D		A01		B03	DR13	
D O N	A01					
0						
R	B03					
	DR13					

Example 1

0 Antigen Mismatch

("blanks" on donor and recipient) No antigens differ between the recipient and donor. This combination would qualify as a 0 antigen mismatch.

		Ι	RECIPIE	ENT			
D		A01	A02	B03	B44	DR13	DR17
O N	A01						
0							
R	B03						
	DR13						

Example 2

0 Antigen Mismatch

("blanks" on donor only)

Because the donor does not express any antigens the recipient does not express, this combination would also qualify as a 0 antigen mismatch.

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		F	RECIPIE	NT		
D		A01		B03	DR13	
D O N	A01					
0	A02					
R	B03					
	B44					
	DR13					
	DR17					

Example 3 <u>3 Antigen Mismatch</u>

("blanks" on recipient only) If Example 2 is reversed and the donor expresses antigens that the recipient does not, these will qualify as mismatched antigens. The recipient immune system may now recognize the A02, B44, and DR 17 from the donor as foreign and mount an immune response.

SUSPECTE	D
MATCH	

Other Data Derivations

Derived data set specifications will be developed according to relevant standard operating procedures (SOPs) and be finalized before creation of derived data sets.

9.4 Listing of Potential Tables and Listings

<u>Tables</u>

Standard and Baseline Summary Tables

Table 14.1.2.1	Patient Disposition
Table 14.1.2.2	Major Protocol Deviations
Table 14.1.1.1	Recipient Demographics and Baseline Characteristics
Table 14.1.1.2	Donor Demographics and Baseline Characteristics
Table 14.1.1.3	Baseline Disease Characteristics
Table 14.1.1.4	Baseline Viral Serology Status
Table 14.1.1.5	Baseline Transplant Information
Table 14.1.1.6	Baseline Immunology Information
Table 14.1.1.7	Baseline Dialysis Information
Table 14.1.3	Medical and Surgical History
Table 14.1.4.1	Concomitant Medications Used During Study
Table 14.1.4.2	Summary of Immunosuppression Medications Used During Study, By Visit

Eculizumab Drug Exposure

Table 14.3.1.1	Summary of Treatment Exposure
Table 14.3.1.2	Summary of Treatment Exposure, By Visit
Primary Endpoint Tables	
Table 14.2.1.1	Summary of Primary Composite Endpoint - Week 9
Table 14.2.1.2	Summary of Primary Composite Endpoint by Highest Enrolling Centers -
	Week 9

Secondary Endpoint Tables

Cumulative Incidence of AMR Between Week 9 and Month 12:

Alexion Pharmaceuticals {Protocol Number: C10-002 0800	CT2013 (Final Version 2.0)}	Statistical Analysis Plan {12NOV2013, Version 2.0}
Table 14.2.2.1	Cumulative Incidence of AMR - Month 12	
Treatment Failure Rate at M	onth 12:	
Table 14.2.2.2	Summary of Primary Composite Endpoint -	- Month 12
Patient and Graft Survival:		
Table 14.2.2.3	Summary of Patient and Graft Survival - M	onth 6 and Month 12
Cumulative Incidence of AM	IR Diagnosed on Histological Evidence:	
Table 14.2.2.4	Incidences of AMR - Day 14, Month 3 and	Month 12
Table 14.2.2.5	Pathological Changes on Protocol Biopsies 12	- Day 14, Month 3 and Month
Plasmapheresis:		
Table 14.2.2.6	Cumulative Number of Plasmapheresis Trea	atments – Week 9 and Month
Cumulative Incidence of Pat	ients Requiring Splenectomy:	
Table 14.2.2.7	Cumulative Incidence of Splenectomy – We	eek 9 and Month 12
Incidence of Delayed Graft F	Function:	
Table 14.2.2.8	Incidence of Delayed Graft Function	
Cumulative Incidence of the	Need for Dialysis:	
Table 14.2.2.9	Summary of Dialysis - Month 12	
Number of Days Serum Crea	tinine > 30% Nadir:	
Table 14.2.2.10	Number of Days Serum Creatinine is Greate	er than 30% Nadir
Change in Renal Function:		
Table 14.2.2.11	Summary of Renal Function: Serum Creatin	ine Over TIme
Table 14.2.2.12	Summary of Renal Function: eGFR Over Ti	me
Table 14.2.2.13	Summary of Time to Stable Renal Function	
Safety Tables		

Proprietary and Confidential

Table 14.3.1.3	Overview of All Treatment-Emergent Adverse Events
Table 14.3.1.4	Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term
Table 14.3.1.5	Treatment-Emergent Adverse Events Leading to Study Treatment Discontinuation by MedDRA SOC and Preferred Term
Table 14.3.1.6	Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term by Relationship
Table 14.3.1.7	Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term by Grouped Relationship (Related/Not Related)
Table 14.3.1.8	Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term by Intensity
Table 14.3.4.1.1	Summary of Laboratory Results: Chemistry and Renal
Table 14.3.4.1.2	Summary of Chemistry and Renal Shifts
Table 14.3.4.2.1	Summary of Laboratory Results: Hepatic Profile
Table 14.3.4.2.2	Summary of Hepatic Profile Shifts
Table 14.3.4.3.1	Summary of Laboratory Results: Complete Blood Count
Table 14.3.4.3.2	Summary of Complete Blood Count Shifts
Table 14.3.4.4.1	Summary of Laboratory Results: Urinalysis
Table 14.3.4.4.2	Summary of Urinalysis Shifts
Table 14.3.4.5.1	Summary of Laboratory Results: Coagulation
Table 14.3.4.5.2	Summary of Coagulation Shifts
Table 14.3.5.1	Summary of Vital Signs
Table 14.3.5.2	Summary of Physical Examination Abnormalities by Visit
Cumulative Incidence of Spec	cial Interest Safety Events
Table 14.3.5.3	Cumulative Incidences of Clinically Significant Infections

Table 14.3.5.4	Cumulative Incidence of CMV Disease
Table 14.3.5.5	Cumulative Incidence of BK Virus
Table 14.3.5.6	Cumulative Incidence of Encapsulated Bacterial Infections
Table 14.3.5.7	Cumulative Incidence of PTLD
Table 14.3.5.8	Cumulative Incidence of Malignancies
Table 14.3.5.9	Cumulative Incidence of Biopsy Proven ACR
Table 14.3.5.10	Cumulative Incidence of Treatment-Resistant ACR
Table 14.3.5.11	Cumulative Incidence of Allograft Loss
<u>Listings</u>	
Listing 16.2.1	Patient Disposition
Listing 16.2.2	Major Protocol Deviations
Listing 16.2.4.1	Recipient Demographics and Baseline Characteristics
Listing 16.2.4.2	Donor Demographics and Baseline Characteristics
Listing 16.2.4.3	Baseline Transplant Information
Listing 16.2.4.4	Baseline Virology Information
Listing 16.2.4.5.1	Medical and Surgical History
Listing 16.2.4.5.2	Previous Kidney Transplants
Listing 16.2.4.6.1	Baseline Immunology Information - Central Laboratory
Listing 16.2.4.6.2	Baseline Immunology Information - Local Laboratory
Listing 16.2.4.7	Baseline ECG
Listing 16.2.4.8	Immunosuppressant Medications
Listing 16.2.4.9	Concomitant Medications
Listing 16.2.4.10	Use of Plasma Therapy/IVIg Post Transplantation

Alexion Pharmaceuticals {Protocol Number: C10-002 08OCT2013 (Final Version 2.0)}

Listing 16.2.5	Treatment Exposure to Study Infusions
Listing 16.2.6.1	Kidney Biopsy Banff Findings (Local Data)
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Serious Adverse Events
Listing 16.2.7.3	Adverse Events Leading to Death
Listing 16.2.7.4	Allograft Failures
Listing 16.2.8.1	Local Laboratory Results: Chemistry and Renal
Listing 16.2.8.2	Local Laboratory Results: Hepatic Profile
Listing 16.2.8.3	Local Laboratory Results: Complete Blood Count
Listing 16.2.8.4	Local Laboratory Results: Urinalysis
Listing 16.2.8.5	Local Laboratory Results: Coagulation
Listing 16.2.9	Vital Signs
Listing 16.2.10	Physical Examination Abnormalities
Listing 16.2.11	Pregnancy Tests