STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP616-302
Protocol Title:	A randomized double-blind placebo-controlled study to evaluate the efficacy and safety of Cinryze® (C1 esterase inhibitor [human]) for the treatment of acute antibody-mediated rejection in kidney transplant patients
Drug:	SHP616, C1 esterase inhibitor [human]
Sponsor:	Shire ViroPharma, Inc. (Shire is now part of Takeda) 300 Shire Way, Lexington, MA 02421 USA
Version No. and Date	Version 3.0, Date 27June2019

Version No:	Document History Description of Update	Author(s)	Effective Date
0.1	Initial draft	[redacted]	06Mar2015
0.2	Updated with all-cause graft failure as key secondary endpoint and sensitivity analysis	[redacted]	31Mar2015
0.3	Updated to final protocol changes, sensitivity analysis, TFL, and PCI value	[redacted]	22Apr2015
0.4	Incorporate Study Team review suggestions. Amended efficacy analysis details in Section 10	[redacted]	01May2015
0.5	Update after DMC member review	[redacted]	10May2015
0.6	Update after first draft CRF and protocol Amendment 1	[redacted]	29May2015
1.0	Final Draft for Protocol Amendment 1.0	[redacted]	04Jun2015

Version No:	Document History Description of Update	Author(s)	Effective Date
2.0	Update for Protocol Amendment 2 dated 22Jun2015	[redacted]	25Jun2015
2.1	Update with regard to the FDA's IND review question: 1. Protocol SHP616-302 permits subjects who have subsequent AMR episodes to be retreated according to their original treatment schedule; retreatments usually complicate the plan for analysis of a study. Please indicate where in your statistical analysis plan you address the analysis of subjects who receive retreatments?	[redacted]	04AUG2015
2.2	Update with regard to the FDA's IND review response and DMC Organizational Meeting	[redacted]	06NOV2015
2.3	• Correct the alpha level for z statistic. • Revise lower cut-off point of the decision rule of stopping for futility.	[redacted]	24APR2016
	• Add additional time to event efficacy endpoints and analyses. • Add sensitivity analysis for change in cg percent.	[redacted]	28APR2016
2.4	Implement the Protocol amendment 3	[redacted]	14MAR2016
2.5	Updated per Shire comments	[redacted]	03AUG2017

Version No:	Document History Description of Update	Author(s)	Effective Date
2.6	Updated to address the rest comments from Shire	[redacted]	08SEP2017
2.7	Updated the conditional power and removed the WHODrug version	[redacted]	22Sep2017
	Updated the TOC to be consistent with the shells and fixed a few typos/formats.	[redacted]	02Oct2017
	Deleted Appendix 2 related to CP and made a few format changes per comments from Shire	[redacted]	15Oct2017
2.8	Updated tables 1 and 2 for the schedule of assessments according to the protocol amendment 4, revised TOC to be consistent with the shells, and fixed a few typos	[redacted]	19JAN2018
3.0	Updated protocol version. Cosmetic issues and typos updated. Updated to be consistent with protocol amendment 4. Updated definition to be consistent with DMC SAP. Updated wording to give clear explanation. Removed average dosing week from AE. Updated section 17. Changes to analyses specified in protocol. Updated section 20 TOC.	[redacted]	05JUN2019
	Updated to be consistent with protocol amendment v4.0. Added link to reference section if needed. Added standard score definition for primary efficacy endpoint.	[redacted]	14JUN2019

Version No:	Document History Description of Update	Author(s)	Effective Date
	Updated granular score definition for sensitivity efficacy endpoint. Updated section 17. Changes to analyses specified in protocol.		
	Added back section 13.2. Added link. Updated section 17 and 20.	[redacted]	19JUN2019
	Updated section 20 (TOC). Updated section 12 to be consistent for PD set definition.	[redacted]	20JUN2019
	Updated Section 12.2.2 and 12.4.2 to change handling values who had <LLOQ: Updated from 'treat as 0' to 'treat as 1/2 of the LLOQ value'.	[redacted]	25JUN2019
	Typo fixed.	[redacted]	27JUN2019

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ABBREVIATIONS

AE	adverse event
AMR	antibody-mediated rejection (of renal allograft)
ANOVA	analysis of variance
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
C1 INH	C1 inhibitor [human]
C3a	anaphylatoxin split product of C3 activation important in chemotaxis
C4d	4th complement protein degradation product
C5a	anaphylatoxin split product of C5 activation important for histamine release and chemotaxis
CBC	complete blood count
cg	chronic glomerulopathy (*cg* score is based on published Banff criteria)
CI	confidence interval
C_{trough}	concentration at end of dosing interval
CMH	Cochran-Mantel-Haenszel
CP	conditional power
Cr	creatinine
CRF	case report form
CRO	contract research organization
df	degree of freedom
DMC	data monitoring committee
DSA	donor-specific antibody
EAC	endpoint adjudication committee
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EM	electron microscopy
EOS	end of study (visit)
EQ-5D-5L	EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire
FAS	Full Analysis Set
FoTA	Final on Treatment Assessment

GBM	glomerular basement membrane
HLA	human leukocyte antigen
IV	intravenous
IVIg	intravenous immunoglobulin
IV/WRS	Interactive Voice/Web Response System
LLOQ	lower limit of quantification
max	Maximum
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MMRM	Mixed-effects model for repeated measures
min	minimum
n	number of subjects/observations
NA	not applicable
PRA	panel reactive antibody
PCI	potentially clinically important
PD	pharmacodynamics
PVRM	pharmacovigilance and risk management
PK	pharmacokinetics
PTC	peritubular capillary
QoL	quality of life
QTcB	QT Interval Corrected for Heart Rate using Bazett's Formula
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TG	transplant glomerulopathy
US	United States
VAS	visual analogue scale
WBC	white blood cell (count)

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the study protocol amendment 4 dated 22NOV17. The shell of tables, figures, and listings are contained in a separate document and will serve as guidance. Modifications of shells might be made if needed.

2. STUDY DESIGN

2.1 General Study Design

This randomized, double-blind, placebo-controlled multicenter, multinational study will assess the efficacy and safety of CINRYZE with protocol-mandated DSA reduction treatment and sucrose-free IVIg for the treatment of acute AMR in kidney transplant recipients. Eligible study subjects will have had a kidney transplant with adequate function defined as having a pre-AMR baseline $eGFR_{MDRD} \geq 20$ mL/min/1.73m^2 if the qualifying AMR episode occurs ≤21 days after transplant or pre-AMR baseline $eGFR_{MDRD} \geq 30$ mL/min/1.73m^2 if the qualifying AMR episode occurs >21 days after transplant. The pre-AMR baseline is the highest $eGFR_{MDRD}$ value obtained following the kidney transplant and within 30 days prior to the qualifying AMR episode. If more than 1 $eGFR_{MDRD}$ value is available, a mean of the 2 highest values (at least 1 day apart and both prior to the AMR episode) will be used as the pre-AMR baseline value. If no $eGFR_{MDRD}$ was obtained within 30 days prior to the qualifying AMR episode, it can be evaluated within a 60-day period.

The qualifying episode of biopsy-proven AMR will be defined by 2013 Banff criteria and will have evidence of circulating DSA. Once the qualifying AMR episode is diagnosed through a biopsy, subjects will enter a screening period for additional eligibility assessments at the investigative site. During this screening, the first $eGFR_{MDRD}$ value obtained after the qualifying biopsy should be used for the screening visit period. Biopsy slides and images (including, but not limited to EM) will be sent to an independent, blinded pathology Endpoint Adjudication Committee (EAC) for confirmation of AMR. Subjects will be stratified across centers for (1) living vs deceased donor and (2) severity of acute AMR as defined by screening period $eGFR_{MDRD}$ (≤15 mL/min/1.73m^2 for severe, or >15 mL/min/1.73m^2 for mild to moderate). CINRYZE or placebo treatment should be started as soon as possible and within 7 days after the biopsy procedure.

Approximately 112 eligible subjects with biopsy-proven AMR will be randomized (56 per treatment arm) to receive either CINRYZE or placebo in a 1:1 ratio after being stratified as described above. Additional eligible subjects may be enrolled and randomized based on the interim data analysis of the first 30 subjects who complete the Month 6 TG assessment for the re-estimation of sample size.

Cinryze: 5000 U CINRYZE (not to exceed 125 U/kg) for IV on Day 1 followed by 2500 U of CINRYZE (not to exceed 62.5 U/kg) for IV on Days 3, 5, 7, 9, 11, and 13 with a total of 20,000 U.

Placebo: 50 mL 0.9% sodium chloride for IV on Day 1 followed by 25 mL 0.9% sodium chloride for IV on Days 3, 5, 7, 9, 11, and 13.

During the study treatment period, subjects will receive a total of 7 doses of investigational product over 13 days in addition to protocol-mandated DSA reduction treatment and sucrose-free IVIg for each qualifying episode of AMR. To minimize variability, the use of DSA reduction treatments and sucrose-free IVIg for the treatment of AMR will be administered as mentioned below.

Donor-specific Antibody Reduction Treatment: Subjects will be required to receive a minimum of 5 plasmapheresis, plasma exchange, or immune adsorption treatments from the time of diagnostic biopsy for qualifying episode of acute AMR through Study Day 13. Each DSA reduction treatment will be followed by sucrose-free IVIg (no less than 100 mg/kg). Additional DSA reduction treatments and sucrose-free IVIg may be administered at the discretion of the investigator as per local standard of care. NOTE: If plasmapheresis, plasma exchange, or immune adsorption treatment occurs on the same day as investigational product dosing, investigational product will be administered after completion of the DSA reduction therapy session and dosing of sucrose-free IVIg. Collection of blood samples for laboratory testing (other than those specified on Table 3) will be performed prior to each DSA reduction treatment, if performed.

In addition to the qualifying kidney biopsy, an additional kidney biopsy will be obtained at the Month 6 study visit. Biopsy slides and pertinent micrographs for the qualifying and Month 6 biopsies will be provided to an independent, blinded pathology EAC for the assessment of the primary endpoint (new or worsening TG at 6 months of initiation of treatment) and other histological changes from baseline. Electron microscopy images will also be used for exploratory analyses of GBM double contouring and endothelial swelling and the effect on long-term graft survival where these changes are observed only on EM. Biopsy slides and pertinent micrographs indicating a new AMR episode or the resolution of an AMR episode will also be provided to the pathology EAC.

Subjects will remain in the study until the clinical confirmatory endpoint of all-cause graft failure is evaluated up to a maximum of 4 years. Graft failure is evaluated by the nephrology EAC. Graft failure, for the purpose of this study, will be defined as 1 or more of the following: (1) institution of permanent dialysis (defined as dialysis treatment >30 days), (2) current transplant nephrectomy, or (3) clinical determination of cessation of kidney graft function and eGFR $\leq$15 mL/min/1.73m^2. If a subject is discontinued for any reason prior to the Month 6 follow-up visit, every effort will be made to obtain AEs, serum blood urea nitrogen (BUN) and creatinine (Cr) results, $eGFR_{MDRD}$, and a biopsy to send slides and images to the pathology and nephrology EACs for determination of TG and graft function status, respectively (see Table 2 for Early Discontinuation Visit procedures). If a subject is discontinued for any reason prior to the end of the study at 4 years, every effort will be made to obtain AEs, serum BUN and Cr and $eGFR_{MDRD}$ results to send to the nephrology EAC for determination of graft function status.

There will be 2 analyses (1st and 2nd interim analyses) assessing the primary endpoint of new or worsening TG at 6 months after initiation of treatment. In addition, there will be 3 analyses (3rd and 4th interim analyses plus 1 final analysis) of proportions of subjects with all-cause graft failure, at approximately 50% (~26 events), 75% (~39 events) and 100% (~51 events) of the

study data. Following the Month 6 evaluation, subjects will enter a long-term follow-up stage of the protocol, which will include allograft function evaluations every 6 months up to a maximum of 4 years. The duration of the study will be event driven, and is based upon an assumption that there will be approximately 51 all-cause graft failures. The study will continue until 51 such events are accrued and adjudicated by the nephrology EAC. However the maximum amount of time each subject will be followed in the study will be 4 years post initial treatment with investigational product.

Resolution will be achieved when, after treatment, the local $eGFR_{MDRD}$ value increases to at least within 20% or above the $eGFR_{MDRD}$ value collected as a pre-AMR baseline. If an AMR episode is diagnosed, in absence of significant decline (≥20%) of eGFR from pre-AMR baseline, a follow-up biopsy within 3 months is recommended in order to assess resolution.

Recurrence is defined as biopsy-proven new evidence of AMR upon resolution of the previous AMR episode. Investigators will also be asked to record the date of recurrence of AMR, when applicable. During the first 6 months of the study only, if the qualifying AMR episode resolves and there is new biopsy-proven acute AMR per protocol definition in the inclusion criteria, the subject may be retreated at the investigative site with the same investigational product to which they were originally randomized as well as DSA reduction treatment and sucrose-free IVIg per protocol. Between the qualifying biopsy that is diagnostic for a recurrent episode of AMR and the first retreatment dose of investigational product, subjects will complete a subset of the screening procedures and follow the assessments noted in the schedule of assessments (Screening through Day 25) for each new episode of AMR occurring during the first 6 months of the study. Retreatment should occur as soon as possible within 7 days of the biopsy that defined the new AMR episode. Retreatment may not occur after the first 6 months of the study. Biopsies at Month 6 following retreatment will not be necessary. The only mandated follow-up biopsy will be at Month 6 after initial treatment.

The effect on the quality of life will be measured by using the EuroQoL Group 5-Dimension 5-Level Self–report Questionnaire (EQ-5D-5L).

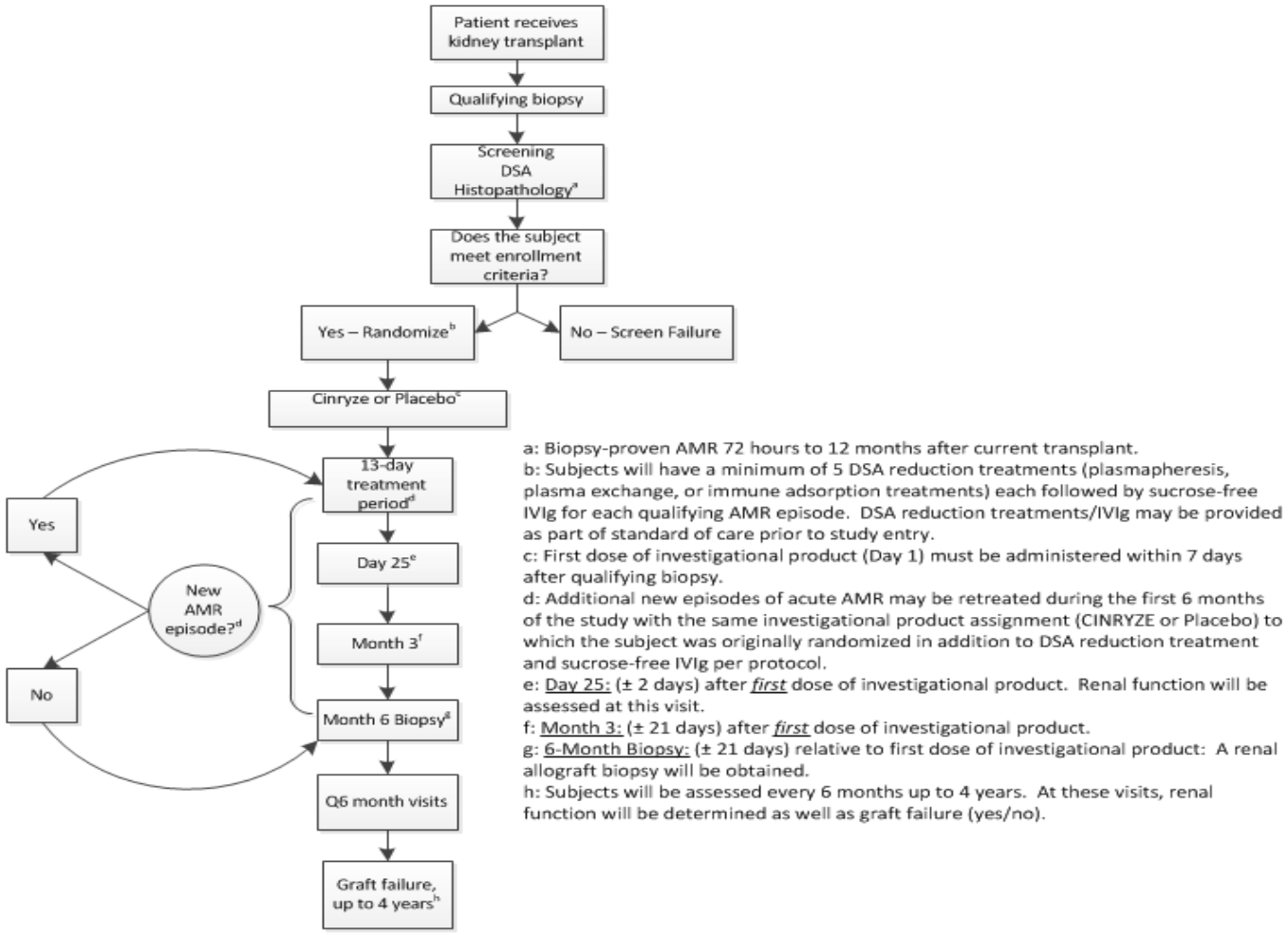
Complement and C1 INH levels will be assessed at specified time points up to Day 13 for pharmacokinetic/pharmacodynamic evaluation.

Safety will be monitored through the recording of adverse events (AEs) and changes in physical examinations, vital signs, antibodies to C1 INH, and clinical safety laboratory testing. The following events of special interest will be closely monitored and reported throughout the study, regardless of relationship to study medication: any thrombotic or thromboembolic event; any hypersensitivity reaction; any new episode of kidney allograft rejection, even if the event does not qualify for retreatment with study medication; and any new kidney allograft failure.

Stopping rules: If a drug-related thrombotic or thromboembolic SAE (as defined in section 4.5.3 of the protocol) occurs in any subject, as defined by the Principal Investigator at the site, enrollment of new subjects will be halted. Study procedures for subjects already enrolled will continue and subjects already enrolled will continue on their assigned dosing regimen.

See the study design flow chart below.

Figure 1: Study Design Flow Chart



2.2 Randomization

Approximately 112 eligible subjects with biopsy-proven AMR will be randomized (56 per treatment arm) to receive either CINRYZE or placebo in a 1:1 ratio.

The actual treatment given to individual subjects is determined by a randomization schedule automatically assigned by the Interactive Web Response System (IWRS) at the Baseline Visit (Day 1) after subject eligibility has been confirmed using the eligibility criteria. Subjects will be stratified across centers as described in section 2.1. CINRYZE or placebo treatment should

be started as soon as possible and within 7 days after the biopsy procedure. Additional eligible subjects may be enrolled and randomized based on the interim data analysis of the first 30 subjects who complete the Month 6 TG assessment for the re-estimation of sample size (Protocol Section 9.5.1).

2.3 Blinding

Qualified subjects will be randomized in a 1:1 ratio to receive CINRYZE or placebo using a centralized procedure. An Interactive Voice/Web Response System (IV/WRS) will be used to randomize subjects and provide the treatment assignment to the unblinded pharmacist. The unblinded pharmacist will prepare the blinded IV solution (CINRYZE or placebo) accordingly.

A Sponsor representative(s) not affiliated with the core team will be unblinded to treatment assignment in order to review drug accountability on an ongoing basis throughout the study (Protocol Section 6.4). This unblinded representative will remain independent of other study activities.

For the first interim analysis, the EACs, sponsor, investigator, and subjects will be blinded to the study treatment. When the criterion to conduct the second interim analysis is met, treatment assignment for those subjects will be unblinded to designated sponsor representatives for analysis. The treatment assignments for all other subjects will be blinded to the EACs, investigator, and subjects during the conduct of the study.

DMC members will remain unblinded for the duration of the study to review efficacy and safety data.

2.4 Schedule of Assessments

Table 1 Schedule of Assessments (Screening through Day 25)

Study Procedure	(Screening)[a]		Investigational Product Administration Period							Post-Treatment Evaluations
	1st Episode	Retreatment (recurrent AMR) within 180 days	Day 1[a]	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	Day 25 (±48 hours)
Informed consent	✔									
Medical history, presence/absence of diabetes	✔	✔								
Inclusion/exclusion eligibility	✔ [a]	✔ [a]	✔ [b]							
Screening Registration/Randomization via IV/WRS (IRT)	✔	✔	✔ [b]							
Physical examination	✔	✔	✔ [b]							
Lower extremity examination [c]	✔	✔	✔ [b]	✔	✔	✔	✔	✔	✔	✔
Height	✔	✔								
Body weight	✔	✔	✔ [b]	✔	✔	✔	✔	✔	✔	✔
Vital signs (BP, HR) [d]	✔	✔	✔ [b]	✔	✔	✔	✔	✔	✔	✔
12-lead ECG [e]	✔									
Central lab Pregnancy testing (also local lab serum and urine pregnancy test at screening, and local urine test on Day 1) f	✔	✔	✔ [b]							
Central lab Virology screen	✔	✔								
Central lab Hematology (also local lab WBC and platelets at screening) [g]	✔	✔	✔ [b]						✔	✔
Central lab clinical chemistry [gs]	✔	✔	✔ [b]						✔	
BUN & Serum Cr with eGFR (both central lab [included in chemistry when applicable] and local lab) [g]	✔ [h]	✔ h	✔	✔	✔	✔	✔	✔	✔	✔
Central lab Proteinuria: Spot urine protein, urine Cr and urine protein/urine creatinine ratio	✔	✔								✔
Kidney allograft biopsy, submission of pathology slides/images [i]	✔	✔								
Central lab Pharmacokinetic/Pharmacodynamic Testing [j]			✔			✔			✔	
Central lab Immunogenicity (anti-C1 INH antibodies)	✔ [k]									✔
Central lab DSA identification (also local lab at screening) [l]	✔	✔								✔
DSA reduction treatments & sucrose-free IVIg [m]	✔ ----------								✔	

Table 1 Schedule of Assessments (Screening through Day 25)

Study Procedure	(Screening)[a]		Investigational Product Administration Period							Post-Treatment Evaluations
	1st Episode	Retreatment (recurrent AMR) within 180 days	Day 1[a]	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	Day 25 (±48 hours)
Investigational product administration [n]			✔	✔	✔	✔	✔	✔	✔	
Concomitant medications	✔	✔	✔ ---------- ✔ [o]							✔ [p]
Adverse event monitoring [q]	✔ ---------- ✔									
Renal allograft assessment [r]	✔	✔ ---------- ✔								
Subject survival status		✔ ---------- ✔								
EQ-5D-5L	✔									✔
Healthcare Resource Utilization	✔		✔	✔	✔	✔	✔	✔	✔	✔

AE=adverse event; AMR=antibody-mediated rejection; BP=blood pressure; BUN=blood urea nitrogen; C1 INH=C1 inhibitor; Cr=creatinine; DSA=donor-specific antibody; ECG=electrocardiogram; $eGFR_{MDRD}$=estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease; EQ-5D-5L= EuroQoL Group 5-Dimension 5-Level Self–report Questionnaire; HR=heart rate; IVIg=intravenous immunoglobulin; IV/WRS=interactive voice/web randomization system; SAE=serious adverse event

[a] Local laboratory testing will be used to determine subject eligibility. Limited inclusion/exclusion criteria are checked at screening for retreatment only if the investigator plans to retreat (retreatment is only allowed for New AMR episodes diagnosed within the first 180 days after the qualifying biopsy, and if the previous AMR episode resolved).

[b] Day 1 procedures to be completed prior to the first dose of investigational product.

[c] A lower extremity exam will be performed and will include a determination of presence or absence of unilateral calf tenderness or leg swelling. If a deep vein thrombosis is suspected, a diagnostic exam will be performed.

[d] On investigational product dosing days, vital signs should be obtained within 30 minutes prior to investigational product administration and then between 30 minutes and 1 hour after completion of investigational product infusion. Additional vital signs measurements will be performed during the study if clinically indicated.

[e] During the study, additional ECGs will be performed if clinically indicated.

[f] Females of child-bearing potential will have urine and serum pregnancy tests at Screening and urine pregnancy test on Day 1 of each episode.

[g] On investigational product dosing days, blood samples for clinical safety laboratory testing should be collected prior to administration of investigational product. Local laboratory hematology results (WBC and platelets) will be used to assess eligibility at screening. Central laboratory BUN and creatinine results are included where a sample is taken for clinical chemistry. Local laboratory results for BUN and creatinine (including $eGFR_{MDRD}$ calculation) are required at all study visits, as well as pre-AMR and resolution of AMR for all AMR episodes.

[h] At screening, the first creatinine value obtained after the qualifying biopsy (or recurrent AMR biopsy if applicable) should be used as the screening creatinine and eGFR values to assess AMR severity for stratification.

[i] Qualifying renal allograft biopsy for assessment of histologic parameters associated with AMR. In the event that the subject has a new episode of AMR as defined in Section 7.2.2.4 of the protocol. the subject may be retreated with the same treatment to which they were previously randomized and following the procedures outlined in Table 1, beginning at Day 1 with the exception of randomization and limited inclusion/exclusion criteria. For each biopsy, the pathology slides and images are to be submitted.

[j] Blood samples for pharmacokinetic/pharmacodynamic analysis will be collected at the time points specified in Table 3.

Table 1 Schedule of Assessments (Screening through Day 25)

Study Procedure	(Screening)[a]		Investigational Product Administration Period							Post-Treatment Evaluations
	1st Episode	Retreatment (recurrent AMR) within 180 days	Day 1[a]	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13	Day 25 (±48 hours)

[k] If sucrose-free IVIg is administered on the same day as the screening visit, blood samples for immunogenicity should be obtained both prior to and after sucrose-free IVIg administration. Subjects where anti-C1 INH antibodies are detected will be followed until negative.

[l] DSA antibody will be determined by central and local laboratory analysis at screening (for initial or recurrent episode of AMR), and only by the central laboratory at all other time points specified. DSA testing may be performed locally at other time points after screening for all clinical assessments as part of standard of care. Additional serum may be collected by the central laboratory for future antibody and titer testing.

[m] Subjects will have a minimum of 5 plasmapheresis, plasma exchange, or immune adsorption treatments each followed by sucrose-free IVIg from the time of diagnostic biopsy for qualifying episode of acute AMR through Study Day 13. Plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free IVIg may be provided as part of standard of care prior to study entry. Protocol-mandated plasmapheresis, plasma exchange, or immune adsorption treatments should be completed by Day 13. Additional DSA reduction treatments or doses of sucrose-free IVIg may be administered at the discretion of the investigator as part of standard of care.

[n] A total of 7 doses of investigational product will be administered: an initial IV infusion of 5000 U CINRYZE or placebo on Day 1, followed by 2500 U of CINRYZE or placebo IV on Days 3, 5, 7, 9, 11, and 13. If plasmapheresis, plasma exchange, or immune adsorption treatments therapy occurs on the same day as investigational product dosing, investigational product will be administered after completion of the DSA reduction therapy session and administration of sucrose-free IVIg.

[o] All medications (and selected blood products) taken from the day of the first dose of investigational product (Day 1) through the day of the last dose of investigational product (Day 13) will be recorded. In addition, medications used to treat AEs, SAEs, and adverse events of special interest (AESI) from time of informed consent through 30 days after the last dose of investigational product for each treatment period will also be recorded.

[p] The following medications will be collected for the duration of the study: Any IV steroids, Rituximab, Muromonab-CD3, Alemtuzumab, Anti-thymocyte globulin (rabbit), Lymphocyte immune globulin, anti-thymocyte globulin (equine), any IV immunoglobulin preparation, Daclizumab or basiliximab. See Section 5.5 of the protocol for additional medications to record.

[q] Adverse events and SAEs will be recorded from the time of Informed Consent through 30 days after the last dose of investigational product regardless of relationship to study treatment. Following the 30-day capture period for all AEs and SAEs, only AE/SAEs deemed related to investigational product or other protocol-mandated procedures, as well as the following AESIs regardless of relationship to investigational product: any hypersensitivity reaction, any thrombotic or thromboembolic event, any new episode of kidney allograft rejection (excluding AMR) even if the event does not qualify for retreatment with investigational product, and any kidney allograft failure, will be collected during the long-term follow-up phase of the study.

[r] Renal allograft function will be assessed by $eGFR_{MDRD}$. Allograft failure and need for splenectomy will be assessed at all timepoints.

[s] Clinical chemistry includes BUN and serum creatinine

Table 2 Schedule of Assessments (Month 3 through Month 48 [End of Study])[a]

Study Procedure	Post-Treatment Evaluations									
	Month 3 (±21 days)[b]	Month 6 (±21 days)[b]	Month 12 (±21 days)[b]	Month 18 (±28 days)[b]	Month 24 (±28 days)[b]	Month 30 (±28 days)[b]	Month 36 (±28 days)[b]	Month 42 (±28 days)[b]	Early Discontinuation Visit Between Day 13 & Month 6	EOS/Month 48 or at patient discontinuation if after Month 6 (±28 days)[b]
Presence/absence of diabetes		✔								✔
Body Weight	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
BUN & Serum Cr with eGFR (both central and local lab) [c]	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Central lab Proteinuria: Spot urine protein, urine Cr and urine protein/urine creatinine ratio	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Kidney allograft biopsy & submission of pathology slides & images [d]		✔							✔	
Central lab Immunogenicity (anti-C1 INH antibodies)	✔	✔	✔ [e]	✔ [e]	✔ [e]	✔ [e]	✔ [e]	✔ [e]		✔ [e]
Central lab DSA identification [f]	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Concomitant medications [g]	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Adverse event monitoring [h]	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Renal allograft assessment	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Subject survival status	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
EQ-5D-5L	✔	✔	✔	✔	✔	✔	✔	✔		✔
Health Resource Utilization	✔	✔	✔	✔	✔	✔	✔	✔		✔

BUN=blood urea nitrogen; C1 INH=C1 inhibitor; Cr=creatinine; DSA=donor-specific antibody; $eGFR_{MDRD}$=estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease; EOS=End of Study Visit; EQ-5D-5L= EuroQoL Group 5-Dimension 5-Level Self–report Questionnaire; SAE=serious adverse event; TG=transplant glomerulopathy

[a] The duration of the study will be event driven, and is based upon an assumption that there will be approximately 51 all-cause graft failures including death. The trial will continue until 51 such events are accrued and adjudicated by the independent, blinded nephrology EAC. See Section 9.5.1of the protocol for additional details. However the maximum amount of time each subject will be followed in the study will be 4 years post initial treatment with investigational product. Subjects will complete visits every 6 months until the study is ended. If the study is stopped prior to the last enrolled subject completing Month 48, all subjects who have not reached Month 48 will be asked to return to the investigational site for their End of Study (EOS) visit.

Table 2 Schedule of Assessments (Month 3 through Month 48 [End of Study])[a]

Study Procedure	Post-Treatment Evaluations									
	Month 3 (±21 days)[b]	Month 6 (±21 days)[b]	Month 12 (±21 days)[b]	Month 18 (±28 days)[b]	Month 24 (±28 days)[b]	Month 30 (±28 days)[b]	Month 36 (±28 days)[b]	Month 42 (±28 days)[b]	Early Discontinuation Visit Between Day 13 & Month 6	EOS/Month 48 or at patient discontinuation if after Month 6 (±28 days)[b]

[b] Visit dates for each visit from Month 3 through EOS will reference back to Day 1 of study entry and will be based on calendar months. Visit windows for each visit in Table 2 will be ±21 days for Months 3, 6, and 12. Visit windows will be ±28 days for Months 18, 24, 30, 36, 42, 48, Early Discontinuation, and End of Study (EOS).

[c] In addition to Central laboratory testing, the local laboratory must obtain BUN, and creatinine values and calculate eGFR values for documentation in CRFs for each of the time points indicated as well as pre-AMR and resolution of AMR for all AMR episodes. Subjects who discontinue before 6 months should complete the Early Discontinuation Visit Between Day 13 & Month 6.

[d] In the event of discontinuation of a fully-dosed subject prior to the Month 6 Visit, every attempt will be made to obtain a biopsy at discontinuation to send to the independent, blinded pathology EAC for determination of TG. The required slides and images for the Screening, Month 6, early discontinuation before Month 6 (if applicable), and any other unscheduled standard of care biopsies, must be submitted to the Sponsor's designee within 30 days after the biopsy procedure, for subsequent submission to the EAC for review.

[e] Subjects where anti-C1 INH antibodies are detected will be followed to measure titers. At Months 12, 18, 24, 36, and 48 the test will be performed ONLY if anti-C1 INH antibodies are detected at the previous time point. At Month 3 and Month 6 the test will be performed in each patient.

[f] DSA antibody analysis will be performed by the central laboratory and will not be reported back to the investigator. Additional DSA testing at these and other time points may be performed by the local laboratory for all clinical assessments as part of standard of care. Additional serum may be collected for the central laboratory for future antibody and titer testing.

[g] For the duration of the study, the following concomitant/post-treatment medications will be collected in the case report form: Any IV steroids, Rituximab, Muromonab-CD3, Alemtuzumab, anti-thymocyte globulin (rabbit), lymphocyte immune globulin, anti-thymocyte globulin (equine), any IV immunoglobulin preparation, Daclizumab or basiliximab. In addition, medications used to treat any related AEs/SAEs or AESIs will also be recorded for the duration of the study as well as those listed in Section 5.5 of the protocol

[h] Adverse events and SAEs will be collected from the time of Informed Consent through 30 days after the last dose of investigational product regardless of relationship to study treatment. Following the 30-day capture period for all AEs and SAEs, only AE/SAEs deemed related to investigational product or other protocol-mandated procedures as well as the following AESIs regardless of relationship to investigational product: any hypersensitivity reaction, any thrombotic or thromboembolic event, any new episode of kidney allograft rejection (excluding AMR) even if the event does not qualify for retreatment with investigational product, and any kidney allograft failure will be collected during the long-term follow-up phase of the study.

Table 3: Blood Sample Collection Time Points for Pharmacokinetic/ Pharmacodynamic Testing (All Subjects)

Sample Day and Time	C1 INH (antigen and function), C3a, and C5a
Day 1: Prior to start of DSA reduction therapy, if performed, on Day 1	X
Day 1: Prior to Day 1 investigational product infusion (within 15 min)	X
Day 1: 1 h (+ 5 min) after start of Day 1 investigational product infusion	X
Day 7: Prior to start of DSA reduction therapy, if performed, on Day 7	X
Day 7: Prior to Day 7 investigational product infusion (within 15 min)	X
Day 7: 1 h (+ 5 min) after start of Day 7 investigational product infusion	X
Day 13: Prior to start of DSA reduction therapy, if performed, on Day 13	X
Day 13: Prior to Day 13 investigational product infusion (within 15 min)	X
Day 13: 1 h (+ 5 min) after start of Day 13 investigational product infusion	X

C1 INH=C1 inhibitor; C3a= anaphylatoxin split product of C3 activation important in chemotaxis; C5a=anaphylatoxin split product of C5 activation important for histamine release and chemotaxis; DSA=donor-specific antibody.

2.5 Determination of Sample Size

A total of 112 subjects (56 CINRYZE, 56 Placebo) will be randomized in a 1:1 ratio into 2 treatment groups: CINRYZE or placebo. Sample size was calculated for the primary endpoint and the key secondary endpoint using nQuery Advisor 7.0.

The primary endpoint in the study is the proportion of subjects with new or worsening TG at 6 months after treatment initiation. A 43% absolute difference in TG at 6 months between treatment groups (3/7 in placebo and 0/7 in CINRYZE) was observed in a subset of subjects (14/18) in the completed randomized Phase 2 pilot study (0624-201). For this study, the assumed proportion of subjects with new or worsening TG at 6 months will be 50% in the placebo group and 10% in the CINRYZE group. A sample size of 60 subjects (30 in placebo and 30 in CINRYZE) would be needed to obtain at least 90% power to detect a significant treatment difference at an alpha level of 0.025 (1-sided test).

The key secondary endpoint in the study is the proportion of subjects with all-cause graft failure. Assuming the proportions of subjects with graft failure due to AMR are 64% and 25% for placebo and CINRYZE, respectively, and all-other-cause graft failure rate is 12% for both placebo and CINRYZE, then the proportions of subjects with all-cause graft failure are 68% and 34% for placebo and CINRYZE, respectively. A total of 100 subjects will provide 90% power to detect an absolute treatment difference of 34% at an alpha level of 0.025 (1-sided test) for all-cause graft failure. These assumptions are based on literature (Haririan et al. 2009; Sharif et al. 2014; OPTN/STRT Annual Data Report 2012). Considering a 10% drop-out rate during the study, 112 subjects will be randomized to the study. Under these assumptions, the expectation is that there will be approximately 34 all-cause graft failures on placebo and approximately 17 all-cause graft failures on CINRYZE, giving 51 events total. The trial will continue until 51 such events are accrued and adjudicated by the nephrology EAC unless stopped prematurely based on findings at an interim analysis or until the final subject enrolled has been followed for 4 years post initial treatment with investigational product.

Additional eligible subjects may be enrolled based on the interim data analysis of the first 30 subjects who complete the Month 6 TG assessment for the re-estimation of sample size.

2.6 Multiplicity Adjustments for Type I Error Control

To control the overall Type I error, the primary and key secondary endpoint will be tested hierarchically with a fixed sequence approach. The study will continue to assess the key secondary endpoint only if the primary null hypothesis has been rejected. Thus, the significance of the key secondary endpoint is contingent, and no adjustment for multiple endpoints is needed.

The primary endpoint will have 2 analyses (1 interim and 1 final for the primary endpoint). The first interim analysis is for futility and sample size recalculation. The second interim analysis, which serves as the final analysis for the primary endpoint, is for the assessment of efficacy (new or worsening TG at 6 months). The alpha level of 0.0001 is to be spent at the first interim

analysis in developing the efficacy boundary of the second interim analysis of TG at 6 months. The overall significance level for the efficacy analysis of primary endpoint will be preserved at 0.025 (1-sided test) by using a significance level of 0.0249 for the second interim analyses. The difference between treatments will be evaluated by using the CHW weighted test statistic (Cui et al., 1999).

The key secondary endpoint will have 3 analyses (2 interim and 1 final), at approximately 50% (~26 events), 75% (~39 events) and 100% (~51 events) of the targeted all-cause graft failure. The Hwang-Shih-DeCani alpha spending function with phi = -4, which is similar to the boundaries from the O'Brien-Fleming method, will be used for the unequal spaced timing of analysis. Using this approach requires $z \geq 2.75$ (or equivalently $p \leq 0.0030$) to consider stopping the study for a positive treatment effect at the first interim analysis (~50% of events), $z \geq 2.43$ (or equivalently $p \leq 0.0075$) to consider stopping the study for a positive treatment effect at the second interim analysis (~75% of events), and $z \geq 2.01$ (or equivalently $p \leq 0.0221$) to claim efficacy at the final analysis (~100% of events), as shown in the table below. This approach maintains a fixed sample p-value close to 0.025 (1-sided test) at the final analysis and an overall significance level at 0.025.

Analysis	Proportion of Targeted Number of Events	Z Scale	p-value (1-sided)
Interim 3	50%	2.751	0.0030
Interim 4	75%	2.428	0.0075
Final	100%	2.012	0.0221

3. OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of CINRYZE administered with plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free immunoglobulin (IVIg) for the treatment of acute AMR of renal allograft in kidney transplant recipients as measured by the proportion of subjects with new or worsening transplant glomerulopathy (TG) at 6 months after treatment initiation.

3.2 Secondary Objectives

The key secondary objective is to evaluate the efficacy of CINRYZE administered with plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free IVIg for the treatment of acute AMR of renal allograft in kidney transplant recipients as measured by the proportion of subjects with all-cause graft failure at 4 years following treatment initiation for the initial qualifying AMR episode.

Secondary objectives from study entry to 6 months are:

- To assess renal function
- To assess proteinuria
- To assess change in histopathology
- To assess graft outcomes

Secondary objectives from study entry to graft failure or 4 years:

- To assess renal function
- To assess proteinuria
- To assess graft outcomes
- To assess resolution of AMR
- To assess safety and tolerability of CINRYZE in kidney transplant recipients
- To assess subject survival status

3.3 Exploratory Objectives

[redacted]

4. SUBJECT POPULATION SETS

4.1 All-enrolled Set

The All-enrolled Set will consist of subjects who have signed informed consent.

4.2 Intent-to-Treat Set (ITT)

The Intent-to-Treat Set will consist of all subjects in the All-enrolled Set for whom a randomization number has been assigned. This set will be used for sensitivity analyses of efficacy endpoints provided that the ITT set differs by the FAS by at least 10%

4.3 Full Analysis Set (FAS)

The Full Analysis Set will consist of all subjects who have taken at least 1 dose of investigational product. The FAS will be used for efficacy analysis according to assigned treatment.

4.4 Safety Analysis Set (SAF)

The Safety Analysis Set will consist of all subjects who have taken at least 1 dose of investigational product. The Safety Analysis Set will be used for safety analysis according to actual treatment received.

4.5 Per-protocol Analysis Set-1 (PPS1)

The Per-protocol Analysis Set-1 will consist of all subjects in the FAS who have taken at least 5 of the 7 planned doses, are assessed for TG at 6 months after initiation of treatment or have post-baseline biopsy-proven new or worsening TG within 6 months of initiation of treatment, and do not have predefined major protocol deviations that may affect the primary efficacy endpoint.

These protocol deviations will be identified prior to unblinding of the study.

4.6 Per-protocol Analysis Set-2 (PPS2)

The Per-protocol Analysis Set-2 will consist of all subjects in the FAS who have taken at least 5 of the 7 planned doses, are assessed for graft failure at 4 years, or have shown graft failure within 4 years, or died, and do not have predefined major protocol deviations that may affect the key secondary endpoint.

These protocol deviations will be identified prior to unblinding of the study.

4.7 Pharmacokinetic and Pharmacodynamic Analysis Set

- PK Analysis Set: all subjects who have at least 1 reported post dose PK concentration value. All PK analyses will be based on the PK Set. The Clinical pharmacology group will identify the PK analysis set.
- PD Analysis Set: all subjects who have at least 1 reported post dose PD value. All PD analyses will be based on the PD Set. The Clinical pharmacology group will identify the PD analysis set.

5. SUBJECT DISPOSITION

This section describes subject disposition for the analysis sets (i.e., All-enrolled Set, Intent-to-Treat Set, Safety Analysis Set, FAS, Per Protocol Analysis Sets, and Pharmacokinetic and Pharmacodynamic Set) and the study status for All-enrolled Set.

The number of subjects included in each subject population set will be summarized by treatment group and overall. The number of subjects in FAS but without post-dose primary or key secondary endpoint assessment will be summarized by treatment group and overall. The denominator for the percentage calculation will be the number of subjects in the Intent-to-Treat Set.

The number and percentage of subjects who completed and prematurely discontinued during the study will be presented for each treatment group and overall for the Intent-to-Treat Set. Primary reasons for premature discontinuation from the study as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment group for the Intent-to-Treat Set.

A listing will also be provided for subject disposition, subjects completing and prematurely discontinued during the study, and study analysis sets.

6. PROTOCOL DEVIATION AND VIOLATION

All protocol violations and deviations will be recorded on the Protocol Deviation / Violation Log. All protocol violation and deviation data will be summarized by treatment group and overall for the Intent-to-Treat Set. A complete listing will also be provided for all protocol deviations and violations for the Intent-to-Treat Set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be determined for enrolled subjects using the screening visit or last observation prior to the first dose of investigational product, whichever is later.

Subject demographics including age, sex, race, ethnicity will be summarized by treatment group and overall for the Intent-to-Treat Set, Safety Analysis Set, FAS and Per-protocol Sets.

Baseline characteristics including, weight, height, BMI, stratification factors, acute AMR severity (severe vs. mild to moderate) defined by the screening period $eGFR_{MDRD}$ ≤15 mL/min/1.73m^2 (severe) or >15 mL/min/1.73m^2 (mild to moderate) and donor characteristic (living vs. deceased donor) will be summarized by treatment group and overall for the Intent-to-Treat Set, Safety Analysis Set, FAS and Per-protocol Sets.

Continuous variables will be summarized by descriptive statistics including number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical variables will be summarized by the number of subjects in each category and the percentage of subjects out of the total in the respective analysis set.

Height and weight will be used to calculate BMI using the formula below:

$$\text{BMI} = \frac{\text{weight [kg]}}{(\text{height [m]})^2}$$

A listing will be created to show all the demographics and baseline characteristics for each subject in the Intent-to-Treat Set.

7.1 Medical History

All medical history findings that have been present/active within 5 years prior to enrollment will be recorded regardless of clinical relevance or presence at study start. Medical history findings that have not been active within the 5 years prior to enrollment will be recorded only if deemed clinically relevant by the investigator to the conduct of the study. The medical history should include any history of allergic reactions to drugs.

Medical history data will be summarized by treatment on the Safety Analysis Set. Medical history data will be listed for all subjects in the Safety Analysis Set.

7.2 Transplant History

The following information associated with Transplant history will be recorded in the eCRF at the screening visit:

- Primary cause of native renal failure: diabetes (type 1 or type 2); hypertension; diabetes and hypertension; any glomerulonephritis (e.g., focalsegmental glomerulosclerosis, rapidly progressing glomerulonephritis, membrano-proliferative glomerulonephritis); any autoimmune nephropathy (e.g., systemic lupus erythematosus, Goodpasture's syndrome, Immunoglobulin A nephropathy); drug toxicity (e.g., lithium, non-steroidal anti-inflammatory abuse); congenital defect (e.g., posterior urethral valves); Polycystic Kidney Disease or other
- Diabetes (yes/no)
- Onset date of AMR that qualifies the subject to the study
- Total number of lifetime kidney transplants
- Other transplants (e.g., heart, lung, liver, small bowel, pancreas, other)
- Total number of plasmapheresis, plasma exchange, or immune adsorption treatments in the 14 days prior to transplant through 14 days post-transplant
- Prior splenectomy (yes/no; if yes, then date of splenectomy)
- Date of current transplant
- Type of current transplant (deceased donor, living related donor, or unrelated living donor, extended criteria donor (per site standard), donor after cardiac death)
- Confirmation that there is no existing lesion in the transplanted allograft
- Active treatment of HCV
- MI or TIA within 6 months prior to study entry
- ABO incompatible kidney transplant (yes/no)
- Lowest serum Cr within 30 days after the current transplant (and before the qualifying episode of AMR)
- Highest serum Cr on day of qualifying renal allograft biopsy (±2 days)
- Need for any dialysis within the first 14 days after the current transplant (yes/no)
- Need for any dialysis within 14 days prior to first dose of investigational product (yes/no)
- Specificity of DSA prior to current kidney transplant, if applicable (HLA class I [yes/no; if yes, specify antigen] and/or HLA class II [yes/no; if yes, specify antigen])
- Specificity of DSA closest to and within ±7 days of the qualifying biopsy (HLA class I

[yes/no; if yes, specify antigen] and/or HLA class II [yes/no; if yes, specify antigen])

- Use of any of the following medications administered for immunosuppression within the period 2 weeks before and 2 weeks after the current transplant (yes/no for each):
  - Any IV steroids
  - Rituximab
  - Muromonab-CD3
  - Alemtuzumab
  - Anti-thymocyte globulin (rabbit)
  - Lymphocyte immune globulin, anti-thymocyte globulin (equine)
  - Any sucrose-free IVIg preparation
  - Daclizumab or basiliximab
  - Other: specify

Descriptive summaries of transplant history will be presented by treatment group for the Safety Analysis Set. A complete listing for transplant history will be created for all subjects in the Safety Analysis Set.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational product

Exposure to double-blind investigational product for the Safety Analysis Set will be summarized in terms of number of treatment periods, number of doses, and total dose. Descriptive statistics (n, mean, SD, min, median, and max) will be presented by treatment group and by treatment period.

A listing will be created by subject and treatment period giving the date and time of dose administration for each treatment given for the Safety Analysis Set.

8.2 Measurement of Treatment Compliance

Investigational product dosing compliance is defined as the dose administered to a subject during the period/study divided by the doses expected to be administered during the same period/study multiplied by 100.

The number of doses administered is calculated by the total number of doses administered on investigational product exposure log during the period/study. The number of doses expected to be administered during a treatment period is 7. The number of doses expected to be administered during the whole study is calculated as 7 × (1 + number of new qualified acute AMR episodes).

The total dose administered is calculated as sum of dose amount administered during the study. The total dose expected to be administered in a treatment period is 20,000 Units. The total dose expected to be administered in the whole study is calculated as 20,000 Units × (1 + number of new qualified acute AMR episodes).

Descriptive statistics for investigational product compliance will be presented by treatment group, by treatment period (applies to patients with repeat dosing due to recurrent AMRs) and overall for the Safety Analysis Set.

9. CONCOMITANT AND POST-TREATMENT MEDICATION

The WHO Drug Dictionary will be used to code concomitant and post-treatment medications.

Concomitant medication is defined as any medications including blood products, immunosuppressive agents, or medications used to treat a pre-existing medical history condition or AE which are recorded in the CRF if taken/administered during the day of the first dose of investigational product (Day 1) through the day of the last dose of investigational product (Day 13) for each treatment period (Table 1), inclusive. Any medication with a start date after the date of the last dose of investigational product in each treatment period will not be considered a concomitant medication.

Post-treatment medication is defined as any CRF recorded medication taken/administered after first treatment end, or between treatment periods, through year 4.

Both concomitant and post-treatment medication usage will be summarized by the number and percentage of subjects in each treatment group by Anatomical Therapeutic Chemical (ATC) classification level 1 (Body System) and preferred term for the Safety Analysis Set. Medications can be counted both as concomitant and post-treatment medication. Multiple medication usage by a subject in the same category will be counted only once. The blood products will be summarized by preferred term and listed separately from other concomitant and post-treatment medications.

All non-study medications taken/administered during the study will be listed, concomitant (taken/administered from the start of the first dose through the last dose in the same treatment period) and post-treatment medications (taken/administered after or between each treatment periods) will be flagged.

10. EFFICACY ANALYSES

The type I error for the primary and key secondary analyses will be preserved at the 1-sided 0.025 level. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

The experiment unit for efficacy analyses is each subject during the entire study period. The efficacy analysis plan described in this document evaluates the effect of initial treatment.

The FAS and Per-protocol Analysis Set-1 will be used to report the primary efficacy endpoint data.

The FAS and Per-protocol Analysis Set-2 will be used to report the key secondary efficacy endpoint data and FAS will be used to report other secondary efficacy endpoint data.

Conditional power calculation, sample size re-estimation, claims for futility or efficacy, and sensitivity analyses will be based on the analyses using the FAS and Per-protocol Analysis Set-1.

If the FAS set deviates from ITT set more than 10%, the robustness of the primary analysis results will be demonstrated by the sensitivity analysis using ITT set. In addition, FAS and the Per-protocol Analysis Set-1 also will be used for the sensitivity analysis of primary endpoint, FAS will also be used for the sensitivity analysis of the key secondary and some other secondary efficacy endpoints.

10.1 Primary Efficacy Endpoint(s) and Analysis

The primary efficacy endpoint is defined as the proportion of subjects with new or worsening TG at 6 months post-treatment as adjudicated by the pathology EAC based on 2013 Banff criteria (standard score). New or worsening TG at 6 months by the standard score is defined as an increase of 1 or more between qualifying biopsy and 6-month biopsy. Subjects who do not have the TG assessment at 6 months post-dose will be assigned as failures, i.e. having ‘new or worsening TG’.

The primary analysis specified below will be performed based on the FAS for the first and second interim analysis of this study. As a sensitivity analysis, the primary analysis will be also performed based on Per-protocol Analysis Set-1 in the second interim analysis of the study.

The primary endpoint will be presented as the proportion of subjects with new or worsening TG determined at 6 months, and their difference between treatments ($\Delta_{Cinryze-Placebo}$) is defined as follows:

$$\Delta_{Cinryze-Placebo} = \Pi_{Cinryze} - \Pi_{Placebo}$$

where $\Pi_{Cinryze}$ is the proportion of new or worsening TG at 6 months post treatment in the CINRYZE group and $\Pi_{Placebo}$ is the proportion of new or worsening TG at 6 months post treatment in the placebo group.

The analysis will employ a type I error rate of 0.025 to test null hypothesis:

$$H_0 : \Pi_{Cinryze} - \Pi_{Placebo} \geq 0$$

Against the 1-sided alternative:

$$H_a : \Pi_{Cinryze} - \Pi_{Placebo} < 0$$

There will be two interim analyses to assess the primary endpoint.

The purpose of the first interim analysis is to allow early stopping of the study for futility, assessing safety of the treatment, and potentially adjusting the sample size. The trial may be stopped for futility at the interim analysis or the sample size of the study may be adjusted up to ensure enough power to detect the treatment effect (section 14). The first interim analysis is planned to be performed when 30 subjects complete (half of the pre-defined sample size for primary endpoint, 15 subjects for each treatment group) the Month 6 visit. A fraction of alpha (0.0001) will be spent at the first interim analysis and accounted for in the overall type I error rate. Even if the value of test-statistics exceeds the efficacy boundary, the trial will not be stopped for efficacy. NOTE: For simplicity, 30 subjects complete the Month 6 visit and balanced arms are assumed to demonstrate statistical analyses in this document.

The futility of the study at the first interim analysis will be determined by calculating the conditional power (CP) based on observed trend at interim.

If the CP is < CP_{min}, the study will be stopped for futility. If the CP is between CP_{min} and 60%, the sample size will be adjusted up to make CP equal to 60%. The CP_{min} is the pre-specified lower limit of conditional power and will be specified in the DMC SAP before the 1st interim analysis. The analysis based on the adjusted number of subjects will be used for the final analysis on primary endpoint (i.e. second interim analysis in the study). The study will continue with the original planned sample size if CP is 60% or above.

The CP at the first interim analysis, assuming that the data that will be observed after the first interim analysis will follow the same distribution as seen at interim and the CHW weighted test statistic Z_{CHW} (Cui et al., 1999) as the final test statistic for second interim analysis (also see definition below), will be determined by the following formulae:

$$CP = P\left(Z_2 > \frac{Z_{1-\alpha} - w_1 Z_1}{w_2} \right)$$

$$= 1 - \Phi\left(\frac{Z_{1-\alpha} - w_1 Z_1}{w_2} - \frac{\Delta}{\sqrt{\frac{2\bar{P}(1-\bar{P})}{n_2}}} \right)$$

Where Z_1 and Z_2 are the Z test statistics from the first interim stage (from beginning to first interim analysis) and second interim stage (from first interim analysis to second interim analysis) respectively, $w_1 = w_2 = \sqrt{\frac{1}{2}}$, n_2 is the sample size at the second interim stage per treatment group, $\Phi(.)$ is cumulative standard normal distribution function, $\Delta = \hat{\Pi}_{Placebo} - \hat{\Pi}_{Cinryze}$, and Z_i ($i = 1,2$) is calculated as below:

$$Z_i = \frac{\hat{\Pi}_{Placebo} - \hat{\Pi}_{Cinryze}}{\sqrt{\bar{P}(1-\bar{P})\left(\frac{1}{n_{i,Placebo}} + \frac{1}{n_{i,Cinryze}}\right)}}$$

$\hat{\Pi}_{Placebo}$ and $\hat{\Pi}_{Cinryze}$ are estimated proportions of new or worsening TG at 6 months post treatment at the first interim stage for the Placebo group and CINRYZE group, respectively. The pooled proportion $\bar{P} = \frac{n_{i,Placebo}\hat{\Pi}_{Placebo} + n_{i,Cinryze}\hat{\Pi}_{Cinryze}}{n_{i,Placebo} + n_{i,Cinryze}}$, where $n_{i,Placebo}$, $n_{i,Cinryze}(i = 1,2)$ are numbers of subjects for the Placebo group and the CINRYZE group at first or second interim stage, respectively. The pre-defined sample size for second interim stage is:

$$n_{2,Placebo} = n_{2,Cinryze} = n_2 = 15$$

If $CP(n_2 = 15) < CP_{\min}$, the futility of the study will be claimed.

If $CP_{\min} \le CP(n_2 = 15) < 60\%$, n_2 will be adjusted to n_2^* satisfy $CP(n_2^*) \ge 60\%$.

If $CP(n_2 = 15) \ge 60\%$, study will continue without sample size adjustment.

The second interim analysis serves as the final analysis for the primary endpoint. The purpose of the second interim analysis is to allow early stopping of the study for futility or for claiming of efficacy based on new or worsening TG at 6 months. This analysis will be done using the FAS when a required number of subjects (based on the sample size adjustment of first interim analysis) complete the Month 6 TG assessments. If the result of the final analysis for primary endpoint analysis is statistically significant at 0.0249, the primary null hypothesis will be rejected. The difference between treatments will be evaluated by using the CHW weighted test

statistic (Cui et al., 1999). The test statistic Z_{CHW} at the second interim analysis for TG will be derived based on CHW method, i.e.,

$$Z_{CHW} = \sqrt{\frac{15}{30}}Z_1 + \sqrt{\frac{15}{30}}Z_2 \qquad \text{(Formulae 1)}$$

where Z_1 is the normalized test statistic at first interim stage, and Z_2 is the normalized test statistic for incremental sample size n_2^* for second interim stage after the sample size adjustment. If the number of TG events exceeds 5 for all four cells in the contingency table of treatment versus TG event, Z_i $(i = 1,2)$ will be obtained using normal approximation, otherwise Z_i $(i = 1,2)$ will be calculated from p-value of Fisher's Exact test as (Lechmacher et al., 1999):

$$Z_i = \Phi^{-1}(1 - p_i)$$

where $\Phi^{-1}(.)$ is the function to return a quantile from the standard normal distribution, p_1 is the p-value from Fisher's Exact test for the first interim stage, and p_2 is the p-value from Fisher's Exact test for incremental sample size n_2^* for second interim stage after the sample size adjustment.

If $Z_{CHW} \geq Z_{1-0.0249}$ (equivalent to the p-value from the test ≤ 0.0249), the null hypothesis will be rejected. Otherwise, the futility of the study will be claimed.

The following sensitivity analyses will be conducted for TG assessment by the granular score for the FAS and then TG assessment by the standard score and the granular score for Per-Protocol Analysis Set-1:

- Sensitivity analysis 1: Primary analysis will be repeated based on Month 6 TG assessment by granular score for the Full Analysis Set
- Sensitivity analysis 2: Primary analysis will be repeated based on Month 6 TG assessment by standard score for the Per Protocol Analysis Set-1
- Sensitivity analysis 3: Primary analysis will be repeated based on Month 6 TG assessment by granular score for the Per Protocol Analysis Set-1

The TG assessment by the granular score at 6 months is defined as the following:

- Worsening TG is defined as an increase of 6.25 in the glomerular capillary double contour percentage between qualifying biopsy and 6-month biopsy.

- New TG is defined by granular Banff (based on 2013 Banff criteria) cg 0 score in the qualifying biopsy and granular Banff (based on 2013 Banff criteria) cg score of greater than 0 in the 6-month biopsy.

In order to demonstrate the stability of the primary analysis method, sensitivity analyses will be performed at the point of final analysis of primary endpoint (i.e. second interim analysis for study) by using multiple imputation (MI) assuming missing at random (MAR) to assign missing endpoint and/or combined with Cochran–Mantel–Haenszel (CMH) test for treatment effect. The CMH model will assess the treatment effect controlling for (1) donor characteristic (living vs deceased), (2) baseline AMR severity (severe vs mild to moderate) and possibly (3) time to onset of qualifying AMR from current transplant (>100 days vs ≤100 days) if degree of freedom allows. Sensitivity analyses defined below will be based on the FAS.

	Statistical Test	Logic to assign the missing TG assessment at 6 months
Primary analysis model	Fisher's Exact with CHW weighted test	If no TG assessment at 6 months, assign as failure.
Sensitivity analysis 4	Fisher's Exact with CHW weighted test	If no TG assessment at 6 months, perform MI.
Sensitivity analysis 5	CMH with CHW weighted test	If no TG assessment at 6 months, assign as failure.
Sensitivity analysis 6	CMH with CHW weighted test	If no TG assessment at 6 months, perform MI

For multiple imputation, a monotone missing pattern will be assumed and logistic regression model will be utilized. The imputation seed will be 83789524 and number of imputations will be set as 100. The logistic regression model may contain the following factors (descending order by importance) to impute the missing TG assessment at 6 months:

(1) Treatment group (CINRYZE vs placebo);
(2) AMR severity at baseline (severe vs mild/ moderate);
(3) Donor characteristics (living donor vs deceased donor);
(4) Normalized eGFR change (Δ_{eGFR}). $\Delta_{eGFR} = \frac{eGFR_{\text{baseline}} - eGFR_{\text{last}}}{T}$,where $eGFR_{\text{baseline}}$ is the last eGFR results prior to the first dose of investigational product, $eGFR_{\text{last}}$ is the last eGFR result before or at Month 6 or early discontinuation visit, and T = (last eGFR assessment date – Date of first dose + 1)/30.25;
(5) Resolution of qualifying AMR (Resolved by 6 months /early discontinuation vs unresolved by 6 months/early discontinuation);

(6) AMR free time in months, which defines as (date of Month 6 or early discontinuation visit – Date of first dose +1 – number of days with AMR)/30.25

For sensitivity analysis 4, multiple imputation will be used to impute the primary endpoint for subjects without TG assessment at 6 months. The p-values from Fisher's Exact tests will be computed for each imputed dataset and transformed to χ^2-distribution with degree of freedom (df) = 2 using Fisher's transformation (Fisher, 1932):

$$\Psi_i^{(m)} = -2\log(p_i^{(m)}) \sim \chi_2^2 \qquad \text{(Formulae 2)}$$

where $p_i^{(m)}$ is the p-value from Fisher's Exact test and $\Psi_i^{(m)}$ is the transformed χ^2-distribution for the *i*-th interim stage $(i = 1,2)$ of the *m*-th $(m = 1,2...100)$ imputed dataset.

Then, Wilson-Helferty transformation (Wilson & Hilferty, 1931; Goria, 1992) will be used to transform the χ^2-distribution to an asymptotic normal distribution with mean 0 and variance 1, as following:

$$Z_{WH,i}^{(m)} = \frac{\left(\frac{\Psi_i^{(m)}}{df}\right)^{1/3} - \left(1 - \frac{2}{9 \times df}\right)}{\left(\frac{2}{9 \times df}\right)^{1/2}} \qquad \text{(Formulae 3)}$$

where $\Psi_i^{(m)}$ is the χ^2-distributed statistic from the *m*-th imputed dataset, df is the number of degrees of freedom associated with $\Psi_i^{(m)}$, and $Z_{WH,i}^{(m)}$ is the transformed value.

The transformed normal statistics $Z_{WH,i}^{(m)}$ will be combined using multiple imputation analysis for the first interim stage and the second interim stage, respectively. Then the combined statistics $Z_{WH,1}$ and $Z_{WH,2}$ will be used to calculate the CHW weighted test statistic Z_{CHW} as:

$$Z_{CHW} = \sqrt{\frac{15}{30}} Z_{WH,1} + \sqrt{\frac{15}{30}} Z_{WH,2} \qquad \text{(Formulae 4)}$$

For sensitivity analysis 5, the same approach for handling missing data as for the primary analysis will be considered. CMH test will be performed to evaluate the treatment effect with controlling for baseline AMR severity and donor characteristic. The p-values from CMH general association statistics for the first and second interim stages will be used to yield the CHW weighted test statistic Z_{CHW} as formulae 1.

For sensitivity analysis 6, multiple imputation will be used to impute the primary endpoint outcome for subjects without any post-dose TG assessment and those who discontinued prior to Month 6 but had TG assessment at time of discontinuation. CMH test will be performed to evaluate the treatment effect controlling for baseline AMR severity and donor characteristic. The CMH general association statistics will be computed for each imputed dataset and transformed to asymptotic normal using Wilson-Helferty transformation as formulae 3. The transformed normal statistics $Z_{WH,i}^{(m)}$ will be combined using multiple imputation analysis for first interim stage and second interim stage, respectively. Then the combined statistics $Z_{WH,1}$ and $Z_{WH,2}$ will be used to calculate the CHW weighted test statistic Z_{CHW} as formulae 4.

Details of transformation and sample SAS code for multiple imputation and Wilson-Helferty transformation can be found in Appendix 1 Transformation of CMH Test statistics AND Fisher's Exact p-value for Multiple imputation.

Descriptive statistics for the primary efficacy outcome will be provided for the following subgroups: donor status at transplant, AMR severity at baseline, age, sex, and race.

10.2 Key Secondary Efficacy Endpoint(s) and Analysis

The key secondary endpoint is defined as the proportion of subjects with all-cause graft failure at 4 years following treatment of the initial qualifying AMR episode. The graft failure is defined as 1 or more of the following: (1) institution of permanent dialysis, (2) current transplant nephrectomy, or (3) clinical determination of cessation of kidney graft function in any subject that had received a pre-emptive kidney transplant prior to starting dialysis. The FAS will be used for analyzing the key secondary endpoint. Subjects who discontinued prior to 4 years (i.e. Month 48) will be considered 'missing assessment for graft failure at 4 years' and assigned as failures.

The hypothesis of the key secondary endpoint will only be tested if the testing for the primary endpoint of new or worsening TG at 6 months is statistically significant.

The key secondary analysis specified below will be performed based on the FAS. As a sensitivity analysis, the key secondary analysis will be also performed based on Per-protocol Analysis Set-2.

The key secondary endpoint will be presented as the proportion of subjects with all-cause graft failure, and their difference between treatments ($\Delta_{Cinryze-Placebo}$) is defined as follows:

$$\Delta_{Cinryze-Placebo} = \Pi_{Cinryze} - \Pi_{Placebo}$$

Where $\Pi_{Cinryze}$ is the proportion of all-cause graft failure post-treatment in the CINRYZE group and $\Pi_{Placebo}$ is the proportion of all-cause graft failure post-treatment in the placebo group.

The analysis will employ a type I error rate of 0.025 to test null hypothesis:

$$H_0 : \Pi_{Cinryze} - \Pi_{Placebo} \geq 0$$

Against the 1-sided alternative:

$$H_a : \Pi_{Cinryze} - \Pi_{Placebo} < 0$$

The key secondary endpoint will have 3 analyses (2 interim and 1 final), at approximately 50% (~26 events), 75% (~39 events) and 100% (~51 events) of the targeted all-cause graft failure. The purpose of the interim analyses is to consider early stopping of the study for claiming of efficacy.

The difference between treatments will be evaluated by a Fisher's Exact test. If the p-value from the test is ≤0.0030 at first interim analysis (~50% of events), or ≤0.0075 at the second interim analysis (~75% of events), or ≤0.0221 at the final analysis (~100% of events), it will be concluded that CINRYZE is efficacious based on the proportion of subjects with all-cause graft failure and the result will serve as confirmatory evidence of clinical benefit based on all enrolled subjects.

Sensitivity analyses will be done at final analysis by using multiple imputation (MI) assuming missing at random (MAR) to assign missing key secondary endpoint and/or by using Cochran–Mantel–Haenszel (CMH) test for treatment effect. The CMH model will assess the treatment effect with controlling for (1) donor characteristic (living vs deceased), (2) baseline AMR severity (severe vs mild to moderate), and possibility (3) time to onset of qualifying AMR from current transplant (>100 days vs ≤100 days) if degree of freedom allows. All the sensitivity analyses defined below will be based on the FAS.

	Statistical Test	Logic to assign the missing assessments for graft failure at 4 years (i.e. discontinued prior to 4 years)
Key Secondary Analysis Model	Fisher's Exact	Assign failure for subjects who discontinued prior to 4 years.
Sensitivity analysis 1	Fisher's Exact	MI for subjects who discontinued prior to 4 years.
Sensitivity analysis 2	CMH	Assign failure for subjects who discontinued prior to 4 years.
Sensitivity analysis 3	CMH	MI for subjects who discontinued prior to 4 years.

For multiple imputation for the key secondary endpoint, a monotone missing pattern will be assumed. The prediction model will consider treatment group, , AMR severity baseline, donor characteristic as factors with available post-dose eGFR results incorporated. The imputation seed will be 83789524 and number of imputations will be set as 100.

For sensitivity analysis 1, multiple imputation will be used to impute the key secondary endpoint outcome for all subjects who discontinued prior to 4 years. The p-values from Fisher's Exact tests will be computed for each imputed dataset and transformed to χ^2-distribution with $df = 2$ using Fisher's transformation as:

$$\Psi^{(m)} = -2\log(p^{(m)}) \sim \chi^2_2$$

where $p^{(m)}$ is the p-value from Fisher's Exact test and $\Psi^{(m)}$ is the transformed χ^2-distribution for the m-th $(m = 1,2...100)$ imputed dataset.

Wilson-Helferty transformation (Wilson & Hilferty, 1931; Goria, 1992) will be used to transform the χ^2-distribution to an asymptotic normal distribution with mean 0 and variance 1, as following:

$$Z_{WH}^{(m)} = \frac{\left(\frac{\Psi^{(m)}}{df}\right)^{1/3} - \left(1 - \frac{2}{9\times df}\right)}{\left(\frac{2}{9\times df}\right)^{1/2}} \qquad \text{(Formulae 5)}$$

where $\Psi^{(m)}$ is the χ^2-distributed statistic from the m-th imputed dataset, df is the number of degrees of freedom associated with $\Psi^{(m)}$, and $Z_{WH}^{(m)}$ is the transformed value.

Then, the transformed normal statistic $Z_{WH}^{(m)}$ for each imputed dataset will be combined using multiple imputation analysis to yield the combined test statistic Z_{WH}.

For sensitivity analysis 2, subjects who discontinued prior to 4 years will be assigned as graft failure. The CMH test will be performed to assess the treatment effect with controlling for baseline AMR severity and donor characteristic.

For sensitivity analysis 3, multiple imputation will be used to impute the key secondary endpoint outcome for all subjects who discontinued prior to 4 years. The CMH test will be performed to assess the treatment effect controlling for baseline AMR severity and donor characteristic. The CMH general association statistics will be computed for each imputed

dataset and transformed to asymptotic normal as shown in formulae 5. Then, the transformed normal statistic $Z_{WH}^{(m)}$ for each imputed dataset will be combined using multiple imputation analysis to yield the combined test statistic Z_{WH}.

Descriptive statistics for the key secondary efficacy outcome will be provided for the following subgroups: donor status at transplant, AMR severity at baseline, age, sex, and race.

10.3 Secondary Efficacy Endpoint(s) and Analysis

Secondary efficacy endpoints from study entry to 6 months are defined as:

- Measurement of renal function ($eGFR_{MDRD}$) at 6 months
- Change in renal function ($eGFR_{MDRD}$) from pre-AMR to 6 months
- Change in renal function ($eGFR_{MDRD}$) from screening to 6 months
- Measurement of proteinuria (spot urine protein, urine creatinine, and urine protein/urine creatinine ratio) at 6 months
- Change in proteinuria (spot urine protein, urine creatinine, and urine protein/urine creatinine ratio) from baseline to 6 months
- Change in histopathology per Banff criteria (Banff 2013 classification) from pre-AMR to 6 months
- Proportion of subjects with all-cause graft failure at 6 months

Secondary efficacy endpoints from study entry to 4 years are defined as:

- Measurement of renal function ($eGFR_{MDRD}$) and change from pre-AMR baseline and screening at 1, 2, 3, and 4 years following the qualifying AMR episode
- Measurement of proteinuria (spot urine protein, urine creatinine, and urine protein/urine creatinine ratio) and change from screening at 1, 2, 3, and 4 years following the qualifying AMR episode
- Time to all-cause graft failure
- Proportion of subjects with graft failure due to AMR at 4 years
- Time to graft failure due to AMR
- Proportion of subjects with resolution of the qualifying AMR episodes

- Time to resolution of qualifying AMR episodes
- Proportion of subjects alive at 4 years
- Time to all-cause mortality

The proportion of subjects with all-cause graft failure at 6 months, the proportion of subjects with graft failure due to AMR at 4 years, the proportion of subjects with resolution of the qualifying AMR episodes, the proportion of subjects alive at 4 years will be summarized descriptively by treatment group.

Time to all-cause graft failure, time to graft failure due to AMR, time to resolution of qualifying AMR episodes, and time to all-cause mortality for both treatment groups will be summarized by Kaplan-Meier estimates. The difference between treatment groups will be assessed by proportional hazard regression with treatment group, baseline acute AMR severity, and donor characteristic as factors. Hazard ratio and the 95% confidence interval will be summarized.

- Date of graft failure will be captured on CRFs as (1) date of return to or institution of permanent dialysis, or (2) date of transplant nephrectomy, or (3) date of clinical determination. Time to graft failure in months will be calculated as (Date of graft failure – Date of first dose + 1)/30.25. Subjects who have not experienced graft failure but still on-study will be censored at the last date of graft survival assessment; subjects who have completed the study without experiencing graft failure will be censored at the date of study completion; subjects who discontinued the study without graft failure will be censored at the last date of graft survival assessment.
- Time to graft failure due to AMR in months will be calculated as (Date of graft failure due to AMR – Date of first dose + 1)/30.25. Subjects who have not experienced any graft failure and still on-study will be censored at last date of graft survival assessment; subjects who have completed the study without experiencing graft failure will be censored at the date of study completion; subjects who have experienced graft failure due to reasons other than AMR will be censored at the date of graft failure; subjects who discontinued from the study without graft failure will be censored at the last date of graft survival assessment.
- Time to resolution of qualifying AMR episodes will be calculated as (Date of qualifying AMR resolution – Date of first dose + 1)/30.25. Subjects who have not had resolution of qualifying AMR episodes and still on-study will be censored at the date of last visit; Subjects who have completed the study without resolution of qualifying AMR will be censored at the date of study completion; subjects who discontinued from the study without resolution of qualifying AMR will be censored at the date of early discontinuation.
- Time to all-cause mortality will be calculated as (Date of discontinuation due to death – Date of first dose + 1)/30.25. Subjects who are alive and still on-study will be censored

at the date of last visit; Subjects who have completed the study will be censored at the date of study completion; subjects who discontinued from the study but not due to death will be censored at the date of early discontinuation.

Renal function and proteinuria will be evaluated as change from the corresponding baseline value. Proteinuria will be log-transformed before analysis. Summary statistics (mean, SD, median, min, max) will be provided by treatment group and assessment time points. Difference between treatments in change from baseline to 6 months will be assessed by a MMRM model including all available scheduled assessments through 6 months. Differences between treatments in change from baseline from 1 year through 4 years will be assessed by a separate MMRM model. The analysis models will include effects of treatment group, visit, treatment*visit, baseline acute AMR severity, donor characteristic as well as the corresponding baseline values as covariates. The baseline diabetic status (diabetic vs non-diabetic) may be included in the MMRM model as a factor for graft function and serum creatinine if degree of freedom allows. The baseline*visit interaction will also be included. An unstructured covariance structure shared across treatment groups will be used to model the within-subject errors. Baseline value for renal function is defined as assessment at screening and pre-AMR, separately, for different analyses. Baseline value for proteinuria is defined as the last measurement prior to the first dose of investigational product during the study.

The renal function, as measured by $eGFR_{MDRD}$, will be estimated by the Modification of Diet in Renal Disease [MDRD] formula shown below:

$$eGFR = 175 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.210 \textit{ if Black}] \times [0.742 \textit{ if female}] \times [0.808 \textit{ if Japanese}]$$

where Serum Creatinine is from the central laboratory and expressed in mg/dL, and age is expressed in years. Note: Age collected at screening visit will be used for all visits before Month 12 visit and then increase by 1 year at Month 12, by 2 years at Month 24, 3 years at Month 36 and 4 years at Month 48.

Number of subjects with all-cause graft failure at 6 months will be summarized by cause of graft failure and by treatment group for FAS.

Number of subjects with resolution of AMR episodes will be summarized by resolution criteria (Clinical criteria vs. Histopathology vs. both) and by treatment group for FAS. Summary statistics for number of days from the first dose of investigational product to AMR resolution will be provided by AMR episode and treatment group.

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10.4 Exploratory Efficacy Endpoint(s) and Analyses

Exploratory endpoints are defined as:

11. SAFETY ANALYSES

The safety analysis will be performed using the Safety Analysis Set, unless specified otherwise. Safety variables include TEAEs, clinical laboratory variables, vital signs, lower extremity exam, and C1 INH antibody variables. For each safety variable, the last value collected prior to the first dose of investigational product during the study will be used as baseline for all analyses of that safety variable.

Summary statistics and changes from baseline to post-baseline for clinical laboratory testing, vital signs, diabetes status, and lower extremity exam by treatment group will be presented. For the clinical laboratory testing results, only the scheduled central lab data will be included in the summary tables. All unscheduled or local lab data will only be provided in the listing.

Number, severity, and causality of AEs will be summarized by treatment group.

Results of C1 INH antibody testing will be reported for individual subjects and summarized as appropriate.

A Final on-Treatment Assessment (FoTA) is defined as the last valid assessment obtained up to 30 days after the last dose of the investigational product during the study.

11.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA)

Adverse events and SAEs will be recorded from the time the informed consent is signed through 30 days after the last dose of investigational product regardless of relationship to investigational product. This includes events occurring during the screening period, regardless of whether or not investigational product has been administered. Following the 30-day capture period for all AEs and SAEs, only those AEs/SAEs deemed related to investigational product or other protocol mandated procedures will be collected during the long-term follow-up phase of the study. If the subject undergoes retreatment with investigational product for a new AMR episode, AEs and SAEs will be captured as described above for the treatment of the initial occurrence of AMR. In addition, the following events of special interest, both serious and non-serious, will be closely monitored and reported to Shire GDS via SAE form throughout the study, regardless of relationship to investigational product: any thrombotic or thromboembolic event, any hypersensitivity reaction, any new episode of kidney allograft rejection (excluding AMR), and any kidney allograft failure.

An adverse event that increases in severity will be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, will be recorded as new AE. An AE (classified by preferred term) that occurs during the study will be considered a treatment-emergent AE (TEAE) if:

- it has a start date and time on or after the first dose of investigational product, or
- it has a start date and time before the date and time of the first dose of investigational product, but increases in severity on or after the date and time of the first dose of investigational product.

If more than 1 AE with the same preferred term is reported before the date and time of the first dose of investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the study under the preferred term. An AE that occurs more than 30 days after the date of the last dose of investigational product in a treatment period will not be counted as a TEAE. For example, an AE occurs more than 30 days after the last dose in the initial treatment period, but before the first dose of any new acute AMR treatment period will not be counted as a TEAE.

An overall summary of all AEs/TEAEs in each treatment group and/or treatment period will be presented respectively, including the number and percentage of subjects experiencing event, and absolute count of events with:

- Any AE/TEAE
- Any serious AE/ TEAE
- Any AE/TEAE related to investigational product in the opinion of the investigator
- Any AE/ TEAE leading to study drug discontinuation from the study
- Any severe AE/TEAE.
- Any AE/TEAE leading to death

The number and percentage of subjects and absolute count of events with AEs/TEAEs in each treatment group and/or treatment period will be tabulated respectively in the following ways:

- By SOC, preferred term
- By Maximum severity, SOC, and preferred term
- By SOC, preferred term for serious AE/TEAE
- By SOC and preferred term for AE/TEAE related to investigational product in the opinion of the investigator
- By SOC and preferred term for AE/TEAE leading to Death
- By SOC and preferred term for AE/TEAE leading to Study Drug Withdrawal

Total number of subjects on treatment for each treatment group will be given in all table headers.

For Serious AEs and AEs related to the investigational product, the table by SOC and preferred term will only be produced if there are greater than 5 events total. If there are less than or equal to 5 events, then only the listing will be provided.

All information about AEs collected on the CRF will be listed alongside the treatment, preferred term, and SOC.

11.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point will be presented by treatment group for the following clinical laboratory variables. Baseline is defined as the last measurement prior to the first dose of investigational product during the study .

Chemistry albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen (BUN),), calcium, spot urine protein, carbon dioxide, chloride, creatinine, calculated eGFR, direct bilirubin, gamma-glutamyl transferase, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total cholesterol, total protein, uric acid. Includes also creatinine, calculated eGFR and BUN for time points that do not include a full chemistry panel.

Hematology complete blood count with differential, hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential.

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 4. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment group. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline PCI value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline values.

All clinical laboratory data will be listed, including pregnancy.

Table 4: Criteria for Potentially Clinically Important Laboratory Tests		
Parameter	**Lower Limit**	**Higher Limit**
Biochemistry		
Alanine aminotransferase (ALT)	NA	≥ 3×ULN
Alkaline phosphatase (ALP)	NA	≥ 3×ULN
Aminotransferase (AST)	NA	≥ 3×ULN
Blood urea nitrogen (BUN)	NA	≥ 30 mg/dL
Creatinine	NA	≥ 250 umol/L
Total bilirubin	NA	≥ 2 mg/dL
Troponin	NA	NA
Hematology		
White blood cell (WBC)	≤ $2.8\times10^3/mm^3$	≥ $16\times10^3/mm^3$
Hemoglobin	8 g/dL	NA
Hematocrit	≤24%	NA
platelet count	≤ $75\times10^3/mm^3$	NA

11.3 Vital Signs

Descriptive statistics for vital signs (e.g. systolic and diastolic blood pressure, and pulse) and their changes from baseline at each post-baseline visit will be presented by treatment group. Baseline is defined as the last measurement prior to the first dose of investigational product during the study.

Vital sign values will be considered PCI if they meet the observed value criteria and the change from baseline criteria listed in Table 5. The number and percentage of subjects with PCI post-baseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline PCI values.

Table 5: Criteria for Potentially Clinically Important Vital Signs			
Vital Sign Parameter	**Flag**	**Criteria Values**	
		Observed Value	**Change from Baseline**
Systolic blood pressure (mmHg)	High	≥180	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤65	Decrease of ≥15
Pulse rate (beats per minute)	High	≥120	Increase of ≥15
	Low	≤50	Decrease of ≥15

11.4 Electrocardiogram (ECG)

All ECG data (e.g. heart rate, RR, PR interval, QRS interval, QT interval, and QTc interval) including ECG abnormalities as reported by the investigators will be provided in the listings. QTc interval will be calculated using both Bazett ($QTcB=QT/(RR)^{1/2}$) and Fridericia ($QTcF=QT/(RR)^{1/3}$) corrections.

11.5 Physical Examinations and lower extremity exam

Abnormalities identified during the Physical Examination done at the Screening Visit will be documented in the subject's source documents and on the medical history CRF. If the abnormality is clearly caused by an event that occurred after the subject signed informed consent and before the Physical Examination of the Screening Visit, the event will be captured as an AE. Changes after the Physical Examination of the Screening Visit will be captured as AEs on the AE CRF page, as deemed by the investigator.

Additionally, a lower extremity exam will be performed at specified time points (Table 1) and will include a determination of presence or absence of unilateral calf tenderness or leg swelling that may be new since the previous examination. If a DVT is suspected, a diagnostic study will be performed.

Lower extremity exam results will be provided in the listings.

11.6 Immunogenicity (Anti-C1 INH)

The positive and negative counts of Immunogenicity (Anti-C1 INH) samples will be summarized by visit and treatment for the Safety Analysis Set. Baseline is defined as the last measurement before first dose of investigational product. All immunogenicity data will be listed.

11.7 Coagulation Panel

In the event that a subject experience an unexplained clinically significant thrombotic or thromboembolic event, the coagulopathy panel will be performed at the site's local laboratory. A listing of coagulopathy panel results will be provided for the Safety Analysis Set.

11.8 Virology

A listing for virology results will be provided for the All-enrolled Set.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

12.1 Pharmacokinetics Population

The Pharmacokinetic Set will consist of all subjects who have at least 1 reported post-dose PK concentration value. All PK analyses will be based on the PK Set.

12.2 Pharmacokinetic Methods

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic Set. Individual subject listing and descriptive summary of concentrations at nominal sampling time points are reported. Additional pharmacokinetic analyses using a population modeling and simulation approach and second interim data will be described in Clinical Pharmacology SAP and analysis results will be reported separately.

12.2.1 Concentration Data

The concentration of C1-INH antigen in human plasma will be determined using a validated sandwich electrochemiluminescent (ECL) assay method and will be expressed in µg/mL. The concentration of C1-INH functional in human plasma will be determined using a validated ELISA method and will be expressed in mU/mL.

12.2.2 Handling BLQ Values

The following procedures will be used for plasma PK concentrations below the lower limit of quantification (LLOQ):

- Samples that are below limit of quantification (BLQ) will be reported as <LLOQ in the data listings, where LLOQ is replaced by the actual value for LLOQ for specific PK assay.

- Samples that are BLQ are treated as half of the LLOQ value in the calculation of summary statistics (e.g. mean, SD, etc.) for the plasma PK concentrations at individual time points. Geometric mean and %CV of geometric mean will be set to missing where zero values exist.

- Mean concentrations are reported as zero if all values are BLQ or zero, and no other descriptive statistics are reported. If the calculated mean (±SD) concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these conventions will be used to create the mean plasma concentration versus time plots.

- Missing values will not be imputed.

12.2.3 Population Pharmacokinetic Analysis

Additional pharmacokinetic analyses using a population modeling and simulation approach and second interim data will be described in Clinical Pharmacology SAP and analysis results will be reported separately.

12.3 Statistical Analysis of Pharmacokinetic Data

Descriptive summary statistics including number of observations, mean (SD), median (min, max), geometric mean (CV%), 95 % CI for the mean (lower, upper) will be assessed for both C1 INH antigen and functional at each nominal time point.

12.4 Pharmacodynamic Methods (if applicable)

All summaries and analyses of the Pharmacodynamic data will be based on the Pharmacodynamic Analysis Set who have at least 1 reported post dose PD value. All PD analyses will be based on the PD Set. Individual subject listing and descriptive summary of PD levels at nominal sampling time points are reported. Additional pharmacodynamic analyses using a population modeling and simulation approach and second interim data will be described in Clinical Pharmacology SAP and analysis results will be reported separately.

12.4.1 C3a and C5a Data

The levels of C3a complement in human plasma will be determined using a validated bioanalytical method. The levels of C5a complement in human plasma will be determined using a validated bioanalytical method

12.4.2 Handling BLQ Values

The following procedures will be used for plasma PD levels below the lower limit of quantification (LLOQ):

- Samples that are below limit of quantification (BLQ) will be reported as <LLOQ in the data listings, where LLOQ is replaced by the actual value for LLOQ for specific PD assay.

- Samples that are BLQ are treated as half of the LLOQ value in the calculation of summary statistics (e.g. mean, SD, etc.) for the plasma PD levels at individual time points. Geometric mean and %CV of geometric mean will be set to missing where zero values exist.

- Mean levels are reported as zero if all values are BLQ or zero, and no other descriptive statistics are reported. If the calculated mean (±SD) levels are less than the LLOQ, the value will be reported as calculated. The mean values derived using these conventions will be used to create the mean plasma levels versus time plots.

- Missing values will not be imputed.

12.4.3 Population Pharmacodynamic Analysis

Additional pharmacodynamic analyses using a population modeling and simulation approach and second interim data will be described in Clinical Pharmacology SAP and analysis results will be reported separately.

12.5 Statistical Analysis of Pharmacodynamic Data (if applicable)

Plasma levels C3a and C5a at each nominal sampling time will be summarized using descriptive statistics including number of observations, mean (SD), median (min, max), geometric mean (CV%), 95 % CI for the mean (lower, upper) at each nominal time point.

12.5.1 Primary Pharmacodynamic Endpoint and Analysis (if applicable)

Not applicable.

12.5.2 Secondary Pharmacodynamic Endpoints and Analysis (if applicable)

Not applicable.

12.5.3 Other Pharmacodynamic Variables and Analysis (if applicable)

Not applicable.

12.6 Analyses of Pharmacokinetic/Pharmacodynamic Relationships (If applicable)

Not applicable.

13. OTHER ANALYSES

13.1 Quality of Life Analyses

The EQ-5D-5L is a standardized measure of a subject's self-reported overall health status. The EQ-5D-5L has two components, the EQ-5D-5L descriptive system and the EQ-Visual Analogue Scale (VAS). The EQ-5D-5L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels of severity (states consisting of 5 dimensions no problems/slight problems/moderate problems/severe problems/extreme problems. The EQ-5D VAS records the subject's self-rated health state on a 100-point vertical VAS (0=worst imaginable health state; 100=best imaginable health state)

Results of the EQ-5D-5L health status questionnaire will be presented in accordance with the EQ-5D-5L User Guide. EQ-5D-5L will be summarized by the number of subjects and the percentage of subjects in each category at each time point for the FAS. Questionnaire completion rates at each assessment at each time point will be estimated for both the EQ-5D-5L VAS and EQ-5D-5L utility index. Descriptive statistics for EQ-5D-5L results at baseline and at each post-dose visit will be presented by treatment. Descriptive statistics for Visual analogue scale (VAS) Score and changes from baseline at each post-dose visit will be presented by treatment. All randomized subjects who have an EQ-5D-5L assessment at baseline and at least 1 subsequent assessment will be included in the analysis describing changes from baseline. The baseline for VAS Score is defined as the last value collected prior to the first dose of investigational product.

13.2 Health Outcomes and Outcomes Research Analyses

Analysis of healthcare resource utilization (HRU) data will be detailed in a supplemental SAP prepared by Outcomes Research and Epidemiology.

14. INTERIM ANALYSIS

The study is designed to have 2 analyses (interim and final analyses) assessing the primary endpoint of new or worsening TG at 6 months after initiation of treatment. In addition, there will be 3 analyses (2 interim analyses plus 1 final analysis) assessing proportions of subjects with all-cause graft failure, at approximately 50% (~26 events), 75% (~39 events), and 100% (~51 events) of the study information. An independent DMC will review the data on 4 interim analyses during the course of the study.

The first interim analysis is after 30 subjects complete the Month 6 TG assessment. The purpose of the first interim analysis is to allow early stopping of the study for futility, assessing safety of the treatment, and potentially adjusting the sample size. An alpha level of 0.0001 will be spent at first interim analysis based on the Haybittle-Peto approach. The trial will not be stopped even if the value of test-statistics exceeds the efficacy. The futility of the study at the first interim analysis will be determined by calculating the conditional power (CP) based on observed trend at interim. If the CP is $\leq CP_{min}$, the study will be stopped for futility. If the CP is between CP_{min} and 60%, the sample size will be adjusted up to make CP equal to 60%. The study will continue without sample size adjustment if CP is 60% or above. The CP_{min} is the pre-specified lower limit of conditional power and will be specified in the DMC SAP before the 1st interim analysis. The details for calculating CP can be found in Section 10.1.

The final analysis for the primary endpoint (i.e. second interim analysis for the study) will be done after the required number of subjects (based on the first interim analysis sample size re-estimation) complete the Month 6 TG assessment. The purpose of the second interim analysis for the study is to allow early stopping of the study for futility or for claiming of efficacy based on new or worsening TG at 6 months. CHW method (Cui et al., 1999) will be used to evaluate the efficacy by using a one-sided alpha significance level of 0.0249. Details of analysis can be found in Section 10.1.

If the result of the final analysis of the primary endpoint (second interim analysis for the study) indicates significant treatment effect on TG at 6 months of initiation of treatment, the study will continue to assess the long term study outcomes including the key secondary endpoint (i.e. proportion of subjects with all cause graft failure).

The third interim analysis of the study will be done when approximately 50% (~26 events) of the targeted sample size has experienced all-cause graft failure. The purpose of the third interim analysis is to consider early stopping of the study for claiming of efficacy. The evaluation of efficacy will use the nominal alpha level based on the Hwang-Shih-DeCani alpha spending function with phi = -4, which requires $p \leq 0.003$ to stop the study early for a positive treatment effect.

The fourth interim analysis will be done when approximately 75% (~39 events) of the targeted sample size has experienced all-cause graft failure. The purpose of the fourth interim analysis

is to consider early stopping of the study for claiming of efficacy. The nominal alpha level for evaluating efficacy is based on the Hwang-Shih-DeCani approach. The study may stop early for claiming a positive treatment effect if $p \leq 0.0075$.

15. DATA MONITORING/REVIEW COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to assess safety, efficacy, and futility during the study, as well as to ensure the validity and scientific merit of the trial. The DMC data review meetings will be held after each interim analysis to review the accumulating safety and efficacy data. Additionally, the DMC will review the safety data approximately every 6 months for the duration of the study.

The roles, responsibilities and rules governing operation of the DMC are discussed in full in the DMC charter v3.0 dated 06 March 2019, which will be finalized prior to the administration of investigational product. The DMC charter will define the primary responsibilities of the DMC; guide its activities, its relationship with other study components, its membership, and the purpose and timings of its meetings. It will provide the procedures for ensuring confidentiality, formal communication, and outline of the content of reports that will be provided to the DMC for each interim analysis. The p-values, conditional power, summary statistics, and data listings will be provided to the DMC by an independent statistician supported by an independent statistical reporting group not otherwise assigned to the study. The statistical analysis details for DMC are discussed in full in the DMC SAP v3.0 dated 06 March 2019.

16. COMPUTER METHODS

Statistical analyses will be performed using Version 9.3(or newer) of SAS® on a suitably qualified environment.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

At the first interim, one primary analysis and three sensitivity analyses were conducted for the primary endpoint mentioned in DMC SAP v3.0 dated 06 March 2019. Results from the primary analysis and two sensitivity analyses suggested very large increase to the sample size making it impractical to continue the study. From the result of the other sensitivity analysis, DMC members recommended to terminate the study based on the futility criteria specified in SAP. It was sponsor's decision to discontinue the study for futility after 1st interim analysis and produce an abbreviated CSR. Due to this decision, final analysis will include selected tables, figures, and listings which can be found in section 20. Simple summaries will be provided for the primary endpoint data and selected sensitivity analyses of the primary endpoint. Tables, figures, and listings presented by timepoint will contain information collected only up to the study termination date.

The followings are the changes from protocol amendment 4 dated 22 November 2017 and SAP.

- Subject demographic and baseline characteristics for Safety set will not be included.
- No sensitivity analyses will be done using ITT set.
- Per Protocol Analysis Set-2 will not be derived.
- Some Sensitivity analyses for primary efficacy endpoint will not be conducted.
- Key secondary and other secondary efficacy analyses will not be conducted.
- Exploratory efficacy analyses will not be conducted.
- Measurement of healthcare resource utilization (HRU) will not be included.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, and maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values.

Unless specified otherwise, median, min/max will be presented to the same decimal places as the raw data. Percentage, mean will be presented to 1 more decimal places than the raw data. Standard deviation and standard error will be presented to 2 more decimal places than the raw data.

The p-value for primary endpoint analysis can be presented up to 8 decimal places. Other p-values will generally be presented to 4 decimal places; values less than 0.0001 will be presented as <0.0001.

18.2 Derived Efficacy Endpoints

Graft function, defined as eGFR ≥40 mL/min/1.73m^2 at 3 months post-transplant, will be estimated by the Modification of Diet in Renal Disease [MDRD] formula for Serum Creatinine in mg/dL shown below:

For standardized (IDMS-calibrated) serum creatinine assays:

$eGFR_{MDRD} = 175 \times (\text{standardized serum Cr})^{-1.154} \times (\text{Age})^{-0.203} \times [1.210 \text{ if Black}] \times [0.742 \text{ if female}] \times [0.808 \text{ if Japanese}]$

For non-standardized (non-IDMS-calibrated) serum creatinine assays:

$eGFR_{MDRD} = 186 \times (\text{serum Cr})^{-1.154} \times (\text{Age})^{-0.203} \times [1.210 \text{ if Black}] \times [0.742 \text{ if female}] \times [0.808 \text{ if Japanese}]$

eGFR is expressed in mL/min1.73m^2, serum creatinine is expressed in mg/dL, and age is expressed in years.

18.3 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the date and time of dose of investigational product, then the results from the last assessment made prior to the date and time of dose of investigational product will be used as baseline. If clinical discharge assessments are repeated or unscheduled, the latest assessment will be used as the clinical discharge assessment for generating descriptive statistics. However, all post-baseline assessments will be used for post-baseline overall PCI value determination, and all assessments will be presented in the data listings.

In the following sections, where missing times are seen on the database, they are handled using the same underlying assumptions as for missing dates.

18.4 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Analysis Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was administrated will be used in the calculation of treatment duration.

18.5 Missing Date Information for Concomitant or Post-Treatment Medications

For concomitant or post-treatment medications, including rescue medications, original missing or partial values of start date and/or stop date will be presented in listings, and imputations will be performed when descriptive summaries are needed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

18.5.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

18.5.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose

of investigational product, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

18.6 Missing Date Information for Adverse Events

For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

18.6.1 Incomplete Start Date

Follow same rules as in Section 18.5.1.

18.6.2 Incomplete Stop Date

When required per the protocol, follow the same rules as in Section 18.5.2.

18.7 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

18.8 Missing Relationship to Investigation Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a relationship of "Related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

19. REFERENCES

Cui L, Hung HM, Wang SJ. 1999. Modification of sample size in group sequential clinical trials. Biometrics; 55: 853-7.

Fisher RA. 1932, Statistical Methods for Research Workers, 4th Ed. Oliver and Boyd, London.

Goria MN. 1992. On the forth root transformation of chi-square. Australian Journal of Statistics, 34 (1), 55-64

Haririan A, Kiangkitiwan B, Kukuruga D, et al. 2009. The impact of C4d pattern and donor-specific antibody on graft survival in recipients requiring indication renal allograft biopsy. Am J Transplant; 9(12): 2758-67.

Lechmacher W, Wassmer G. 1999. Adaptive Sample Size Calculations in Group Sequential Trials. Biometrics; 55(4):1286-1290.

Ratitch B, Lipkovich I, O'Kelly M. 2013. Combining Analysis Results from Multiply Imputed Categorical Data. The Pharmaceutical Industry SAS Users Group 2013, Paper SP03.

Rubin DB. 1987. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons.

Sharif A, Kraus ES, Zachary AA, et al. 2014. Histologic phenotype on 1-year posttransplantation biopsy and allograft survival in HLA-incompatible kidney transplants. Transplantation; 97: 541-7.

United States Organ Transplantation SRTR & OPTN Annual Data Report, 2012.

Wilson E, Hilferty MM. 1931. The distribution of chi-squared. Proceedings of the National Academy of Sciences, Washington, 17, 684–688.

20. TABLE OF CONTENTS FOR FIGURES, TABLES, AND LISTINGS

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16.2.6.1.2a	Histopathology Results from Individual Pathologist Scoring Worksheet (Full Analysis Set)	Y
16.2.6.1.2b	Histopathology Results from Final EAC Biopsy Assessment (Full Analysis Set)	Y
16.2.6.1.3	Electron Microscopy Analysis (Full Analysis Set)	Y
16.2.6.1.4	Pathology EAC Biopsy Assessment (Full Analysis Set)	Y
16.2.6.2.1	Renal Allograft Assessment (Full Analysis Set)	Y
16.2.6.2.2	Nephrology EAC Assessment (Full Analysis Set)	Y
16.2.6.3	eGFR and Serum Creatinine (Full Analysis Set)	Y
16.2.6.4	Proteinuria (Full Analysis Set)	Y
16.2.6.5	Recurrent AMR Episodes and Resolution of AMR Episodes (Full Analysis Set)	Y
16.2.6.6	Patient Survival (Full Analysis Set)	Y
16.2.6.7	Donor-specific Antibody (DSA) Identification and Titer (Full Analysis Set)	Y
16.2.6.8	Salvage Splenectomy (Full Analysis Set)	N
16.2.6.9	EQ-5D-5L (Full Analysis Set)	Y
16.2.7.1	Adverse Events (Safety Analysis Set)	Y
16.2.7.1a	Adverse Event Special Interest (Safety Analysis Set)	Y
16.2.7.1b	Thrombotic and Thromboembolic Events (Safety Analysis Set)	Y
16.2.7.2	Serious Adverse Events (Safety Analysis Set)	Y
16.2.8.1.1	Clinical Laboratory Test Results (Safety Analysis Set)	Y
16.2.8.1.2	Subjects with Potentially Clinically Important Laboratory Test Results (Safety Analysis Set)	Y
16.2.8.2.1	Vital Signs (Safety Analysis Set)	Y
16.2.8.2.2	Subjects with Potentially Clinically Important Vital Signs (Safety Analysis Set)	Y
16.2.8.3	12-Lead Electrocardiogram Results (All-enrolled Set)	Y
16.2.8.4	Lower Extremity Exam (Safety Analysis Set)	Y
16.2.8.5	Immunogenicity (Anti-C1 INH antibody) Results (Safety Analysis Set)	Y
16.2.8.6	Diabetes Status (Safety Analysis Set)	Y
16.2.8.7	Coagulopathy Panel Results (Safety Analysis Set)	Y
16.2.8.8	Virology Results (All-enrolled Set)	Y

APPENDIX 1 TRANSFORMATION OF CMH TEST STATISTICS AND FISHER'S EXACT P-VALUE FOR MULTIPLE IMPUTATION

Rubin's pooling methodology to combine inference from multiple imputation assumes the test statistic estimates are asymptotically normally distributed. In order to satisfy Rubin's rule (Rubin, 1987), transformation is needed to convert the test statistics to asymptotic normal.

CMH general association statistic, under the null hypothesis of no association, has an asymptotic chi-square distribution. The p-value of Fisher's exact test can be transformed to a chi-square distribution with degree of freedom (*df*) = 2 using Fisher's transformation (Fisher, 1932):

$$\Psi = -2\log(p) \sim \chi^2_2$$

where p is the *p*-value from Fisher's Exact test.

The chi-square distributed statistic obtained from Fisher's Exact test or CMH test can be transformed to an asymptotic normal by using Wilson-Hilferty transformation (Wilson & Hilferty, 1931; Lechmacher, 1992; Ratitch et al. 2013) as:

$$wh\_\Psi^{(m)} = \sqrt[3]{\Psi^{(m)}/df}$$

where $\Psi^{(m)}$ is the chi-square distributed test statistic computed from the *m*-th imputed dataset, df is the number of degrees of freedom associated with $\Psi^{(m)}$, and $wh\_\Psi^{(m)}$ is the transformed value. The transformed statistic is approximately normally distributed with mean $1 - 2/(9 \times df)$ and variance $2/(9 \times df)$ under the null hypothesis. We can standardize this transformed statistic to obtain a variable that is normally distributed with mean 0 and variance 1:

$$Z_{wh\_cmh^{(m)}} = \frac{\sqrt[3]{\frac{\Psi^{(m)}}{df}} - \left(1 - \frac{2}{9\times df}\right)}{\sqrt[2]{\frac{2}{9\times df}}}$$

This transformed statistic can now be passed to PROC MIANALYZE in order to perform a combined test.

A sample code to impute missing data using logistic regression, perform Fisher's Exact test, transform Fisher's Exact p-value, perform CMH test, transform the CMH statistic, and perform PROC MIANALYZE for the combined normal score:

```
/*impute missing data using logistic regression*/
proc mi data=TG out=datain mi seed=83789524 nimpute=100;
   var treatment AMR donor response;
```

```
   class treatment AMR donor response;
   monotone logistic;
run;

/*perform Fisher's exact test*/
proc freq data=datain mi;
      tables Treatment*Response /fisher;
      ods output FishersExact=FishersExact;
      by _imputation_;
run;

/*perform transformation of p-value from Fisher's exact test to normal*/
Data Fisher WH;
      set FishersExact(Where=(Label1="Right-sided Pr >= F"));
       /*transform fisher's p to chi-square with df=2*/
      fisher chi=-2*log(nValue1);
      /*transform chi-square with df=2 to standard normal*/
      fisher_value_wh=((fisher_chi/2)**(1/3) - (1-2/(9*2)))/SQRT(2/(9*2));
      fisher_sterr_wh = 1.0;
run;

/*perform CMH test*/
proc freq data=datain mi;
      tables AMR*Donor*Treatment*Response / cmh;
      ods output CMH=CMH;
      by _imputation_;
run;

/*perform WH transformation of p-value from CMH to normal*/
Data CMH WH;
      set cmh(Where=(AltHypothesis="General Association"));
      cmh_value_wh=((VALUE/DF)**(1/3) - (1-2/(9*DF)))/SQRT(2/(9*DF));
      cmh_sterr_wh = 1.0;
run;

/*MI analysis to combine statistics from each imputed dataset, take
Fisher's for example. CMH is similar*/
PROC MIANALYZE DATA=Fisher_wh;
 ODS OUTPUT PARAMETERESTIMATES=mian_Fisher_wh;
 MODELEFFECTS Fisher value_wh;
 STDERR Fisher_sterr_wh;
RUN;
```

APPENDIX 2 THE ALGORITHM OF DERIVING THE TG ASSESSMENT BY GRANULAR SCORE AND STANDARD SCORE

A. By Standard Score

Q6 on Final EAC Biopsy Assessment Form (New or worsening TG)	TG Assessment at Month 6 (Standard Score) YES = Failure (Having new or worsening TG) NO = No Failure
NO	NO
YES	YES
INSUFFICIENT DATA	YES

B. By Granular Score

Q3 on Final EAC Biopsy Assessment Form (Worsening TG)	Q4 on Final EAC Biopsy Assessment Form (New TG)	TG Assessment at Month 6 (Granular Score) YES = Failure (Having new or worsening TG) NO = No Failure
NO	NO	NO
NO	NOT APPLICABLE	NO
NO	YES	YES
YES	NO	YES
YES	NOT APPLICABLE	YES
INSUFFICIENT DATA	INSUFFICIENT DATA	YES
YES	YES	YES