PROTOCOL: SHP616-302

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]
IND:	IND 16417
EUDRACT NO.:	2015-000726-11
SPONSOR:	Shire ViroPharma, Inc. 300 Shire Way, Lexington, MA 02421 USA
INVESTIGATORS:	Multicenter
PROTOCOL HISTORY:	Amendment 4: 22 Nov 2017 Amendment 3: 01 Sep 2016 Amendment 2: 25 Jun 2015 Amendment 1: 28 May 2015 Original Protocol: 01 Apr 2015

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire ViroPharma, Inc.) Approval

[redacted]	[redacted]

Investigator's Acknowledgement

I have read this protocol for Shire ViroPharma Study SHP616-302.

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.

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address:	
(please hand print or type)	

Signature: _____ **Date:** _____

AMENDMENT SUMMARY AND RATIONALE

Clinical protocol SHP616-302 has been amended to provide increased clarity and guidance to investigational sites on the exclusion of subjects with a medical history that would render them ineligible for study participation. Exclusion criteria on history of thrombotic/thromboembolic events have been clarified to better define the patient population. Guidance to provide additional clarity on study procedures has been included without actual change to those procedures. Changes include clarification of laboratory testing requirements and other study testing. Clarification regarding treatment discontinuation and implementation of the stopping rules has been provided.

Changes in grammar, spelling, punctuation, format, minor editorial changes, and updates to the list of abbreviations and cross-references have been made for consistency and clarity and are not reflected in the summary of changes.

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **22 Nov 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated the high-level amendment summary and rationale to provide a general overview and justification of amendment revisions		Amendment Summary and Rationale
Updated the emergency contact information		Emergency Contact Information Section 8.2.2
Updated the planned study period and provided rationale for extension. Rationale: Study period will be longer than expected due to slow enrollment in this rare disease		Synopsis Section 3.1
Updated/clarified as follows: • "Randomization via IV/WRS" changed to "Screening Registration / Randomization via IV/WRS (IRT) and added to rescreening visit • Central and local lab requirements clarified • BUN and Serum Cr updated to Serum Cr, BUN and eGFR • BUN and serum creatinine to be tested at all visits, including recurrent AMR, Day 1 and Day 13 and clarification provided on the purpose of the first Serum Cr after biopsy • "Proteinuria Spot Urine Protein to Cr Ratio" updated to "Urine Protein, Urine Creatinine and Urine Protein/Urine Creatinine Ratio" • Renal allograft assessment procedure added to screening visit Rationale: IRT and lab description term changes for consistency in terminology used in the IRT system and by Central lab, respectively; clarifications of Central vs Local labs to make it consistent and clear throughout the protocol		Synopsis Study Schedules, Table 1 Section 7 Section 9.8.2.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **22 Nov 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated/clarified as follows: • Central and local lab requirements clarified • BUN and Serum Cr updated to Serum Cr, BUN and eGFR • "Proteinuria Spot Urine Protein to Cr Ratio" updated to "Urine Protein, Urine Creatinine and Urine Protein/Urine Creatinine Ratio" • Anti-C1 INH antibody testing updated for Month 3 to be performed without regard to positivity of previous result Rationale: For consistency in terminology between lab and protocol; Month 3 Anti-C1 INH not dependent on previous result as it is needed for proper detection and monitoring of immunogenic response		Synopsis Study Schedules, Table 2 Section 7
Clarified the Study Design as follows: • Retreatment of recurrent AMR episodes may occur "during the first 180 days after the qualifying biopsy for AMR", which was updated from "during the first 6 months of the study" Rationale: To avoid confusion with the window of the Month 6 visit, the time to allow retreatment was set to 180 days		Synopsis Section 3.1 Section 6.2.3 Section 7.2.2.2 Section 7.2.2.4 Section 7.2.3.5.2 Schedule of Assessments, Table 1
Updated exclusion criteria as follows: • Exclusion criterion #3: clarified that double kidney transplant procedure is considered to be one procedure Rationale: frequently asked clarification from clinical sites. • Exclusion criterion #7: removed transient ischemic attack (TIA) to be included in exclusion criterion #8, clarified exclusion criteria of myocardial infarction and treatment with anticoagulants • Exclusion criterion #8: clarified and detailed exclusion criterion of history of abnormal bleeding, clotting events or disorders, and coagulopathy Rationale: request from DMC to clarify criteria to ensure exclusion of subjects with the above thrombotic/thromboembolic events • Exclusion criterion #12: time frame for exclusionary range of platelet was updated to 24 hours Rationale: To make window consistent with WBC in order to assess eligibility from one hematology time point		Synopsis Section 4.2 Section 7.2.3.1
Stopping rules provided in more detail: • Listed events leading to stop of enrollment of new subjects • Specified process for DMC safety review of such events Rationale: To specify the clinically significant events, consistently with Section 8.2.4 in the protocol that trigger the stopping rule		Synopsis Section 3.1 Section 4.5.3 Section 9.5.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **22 Nov 2017**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated definition of Pharmacokinetic (PK) and Pharmacodynamic (PD) Analysis Set. Rationale: The definition was updated as the previous wording raised questions regarding the interpretation of the measured PK/PD concentrations or levels.		Synopsis Section 9.7
Clarified procedure for subjects discontinuing from treatment, but not from the study. Rationale: To maintain sequence of visits if subjects discontinue from treatment only, and to allow for safety data collection shortly after discontinuation		Section 3.2 Section 4.5
Clarified what new findings identified during the physical examination at screening should be considered adverse events as opposed to medical history Rationale: To clarify what adverse events may fall within the adverse event collection window between consent and the physical examination at screening, and are not considered medical history.		Section 7.2.3.2 Section 7.2.3.3.
Reporting of events of special interest updated Rationale: To clarify how to report non-serious events of special interest via the SAE form		Section 8.1.4
Serious Adverse Event procedure for thrombotic and thromboembolic events updated Rationale: To clarify that superficial thrombophlebitis, dialysis access clotting, or catheter-related thrombotic events can be reported as serious via SAE form if they meet SAE definition		Section 8.2.4
Correction of typographical error: Units for eGFR MDRD value updated from mL/min/1.72m2 to mL/min/1.73m2)		Throughout protocol

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

Please refer to Section 8.2.2 for additional information on serious adverse event reporting.

In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Trial Serious Adverse Event Form within 24 hours to the Shire Pharmacovigilance Department and the PPD Clinical Study mailbox. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover) and are provided below.

US and Canadian Sites

Fax: [redacted]

Email: [redacted] **AND** [redacted] (email should include both addresses)

EU/ROW Sites

Fax: [redacted]

Email: [redacted] **AND** [redacted] (email should include both addresses)

For protocol- or safety-related issues, the investigator must contact the Shire / PPD Medical Monitor (please refer to the study-specific contact list):

[redacted] (Shire Medical Monitor)

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire ViroPharma product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please report all Product Quality Complaints to:

300 Shire Way, Lexington, MA 02421 USA

[redacted]

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ABBREVIATIONS

ABO	blood type
ADR	expected adverse reaction
AE	adverse event
AESI	adverse event of special interest
AMR	antibody-mediated rejection (of renal allograft)
beta-HCG	beta human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
C1 INH	C1 inhibitor
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)
CL	clearance
C_{max}	maximum concentration
C_{min}	minimum concentration
CP	conditional power
Cr	creatinine
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
DSA	donor-specific antibody
DVT	deep vein thrombosis
EAC	Endpoint Adjudication Committee
EC	ethics committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EM	electron microscopy
EMA	European Medicines Agency
EOS	end of study (visit)
EQ-5D-5L	EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
g	glomerulitis
GBM	glomerular basement membrane
GCP	Good Clinical Practice
HAE	hereditary angioedema
HIPAA	Health Insurance Portability and Accountability Act
HLA	human leukocyte antigen

HRU	healthcare resource utilization
HSCT	hematopoietic stem cell transplant
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IV	intravenous
IVIg	intravenous immunoglobulin
IV/WRS	Interactive Voice/Web Response System
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MI	myocardial infarction
PRA	panel reactive antibody
PTC	peritubular capillaries
PVRM	pharmacovigilance and risk management
rhC1INH	recombinant human C1 inhibitor
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
TEAE	treatment-emergent adverse event
TG	transplant glomerulopathy
TIA	transient ischemic attack
$t_{1/2}$	terminal half-life
t_{max}	time of maximum observed concentration sampled during a dosing interval
US	United States
WBC	white blood cell (count)

STUDY SYNOPSIS

Protocol number: SHP616-302	**Drug:** C1 esterase inhibitor [human]
Title of the study: 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.	
Number of subjects (total and for each treatment arm): Approximately 112 subjects are planned for randomization (56 for each treatment arm) to ensure 100 subjects complete; sample size may be increased based on the interim analysis for sample size re-estimation.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 40 sites planned in North America and the European Union	
Study period (planned): Enrollment was originally expected to occur from 2015 through 2017; however, it will be extended since enrollment was found to be slower than expected and the sample size may increase following the first interim analysis for sample size re-estimation. Subjects could be followed for up to a maximum of 4 years.	**Clinical phase:** 3

Objectives:

Primary: To evaluate the efficacy of CINRYZE administered with plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free intravenous immunoglobulin (IVIg) for the treatment of acute antibody-mediated rejection (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.

Key Secondary: 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:

Secondary objectives from study entry to 6 months:

- 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

Exploratory:

[redacted]

Rationale: Since AMR results in complement-mediated damage to a transplant, the sponsor hypothesized that a complement inhibitor such as plasma-derived C1 inhibitor (C1 INH) could effectively protect a renal allograft while reduction of DSA is achieved with standard-of-care plasmapheresis, plasma exchange, or immune adsorption treatments with sucrose-free IVIg, resulting in less long-term damage to the kidney and prolonged graft survival.

Investigational product, dose, and mode of administration:

- CINRYZE: an initial intravenous (IV) infusion of 5000 U CINRYZE on Day 1, followed by 2500 U of CINRYZE IV on Days 3, 5, 7, 9, 11, and 13
- Placebo (0.9% sodium chloride for infusion): an IV infusion on Days 1, 3, 5, 7, 9, 11, and 13 (100 mL)

Methodology:

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 biopsy for 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 biopsy for 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 period, 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 for (1) living vs deceased donor and (2) severity of acute AMR 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. 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.

As shown in Table 2, in addition to the qualifying kidney biopsy, an additional kidney biopsy will be obtained at the Month 6 study visit. See Section 7.2.2.2 for details. Biopsy slides and pertinent micrographs (including, but not limited to EM images) for the qualifying and Month 6 biopsies will be provided to an independent, blinded pathology EAC for confirmation of AMR diagnosis and the assessment of the primary endpoint (new or worsening TG at 6 months of initiation of treatment). [redacted]

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 $eGRF_{MDRD} \leq 15$ 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 adverse events (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 (see Table 2 for End of Study Visit procedures).

There will be 3 analyses (2 interim, 1 final) 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. See Section 9.5.2 for additional details.

Resolution: 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. Resolution is defined initially by the local pathologist according to histological findings, and later confirmed by the pathology EAC, and should be based on improvement from previous biopsy and characterized by Banff criteria as: glomerulitis (g + ptc) <2 if C4d-negative; (g + ptc) = 0 if C4d-positive. The investigator will record the applicable $eGFR_{MDRD}$ values and the date of resolution of the qualifying and recurrent AMR episodes in the CRF, when applicable, including the criteria used for determination of resolution (clinically and/or through histopathology).

Recurrence: 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 180 days after the qualifying biopsy, 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 as indicated in Table 1. Subjects will follow the assessments noted in Table 1 and Table 2. For each new episode of AMR occurring during the first 180 days after the qualifying biopsy. Retreatment should occur as soon as possible within 7 days of the biopsy that defined the new AMR episode. Retreatment may not occur for recurrent AMR episodes diagnosed through biopsies done after the first 180 days after the qualifying biopsy date. Biopsies at 6 months following retreatment are not required to be performed by the protocol. The only mandated follow-up biopsy will be at Month 6 after initial treatment. With the exception of the Month 6 biopsy, completion of follow-up biopsies after the qualifying AMR episode is at the discretion of the study sites per local standard of care. Biopsy slides and images for unscheduled standard of care biopsies will also be submitted to the EAC.

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). The effect on healthcare utilization will also be assessed.

Complement and C1 INH levels will be assessed at specified time points up to Day 13 for pharmacokinetic/pharmacodynamic evaluation (Table 2 and Table 3).

Safety will be monitored through the recording of AEs and changes in physical examinations, vital signs, antibodies to C1 INH, and clinical safety laboratory testing. Adverse events and serious adverse events (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 study treatment. 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 also be captured as described above for the treatment of the initial occurrence of AMR. In addition, the following adverse events of special interest (AESI) will be closely monitored, both serious and non-serious, and reported throughout the study to Shire Pharmacovigilance and Risk Management (PVRM) via SAE form, regardless of relationship to investigational product:

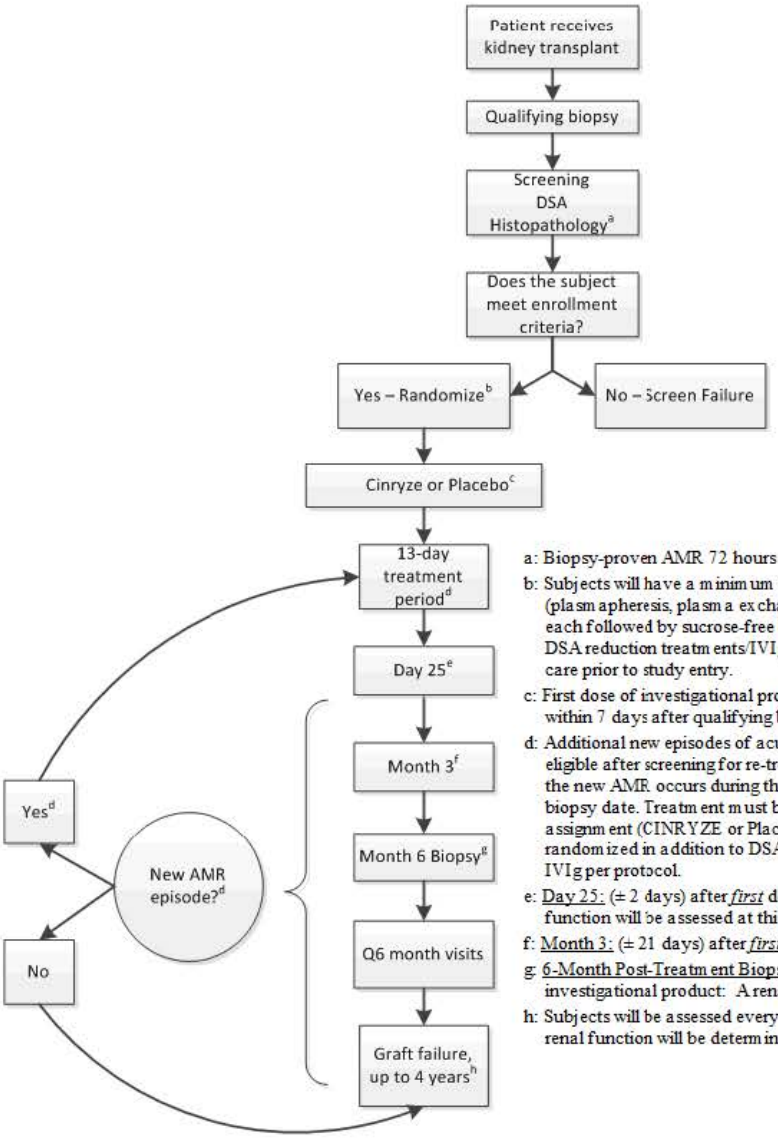
- any thrombotic or thromboembolic event (Section 8.2.4)
- any hypersensitivity reaction
- any new episode of kidney allograft rejection (excluding AMR), even if the event does not qualify for retreatment with investigational product
- any kidney allograft failure

Stopping rules: If clinically significant drug-related thrombotic or thromboembolic events (as defined in Section 4.5.3) are reported as a study-drug-related SAE, enrollment will be halted (See Section 4.5.3). The DMC will review the case and will issue a recommendation to the Sponsor with regard to re-starting enrollment.

The schedules of study procedures are provided immediately following the synopsis:

Table 1: Schedule of Assessment (Screening though Day 25)
Table 2: Schedule of Assessments (Month 3 through Month 48 [End of Study]
Table 3: Blood Sample Collection Time Points for Pharmacokinetic/Pharmacodynamic Testing (All Subjects)

See the study design flow chart below.



a: Biopsy-proven AMR 72 hours to 12 months after current transplant.

b: Subjects will have a minimum of 5 DSA reduction treatments (plasmapheresis, plasma exchange, or immune adsorption treatments) each followed by sucrose-free IVIg for each qualifying AMR episode. DSA reduction treatments/IVIg may be provided as part of standard of care prior to study entry.

c: First dose of investigational product (Day 1) must be administered within 7 days after qualifying biopsy.

d: Additional new episodes of acute AMR may be retreated if subject is eligible after screening for re-treatment and if the biopsy diagnostic for the new AMR occurs during the first 180 days after the qualifying biopsy date. Treatment must be with the same investigational product assignment (CINRYZE or Placebo) to which the subject was originally randomized in addition to DSA reduction treatment and sucrose-free IVIg per protocol.

e: Day 25: (± 2 days) after *first* dose of investigational product. Renal function will be assessed at this visit.

f: Month 3: (± 21 days) after *first* dose of investigational product.

g: 6-Month Post-Treatment Biopsy: (± 21 days) relative to first dose of investigational product: A renal allograft biopsy will be obtained.

h: Subjects will be assessed every 6 months up to 4 years. At these visits, renal function will be determined as well as graft failure (yes/no).

Inclusion and exclusion criteria:

Inclusion Criteria:

To be eligible for this protocol, a subject must:

1. Be ≥18 and ≤70 years of age.
2. Weigh ≥45 kg with a body mass index (BMI) <35 kg/m^2 at screening.
3. Have HLA DSA identified at the time of diagnosis of AMR. If it is anticipated that the local DSA results will not be available within the screening period, previously obtained local DSA results can be used to assess eligibility, if obtained after kidney transplant and within 30 days prior to the qualifying AMR episode. In any instance, a local DSA test should still be performed at the time of AMR diagnosis.
4. Have a first qualifying episode of AMR in the subject's current renal allograft between 72 hours and 12 months after transplant defined by a renal allograft biopsy demonstrating neutrophil and/or monocyte infiltration in the peritubular capillaries and/or glomeruli with or without evidence of C4d by immunohistopathology according to 2013 Banff criteria for AMR.
5. Have achieved adequate renal function defined as: Pre-AMR baseline $eGFR_{MDRD}$ ≥20 mL/min/1.73m^2 for a qualifying AMR episode occurring ≤21 days after transplant or pre-AMR baseline $eGFR_{MDRD}$ ≥30 mL/min/1.73m^2 for a qualifying AMR episode occurring >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 one $eGFR_{MDRD}$ 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 biopsy, it can be evaluated within a 60 day period.
6. Receive first dose of investigational product after 7 days after the kidney transplant procedure and within 7 days after the qualifying renal allograft biopsy procedure that was positive for AMR.
7. Be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.
8. If female and of child-bearing potential, must have a negative urine pregnancy test confirmed by a negative serum beta human chorionic gonadotropin pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Day 1 visit.
9. Agree to comply with any applicable contraceptive requirements of the protocol.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Have received pediatric en bloc kidney transplant.
2. Have primary Focal Segmental Glomerulosclerosis, rapidly progressive glomerulonephritis, membrano-proliferative glomerulonephritis type 1 (including C3 Glomerulopathy), "dense deposit disease", or thrombotic microangiopathy as the cause of native kidney failure.
3. Have prior or concurrent non-renal solid organ transplant or hematopoietic stem cell transplant (HSCT) or have more than 2 completed kidney transplant procedures (note: 1 double kidney transplant procedure is considered 1 procedure) .
4. Have a known neoplastic lesion in the transplanted allograft.
5. Have, any ongoing infection that causes hemodynamic compromise or as determined by the investigator, any surgical or medical condition that could interfere with the administration of investigational product, interpretation of study results, or could compromise patient safety, including (as determined by the transplanting surgeon and documented in the operative report) any major technical complications of the renal artery, renal vein, or ureteral anastomosis.

6. Have ongoing treatment for hepatitis C virus (HCV) infection.
7. Have had a recent myocardial infarction (MI) within the past 6 months and/or at the time of screening are treated with anticoagulants and/or antiplatelet agents (excluding aspirin) for a previous myocardial infarction.
8. Have a history of:
   - abnormal bleeding,
   - clotting events or disorders (excluding a history of clotted hemodialysis access or superficial thrombophlebitis in the absence of medically confirmed coagulopathy),
   - any coagulopathy (documented or clinically suspected)

   For example patients should be excluded if they have a history of renal allograft arterial or venous thrombosis, deep vein thrombosis, pulmonary embolism, ischemic cerebrovascular accident (stroke) or transient ischemic attack (TIA), any large vessel thrombosis.
9. Have a history of allergic reaction to CINRYZE or other blood products.
10. Have had any change in androgen therapy (eg, danazol, oxandrolone, stanozolol, testosterone), tranexamic acid, epsilon-aminocaproic acid, or other fibrinolytics within 3 months before the first dose of investigational product.
11. Have participated in the active dosing phase of any other investigational drug study within 30 days prior to dosing with investigational product.
12. Have any of the following local laboratory values reported prior to dosing with investigational product:
    - Within 24 hours prior to subject dosing, white blood cell count $<0.5\times10^9$/L or $>20\times10^9$/L (the value of >20 x 10^9/L should be excluded if obtained during steroid treatment)
    - Within 24 hours prior to dosing , platelet count $<25\times10^9$/L or $>600\times10^9$/L
13. Be pregnant or breastfeeding.
14. Have received any of the following agents within 1 month prior to the first dose of investigational product:
    - Sucrose-containing IVIg
    - Any C1 INH (plasma-derived [eg, CINRYZE®, Berinert®, Cetor®] or recombinant [eg, Rhucin®])
    - Eculizumab (Soliris®)
    - Ecallantide (Kalbitor®)

Maximum duration of subject involvement in the study:

- Planned duration of screening period: up to 7 days
- Planned duration of investigational product administration period: 13 days
- Planned duration of post-treatment evaluations: up to 4 years

Endpoints and statistical analysis:

Subject Populations:

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

The **Intent-to-Treat Population** 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.

The **Full Analysis Set (FAS)** 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.

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.

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.

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.

The **Pharmacokinetic (PK) and Pharmacodynamic (PD) Analysis Set** is defined as all subjects who received at least 1 dose of CINRYZE and have at least 1 evaluable post-dose PK/PD concentration value.

Primary Efficacy Endpoint:

Proportion of subjects with new or worsening TG at 6 months after treatment initiation as determined by Banff criteria.

Key Secondary Efficacy Endpoint:

Proportion of subjects with all-cause graft failure (ie, return to permanent dialysis and/or removal of the transplanted kidney and/or clinical determination of cessation of graft function) at 4 years following treatment of the initial qualifying AMR episode.

***Secondary Efficacy Endpoints from study entry to 6 months*:**

- 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 screening to 6 months
- Change in histopathology per Banff criteria 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*:**

- 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
- Proportion of subjects with graft failure due to AMR at 4 years
- Time to all-cause graft failure
- Time to graft failure due to AMR
- Proportion of subjects with resolution of the qualifying AMR episodes
- Time to resolution of AMR episodes
- Proportion of subjects alive at 4 years
- Time to all-cause mortality

Exploratory Endpoints:

[redacted]

Safety Endpoints:

- Assessment of treatment-emergent adverse events (TEAEs), vital signs measurements, antibodies to C1 INH, and clinical safety laboratory testing

Pharmacokinetic/Pharmacodynamic Endpoints:

- Analysis of serum complement factors (anaphylatoxin split product of C3 activation important in chemotaxis [C3a] and anaphylatoxin split product of C5 activation important for histamine release and chemotaxis [C5a]) and their potential relationship to C1 INH concentrations
- Analysis of the pharmacokinetics of CINRYZE and the effect of plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free IVIg for the treatment of AMR on C1 INH levels

Health Economics and Outcomes Endpoints:

- Measurement of the EQ-5D-5L
- Measurement of healthcare resource utilization (HRU)

Primary hypothesis and statistical model used to analyze the primary efficacy endpoint:

The FAS population will be used to report the primary efficacy data. Subjects who do not have the primary efficacy endpoint assessed at 6 months post-dose will be assigned as failures. The primary endpoint will be presented as the proportion of subjects with new or worsening TG occurring at 6 months post-treatment, 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 subjects with new or worsening TG at 6 months post-treatment in the CINRYZE group and $\Pi_{Placebo}$ is the proportion of subjects with 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 (1-sided test) to test null hypothesis:

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

Against the 1-sided alternative:

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

In the initial plan, the statistical difference between treatments will be evaluated by the CHW weighted test statistics Z_{CHW} (Cui et al. 1999) when the first 60 subjects complete the assessments for the primary endpoint (second interim analysis). If the $Z_{CHW} \geq Z_{0.0249}$ (equivalent to the p-value from the test is ≤0.0249 [1-sided test]), it will be concluded that CINRYZE is efficacious based on the proportion of subjects with new or worsening TG at 6 months post-treatment and the result will serve as evidence of efficacy based on these 60 subjects. However, the number of subjects might be changed (increased) depending on the results of the first interim analysis in which the sample size will be re-estimated based on the first 30 subjects who complete the Month 6 TG assessment.

Design features are in place to protect the study-wise error level at 0.025 (1-sided test) for testing the hypotheses related to primary and key secondary endpoints. As, for declaration of a successful study, statistical significance must be declared successively on the surrogate endpoint of proportions of subjects with new or worsening TG at 6 months post-treatment and on the endpoint of all-cause graft failure. No adjustment for multiple co-primary endpoints is needed. The alpha spent at each endpoint will be controlled by sequential testing boundaries assuring that no more than 0.025 alpha (1-sided test) is expended in the multiple analyses across time for each of the primary and key secondary endpoints.

Safety variables and analysis:

Safety endpoints include TEAEs, vital signs measurements, antibodies to C1 INH, and clinical safety laboratory testing. The safety analysis set will be used to report the safety data. Treatment-emergent AEs will be summarized according to the coded MedDRA preferred term and system organ class. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Treatment-emergent AEs leading to withdrawal, SAEs, and deaths will be similarly summarized and listed. Clinical laboratory tests, vital signs, and antibodies to C1 INH will be summarized. Potentially clinically significant laboratory values will also be summarized and listed.

STUDY SCHEDULES

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]	✔ ----------								✔	
Investigational product administration [n]			✔	✔	✔	✔	✔	✔	✔	
Concomitant medications	✔	✔	✔ ----------						✔ [o]	✔ [p]
Adverse event monitoring [q]	✔ ----------									✔
Renal allograft assessment [r]	✔	✔ ----------								✔

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)
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, 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.

[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.

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)

[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 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 9.5.1 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.

[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.

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]

[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.

[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.

1. BACKGROUND INFORMATION

1.1 Preclinical Experience

Acute and repeated-dose toxicity studies were performed in rats with intravenous (IV) administration of CINRYZE® (lyophilized formulation) at dose levels of 20, 100, and 400 U/kg/day. No signs of toxicity at up to 28× the normal human dose (based upon a 70 kg adult) were observed in the single-dose study. In the repeated-dose study, the signs of toxicity were limited to minor increases in inflammatory changes in the lungs and germinal center hypertrophy in the spleens of animals dosed at 400 U/kg/day for 14 days, as compared to control animals. The amount of germinal center hypertrophy in the spleens of rats treated at 400 U/kg/day was within the normal background histopathological range in both incidence and severity, but did correlate with a small increase in splenic weights, which may have been a reflection of the inflammatory increase in the lungs. Since CINRYZE is derived from human plasma, an immunological effect in rats is to be expected. An in vivo thrombogenicity study performed by ViroPharma Inc. in 1994 in rabbits suggested a potential for clot formation when another C1 inhibitor (C1 INH) product was administered at doses 14-fold greater than the recommended clinical dose (greater than 200 U/kg). However, results of an ex vivo thrombogenicity study utilizing healthy human volunteer whole blood/platelet poor plasma showed no evidence of a hypercoagulable effect of CINRYZE at concentrations of 0.14 to 7.0 U/mL (approximately 7× physiologic concentration) (Levy et al. 2014). No effects of C1 INH on embryo-fetal development were observed at dose levels up to 400 U/kg. No animal studies have been completed to evaluate the effects of CINRYZE on carcinogenesis, mutagenesis, or impairment of fertility.

A 14-day study in male and female Sprague Dawley rats is in progress to evaluate the toxicological potential of a liquid formulation of C1 esterase inhibitor [human]. C1 esterase inhibitor [human] liquid for injection was administered once daily for 14 days in the following doses: 0 (vehicle control), 200, 400, and 1000 U/kg subcutaneous (SC) and 0 and 1000 U/kg IV. Audited draft data shows that all animals survived to necropsy. There were no test-article related clinical observations, effects on body weight or food consumption, or ophthalmic findings. Nor were there any test-article related hematology, coagulation, or urinalysis parameter alterations or organ weight differences at the end of dosing or recovery periods. Non-adverse treatment-related findings included an increased incidence and severity of localized dermal, muscular, and SC inflammation at the SC injection sites and secondary responses to the localized antigenic stimulation (higher globulin values, lower albumin to globulin ratio values, higher total protein values (200 and 1000 U/kg/day SC females only), enlarged axillary lymph nodes, and an increased incidence of enlarged mediastinal lymph nodes (400 and 1000 U/kg/day SC) which were reversible. Reversible secondary responses to the localized antigenic stimulation in the 1000 U/kg/day IV males and females included higher globulin values (females only), lower albumin to globulin ratios (females only), and enlarged axillary lymph nodes. Toxicokinetic data are not yet available. Therefore, based upon the absence of overt toxicity, the no-observed-adverse-effect level (NOAEL) was considered to be 1000 U/kg/day administered via SC or IV injection.

1.2 Indication and Current Treatment Options

Each year, several thousand end-stage renal disease patients are prohibited from receiving a potentially life-saving kidney transplant because of pre-existing antibody directed against the donor's cell surface human leukocyte antigens (HLA). The presence of these circulating donor-specific antibodies (DSA), identified through pre-transplant cross-match screening, is a contraindication to transplantation (Patel and Terasaki 1969; Bryan et al. 1998). Donor-specific antibodies can cause immediate, or "hyperacute," antibody-mediated rejection (AMR) (of renal allograft) resulting in complement-mediated destruction and loss of the kidney soon after transplant. In the US, there are more than 25,000 people on the wait list that have HLA antibodies (Department of HHS 2009) and thus, experience a prolonged wait for an organ to which they are not sensitized. More than 6,000 patients currently on the wait list have willing living kidney donors, but transplantation is not performed because of DSA. Another 3,500 patients per year have willing donors, but will be added to the wait list because of DSA (Montgomery 2010). The inability to transplant sensitized patients with kidneys from willing live donors further increases the demand for deceased donor kidneys, and thus, increases wait times for all listed patients. Further, it has recently been described that the majority of standard (no identified pre-transplant DSA) kidney transplant grafts lost due to chronic rejection are the result of de novo development of DSA from graft sensitization after the transplant. An effective treatment regimen for AMR would not only increase access to transplants for patients with pre-existing DSA, it could salvage a portion of the grafts lost to acute and early chronic AMR from de novo DSA that form following transplantation.

Decreasing DSA titers in cross-match-positive patients through the use of intravenous immunoglobulin (IVIg) (Glotz et al. 2002) or a combination of plasmapheresis and IVIg (Sonnenday et al. 2002; Montgomery and Zachary 2004) has allowed for "desensitization" and conversion to negative cross-match for successful kidney transplantation (Akalin et al. 2003; Jordan et al. 2003). However, despite such practices, more than 10% of patients will lose their graft immediately or very early after transplantation due to hyperacute rejection or aggressive acute AMR (Lefaucheur et al. 2008), and 25-50% will still experience acute AMR, most within the first 1 to 3 months post-transplant (Montgomery 2010; Stegall et al. 2010; Loupy et al. 2009). In fact, 1-year graft survival was only 60-70% in patients with DSA and AMR compared to approximately 95% in patients with no DSA (Lefaucheur et al. 2008). Nevertheless, for some patients, the morbidity and mortality rates associated with dialysis warrant the risks of cross-match-positive kidney transplantation. It is clear that there remains an unmet medical need to improve overall outcomes for DSA-positive transplant recipients at high risk for AMR.

Because of the selection bias that excludes patients from transplant access if they have identified DSA, acute AMR episodes are extremely rare, so a small study for treating AMR is a necessity given the limited patient population. In addition, graft loss due to acute AMR may be delayed for several years due to therapies such as plasmapheresis, plasma exchange, or immune adsorption treatments and IVIg. However, it has been shown that graft survival for patients with acute AMR (where DSA is identified and the 4th complement protein degradation product [C4d] is demonstrated on biopsy) begins to deviate from standard kidney graft survival within 3 years, so assessing efficacy with a surrogate marker earlier in the disease process and continuing to follow patients for long-term graft survival to confirm clinical benefit is warranted.

Finally, transplant glomerulopathy (TG), defined by double contouring of the glomerular basement membrane (GBM), is the most plausible and reliable of surrogate markers for poor outcomes in kidney transplantation. Early evidence of transplant glomerulopathy can be identified by electron microscopy (EM) when contouring of the GBM is associated with evidence of endothelial swelling (Haas 2014); however, long-term association with early graft loss has not been demonstrated with such early changes. Despite treatment with plasmapheresis and IVIg, TG evident by light microscopy (chronic glomerulopathy [cg] ≥1b, ie, ≥1 glomerular capillaries with GBM double contours in 1 nonsclerotic glomerulus by light microscopy; EM confirmation recommended if available [Haas 2014]) has been associated with later formation of irreversible scarring observed on biopsy as interstitial fibrosis, glomerulosclerosis, and/or fibrointimal thickening (Montgomery 2010; Racusen et al. 1999) that eventually results in graft loss. Patients with TG on biopsy have greatly shortened graft survival compared with patients who have no evidence of TG (Sharif et al. 2014; Sun et al. 2012). Furthermore, TG on light microscopy has been universally accepted by transplant physicians and pathologists as a reliable surrogate marker of impending allograft loss.

Since TG, as described above, is indicative of poor graft survival, an effective treatment for AMR must modulate the underlying destructive host immune response that results in TG. Plasmapheresis, plasma exchange, or immune adsorption treatments and IVIg can decrease DSA titers; however, their use may not address the tissue destruction that occurs as a result of complement activation. Human leukocyte antigen-DSA complexes activate the classical pathway of the complement cascade, ultimately resulting in the formation of membrane attack complexes and continuous release of inflammatory cytokines and leukocyte infiltration (Levy and O'Donnell 2006).

As evidence of the role of complement in graft destruction, accumulation of C4d along with inflammation of the peritubular capillaries (PTC) is pathognomonic for AMR and is associated with poor allograft survival (Mauiyyedi et al. 2002; Sis et al. 2010). After adjusting for risk factors commonly associated with graft failure, patients who required renal allograft biopsy for diminished kidney function and who had DSA in their serum with C4d staining on biopsy had a risk of graft failure 3× higher than patients without DSA or C4d staining on biopsy (Haririan et al. 2009). Therefore, a complement inhibitor may be a useful adjunct in the treatment of AMR to mitigate tissue damage and prolong allograft survival.

1.3 Product Background and Clinical Information

CINRYZE (C1 esterase inhibitor [human]) consists of a protein fraction prepared from human plasma. The manufacturing process includes 3 virus inactivation/removal steps: polyethylene glycol precipitation, pasteurization, and nanofiltration. CINRYZE is a normal human plasma protein that is not subject to Cytochrome P450 metabolism, excretion, or pharmacokinetic drug-drug interactions exhibited by low molecular weight compounds. CINRYZE (lyophilized formulation) was approved by the US FDA for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE) in October 2008. CINRYZE was approved throughout the EU, via the Centralized Procedure, in June 2011 for treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with HAE, and routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of

HAE who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment. Additional approvals have occurred in Canada (2012), Australia (2012), and Switzerland (2013).

1.3.1 Clinical Experience with Hereditary Angioedema

Per the approved CINRYZE US Prescribing Information, more than 14,000 IV infusions of CINRYZE were administered to over 260 different subjects in 8 completed clinical studies in the HAE development program for IV CINRYZE. The vast majority of infusions were CINRYZE doses of 1000 U. In the placebo-controlled study with the longest administration period (Study LEVP 2005-1/B, prevention of angioedema attacks), 1000 U of IV CINRYZE was administered every 3 or 4 days for 12 weeks. In this study, the only CINRYZE-related treatment-emergent adverse events (TEAEs) that occurred in more than 1 subject were viral upper respiratory tract infection and rash, each occurring in 3 subjects (12%). Across studies, there were only occasional reports of infusion site pain, bruising, rash, or other local reactions. No subjects were discontinued from CINRYZE due to an adverse event (AE) in any of the studies. Refer to the CINRYZE investigator's brochure for efficacy results.

Evaluation of the clinical pharmacokinetics and pharmacodynamics following IV administration of CINRYZE in subjects with HAE was primarily based on the results of Protocol LEVP 2006-5. After IV administration of CINRYZE 1000 U, functional C1 INH concentrations increased from a mean baseline value of 0.31 U/mL to a maximum concentration (C_{max}) of 0.68 U/mL. Two consecutive 1000 U doses administered 60 minutes apart produced a mean C_{max} of 0.85 U/mL. Median t_{max} was approximately 1 to 2 hours. The mean $t_{1/2}$ of functional C1 INH was approximately 60 hours using non-compartmental methods. Mean clearance (CL) values for functional C1 INH were 0.85 and 1.17 mL/minute for the single and double doses, respectively. Mean C_{max} values for C1 INH antigen following IV administration of CINRYZE were 1.48 and 1.70 U/mL for the single and double doses, respectively. Median t_{max} was approximately 1.5 hours. The mean $t_{1/2}$ of antigenic C1 INH was approximately 45 to 47 hours and mean CL was 0.70 mL/minute.

CINRYZE, in doses utilized to treat HAE, does not require pre-administration medications such as antihistamines or acetaminophen.

1.3.2 Clinical Experience with Antibody-mediated Rejection

One clinical study (0624-201) was conducted to assess the safety and effect of CINRYZE in the treatment of acute AMR in HLA-donor-sensitized kidney transplant recipients. Eighteen subjects with AMR were enrolled in the study and received an initial IV infusion of 5000 U of CINRYZE or placebo on Day 1, followed by 2500 U of CINRYZE or placebo IV on Days 3, 5, 7, 9, 11, and 13. All 18 subjects completed treatment and the study. Seven of 9 (78%) subjects who received CINRYZE and 6/9 (67%) who received placebo had a resolution of the qualifying episode of AMR based on clinical improvement of renal function and on classic Banff categorization of histopathology findings. The median number of days from the first dose of investigational product until AMR resolution was 20.0 days (range: 19 to 86 days) for subjects who received CINRYZE and 20.5 days (range: 20 to 22 days) for subjects who received placebo. All 7 (100%) subjects who received CINRYZE and had resolution of the qualifying episode had AMR resolution determined by histopathology.

Of the 6 subjects who received placebo and had resolution of the qualifying episode, 3 (50%) had AMR resolution based on clinical criteria and 4 (67%) had AMR resolution based on histopathology.

All 18 subjects had early protocol-mandated biopsies at Day 20; however, the 14 subjects from Johns Hopkins Medical Institute also had center-mandated biopsies 3-6 months after completion of investigational product therapy (n=7 CINRYZE; n=7 placebo). Since these 14 subjects had also been treated with the same standard of care regimen, the Central Pathologist read the long-term follow-up biopsies blinded to treatment assignment and determined the presence or absence of new TG by the published Banff criteria (Racusen et al. 1999; Sis et al. 2010). Of these 14 subjects, 3 of 7 placebo subjects had evidence of new TG as determined by double contouring of the GBM (cg≥1b; personal communication) with thickening of the PTC and ongoing PTC inflammation on histopathology. Notably, there were no new cases of Banff-qualified TG (cg≥1b; personal communication) with PTC inflammatory changes in the 7 subjects receiving CINRYZE (Montgomery et al. 2014).

Intravenous administration of an initial infusion of 5000 U of CINRYZE followed by 2500 U CINRYZE every other day for 2 weeks (20,000 U over 13 days) was safe and generally well tolerated in kidney transplant patients with acute AMR. Fifteen (83.3%) subjects had 1 or more TEAEs during the study (6 [67%] subjects in the placebo group and 9 [100%] subjects in the CINRYZE group). No subject discontinued from investigational product or had their investigational product interrupted due to an AE. Only 1 (11%) subject in the CINRYZE group had a TEAE that was considered by the investigator to be related to investigational product (mild blurred vision that resolved without treatment). The majority of TEAEs were of mild or moderate intensity. Four (22.2%) subjects had 1 or more treatment-emergent serious adverse events (SAEs) during the study (3 [33%] subjects in the placebo group and 1 [11%] subject in the CINRYZE group). None of the SAEs were considered to be related to investigational product. No subject died during the study and no subject experienced a thrombotic or thromboembolic event. There were no clinically significant safety signals in clinical laboratory parameters or vital signs associated with CINRYZE administration.

CINRYZE-treated subjects achieved higher exposure of C1 INH functional activity on Day 13, with baseline-corrected steady-state C_{max} and area under the concentration-time curve from the time of dosing to the last measurable concentration for functional activity ranging from 3.7 to 8.8-fold higher than placebo subjects. Mean minimum concentration (C_{min}) C1 INH functional activity obtained prior to each CINRYZE dose was consistent across the entire study period, indicating that accumulation of C1 INH was minimal. For subjects receiving plasmapheresis as part of their standard of care, it was observed that this decreased the mean C1 INH functional activity by 43.3%, for the combined treatment groups compared to the pre-dose level.

Always refer to the latest version of the CINRYZE investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of CINRYZE.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale

2.1.1 Rationale for the Study

Transplantation of an organ involves exposure of the recipient to non-self HLA. Recipient immune recognition of these non-self markers results in production of DSA. The process of DSA production may occur before transplantation (ie, blood transfusion, pregnancy, or prior transplant) or any time after transplantation. Donor specific antibody complexes with the first complement protein (C1) to activate the classical pathway of the complement system resulting in AMR. If there is pre-existing DSA prior to the transplant, the process can result in rapid graft loss with activation of all 3 major inflammatory pathways (coagulation, contact, and complement systems) and immediate clotting of the transplanted organ within hours. This process is known as hyperacute rejection and is the reason why the presence of pre-existing DSA is a contraindication to transplantation.

Clinical evidence from Haririan et al. (2009) indicates that patients who had DSA with evidence of complement activation on biopsy had a risk of graft loss 3× higher than patients without DSA or complement activation. Monkeys with a chronic form of AMR (DSA and complement activation on biopsy) developed TG (Smith et al. 2008), which is a marker of eventual graft loss. Sensitized kidney transplant patients who received peri-transplant eculizumab still had evidence of early-stage complement pathway activation on biopsy (evidenced by ongoing C4d staining). The incidence of early AMR was significantly less than a historic control, although the incidence of chronic glomerulopathy (cg score >0) at 1 year on protocol biopsies was not improved for subjects receiving eculizumab for AMR prophylaxis after transplantation (31.9%) compared with historical controls that received plasma exchange without eculizumab for desensitization (26.7%) (Cornell et al. 2015). Thus, an earlier stage complement pathway inhibitor, like C1 INH, may be more advantageous for the treatment of AMR given its activity early in the complement, contact, and coagulation pathways.

Preclinical studies support this hypothesis as mice deficient in complement protein C3 or C4 had impaired immune responses to disparate skin grafts, while C5-deficient mice did not exhibit an impaired immunity (Marsh et al. 2001). As proof of concept that C1 INH may be a useful agent for AMR, baboons presensitized by transfusion with allogeneic blood of another (kidney donor) baboon and in which DSA were formed did not reject the transplanted graft during treatment with recombinant human C1 inhibitor (rhC1INH). In contrast, presensitized baboons that did not receive rhC1INH rejected the kidney grafts within 48 hours. In baboons receiving IV rhC1INH 3× daily, cessation of investigational product led to accelerated graft loss from acute AMR (Tillou et al. 2010).

2.1.2 Rationale for Dose Selection

An in vitro model analogous to the treatment of acute AMR required concentrations of rhC1INH approximately 2-3× serum physiologic concentration to inhibit >90% antibody-dependent cytotoxicity (Poirier and Blancho 2008).

Recombinant human C1 INH was used in a baboon allotransplant model to successfully prevent acute AMR. This study demonstrated successful prevention of acute AMR when rhC1INH was given at a dose of 200 U/kg (Tillou et al. 2010). Notably, all baboons rejected their grafts upon cessation of C1 INH therapy, indicating that additional adjunctive therapy is most likely necessary to address the continuing presence of DSA.

It is also important to point out that the complement system could theoretically contribute to thrombus formation by enhancing blood-clotting properties and augmenting the inflammatory response, which, in turn, potentiates coagulation (Amara et al. 2008). This procoagulatory potential for C1 INH has been noted in animals when used at single doses of 200 U/kg (Horstick et al. 2001), and clinically, in neonates undergoing cardiac surgery and cardiopulmonary bypass who were given intra- and post-operative doses up to 500 U/kg (German Federal Medical Council 2000).

Based on available preclinical and clinical data, the levels of C1 INH sufficient for complement pathway inhibition elicited by antigen-antibody complexes are at least 100% above normal physiologic levels. Preliminary data from the pilot pharmacokinetic study 0624-100 demonstrated that following IV administration of 2000 U of CINRYZE in healthy subjects, the mean change from baseline in functional C1 INH activity was approximately 50-60%. Given that 1 U of C1 INH activity is found in 1 mL of plasma, to increase the functional activity of C1 INH by at least 100% (2-fold) in patients with acute AMR, a dose of ~5000 U will be required in an average adult. Given that CINRYZE has a half-life of ~60 hours in HAE patients and possibly shorter in patients with active inflammation such as AMR patients, subsequent doses of 2500 U given every other day are likely to maintain adequate functional C1 INH levels throughout the dosing period. Therefore, subjects randomized to the CINRYZE group in the randomized Phase 2 AMR pilot study (0624-201) received a loading dose of 5000 U (not to exceed 100 U/kg) followed by 2500 U (not to exceed 50 U/kg) every other day for a total of 7 doses. This regimen balanced the apparent dose-dependent nature of inhibiting complement activation elicited by antigen-antibody complexes, while minimizing the potential risk of coagulation observed in preclinical and clinical studies of C1 INH at doses ≥200 U/kg. In fact, in the pilot study 0624-201 in kidney transplant recipients with acute AMR, CINRYZE subjects achieved a mean C1 INH functional activity of 1.73 U/mL, near but not quite at twice the physiologic level for which we aimed. In the 0624-201 study, 14/18 subjects at a single site had a 6-month post-transplant allograft biopsy per center standard of care (n=7 CINRYZE; n=7 placebo). A lower incidence of new TG (cg≥1b with PTC inflammation) was observed in the CINRYZE cohort biopsies as compared to placebo (0 vs 43%, respectively) 3-6 months after initial AMR treatment (6 months post-transplant).

Balancing the risk of thrombotic events and the lower incidence of new TG observed in the CINRYZE cohort of the 0624-201 study, it is felt that 20,000 U given over 13 days is the optimal dosing regimen that maintains an appropriate balance between clinical requirements for replacement of endogenous C1 INH and the risk of AEs with a higher dose.

2.2 Study Objectives

2.2.1 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.

2.2.2 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:

- 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

2.2.3 Exploratory Objectives

[redacted]

3. STUDY DESIGN

3.1 Study Design and Flow Chart

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 biopsy for 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 biopsy for 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 for (1) living vs deceased donor and (2) severity of acute AMR 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 (Section 9.5.1). 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.

As shown in Table 2, in addition to the qualifying kidney biopsy, an additional kidney biopsy will be obtained at the Month 6 study visit. See Section 7.2.2.2 for details. Biopsy slides and pertinent micrographs (including, but not limited to EM images) for the qualifying and Month 6 biopsies will be provided to an independent, blinded pathology EAC for confirmation of AMR diagnosis and the assessment of the primary endpoint (new or worsening TG at 6 months of initiation of treatment). [redacted]

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 ≤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 (see Table 2 for End of Study Visit procedures).

There will be 3 analyses (2 interim, 1 final) 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. See Section 9.5.2 for additional details.

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.

Resolution is defined initially by the local pathologist according to histological findings and later confirmed by the pathology EAC, and should be based on improvement from previous biopsy and characterized by Banff criteria as: glomerulitis (g + ptc) <2 if C4d-negative; (g + ptc) = 0 if C4d-positive. The investigator will record the applicable $eGFR_{MDRD}$ values and the date of resolution of the qualifying and recurrent AMR episodes in the CRF, when applicable, including the criteria used for determination of resolution (clinically and/or through histopathology).

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 180 days after the qualifying biopsy, 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 as indicated in Table 1. Subjects will follow the assessments noted in Table 1 and Table 2. For each new episode of AMR occurring during the first 180 days after the qualifying biopsy. Retreatment should occur as soon as possible within 7 days of the biopsy that defined the new AMR episode. Retreatment may not occur for recurrent AMR episodes diagnosed through biopsies done after the first 180 days after the qualifying biopsy date. Biopsies at 6 months following retreatment are not required to be performed by the protocol. The only mandated follow-up biopsy will be at Month 6 after initial treatment. With the exception of the Month 6 biopsy, completion of follow-up biopsies after the qualifying AMR episode is at the discretion of the study sites per local standard of care. Biopsy slides and images for unscheduled standard of care biopsies will also be submitted to the EAC.

The effect on the quality of life will be measured by using the EQ-5D-5L. The effect on healthcare utilization will also be assessed.

Complement and C1 INH levels will be assessed at specified time points up to Day 13 for pharmacokinetic/pharmacodynamic evaluation (Table 2 and Table 3).

Safety will be monitored through the recording of AEs and changes in physical examinations, vital signs, antibodies to C1 INH, and clinical safety laboratory testing. 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 study treatment. 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 also be captured as described above for the treatment of the initial occurrence of AMR. In addition, the following adverse events of special interest (AESI) will be closely monitored, both serious and non-serious, and reported throughout the study to Shire Pharmacovigilance and Risk Management (PVRM) via SAE form, regardless of relationship to investigational product:

- Any thrombotic or thromboembolic event (Section 8.2.4)

- Any hypersensitivity reaction
- Any new episode of kidney allograft rejection (excluding AMR), even if the event does not qualify for retreatment with investigational product (Section 7.2.2.4)
- Any new kidney allograft failure

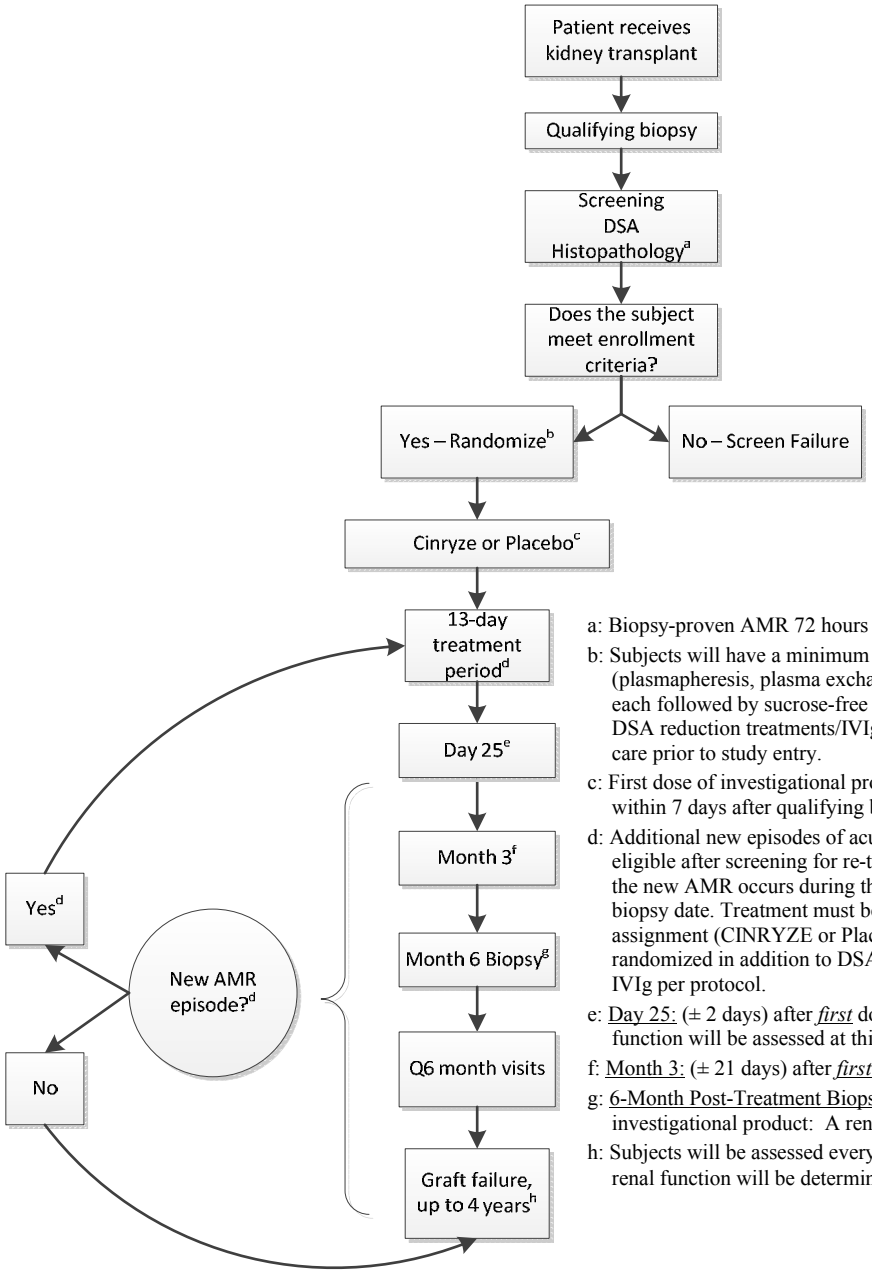
Stopping rules: If clinically significant drug-related thrombotic or thromboembolic events (as defined in Section 4.5.3) are reported as a study-drug-related SAE, enrollment will be halted (See Section 4.5.3). The DMC will review the case and will issue a recommendation to the Sponsor with regard to re-starting enrollment.

Please see Section 8.2.4 and Appendix 4 for further information on thrombotic and thromboembolic events.

The schedules of study procedures are provided immediately following the synopsis:

- Table 1: Schedule of Assessment (Screening though Day 25)
- Table 2: Schedule of Assessments (Month 3 through Month 48 [End of Study])[a]
- Table 3: Blood Sample Collection Time Points for Pharmacokinetic/Pharmacodynamic Testing (All Subjects)

Figure 1 Study Design Flow Chart



a: Biopsy-proven AMR 72 hours to 12 months after current transplant.

b: Subjects will have a minimum of 5 DSA reduction treatments (plasmapheresis, plasma exchange, or immune adsorption treatments) each followed by sucrose-free IVIg for each qualifying AMR episode. DSA reduction treatments/IVIg may be provided as part of standard of care prior to study entry.

c: First dose of investigational product (Day 1) must be administered within 7 days after qualifying biopsy.

d: Additional new episodes of acute AMR may be retreated if subject is eligible after screening for re-treatment and if the biopsy diagnostic for the new AMR occurs during the first 180 days after the qualifying biopsy date. Treatment must be with the same investigational product assignment (CINRYZE or Placebo) to which the subject was originally randomized in addition to DSA reduction treatment and sucrose-free IVIg per protocol.

e: Day 25: (± 2 days) after *first* dose of investigational product. Renal function will be assessed at this visit.

f: Month 3: (± 21 days) after *first* dose of investigational product.

g: 6-Month Post-Treatment Biopsy: (± 21 days) relative to first dose of investigational product: A renal allograft biopsy will be obtained.

h: Subjects will be assessed every 6 months up to 4 years. At these visits, renal function will be determined as well as graft failure (yes/no).

3.2 Duration and Study Completion Definition

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 that will be adjudicated by the nephrology EAC. The trial will continue until 51 such events are accrued and adjudicated by the nephrology EAC. See Section 9.5.2 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 a subject is discontinued from the study (not only from treatment) for any reason prior to the Month 6 follow-up Visit, every effort will be made to obtain AEs, serum BUN and Creatinine results, $eGFR_{MDRD}$, and a biopsy to send 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 from treatment for any reason for the remainder of a treatment cycle before receiving 7 doses, the subject will continue in the study and no Early Discontinuation Visit will be performed. In this instance, the next scheduled treatment visit in the treatment cycle should be conducted and all procedures for that visit should be performed other than those related to study drug administration, and the scheduled Day 25 post-treatment visit will follow (any remaining treatment visits for that cycle are not required). If a subject is discontinued from the study for any reason after the Month 6 visit and 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 (see Table 2 for End of Study Visit procedures).

The subject's maximum duration of participation is expected to be approximately 4 years.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

Approximately 40 sites in approximately 6 countries are expected to participate in this study in North America and Europe.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed. Local laboratory testing will be used to determine subject eligibility.

4.1 Inclusion Criteria

To be eligible for this protocol, a subject must:

1. Be ≥18 and ≤70 years of age.
2. Weigh ≥45 kg with a body mass index (BMI) <35 kg/m^2 at screening.
3. Have HLA DSA identified at the time of diagnosis of AMR. If it is anticipated that the local DSA results will not be available within the screening period, previously obtained local DSA results can be used to assess eligibility, if obtained after kidney transplant and within 30 days prior to the qualifying AMR episode. In any instance, a local DSA test should still be performed at the time of AMR diagnosis.
4. Have a first qualifying episode of AMR in the subject's current renal allograft between 72 hours and 12 months after transplant defined by a renal allograft biopsy demonstrating neutrophil and/or monocyte infiltration in the PTC and/or glomeruli with or without evidence of C4d deposition by immunohistopathology according to 2013 Banff criteria.
5. Have achieved adequate renal function defined as: Pre-AMR baseline $eGFR_{MDRD}$ ≥20 mL/min/1.73m^2 for a qualifying AMR episode occurring ≤21 days after transplant or pre-AMR baseline $eGFR_{MDRD}$ ≥30 mL/min/1.73m^2 for a qualifying AMR episode occurring >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 biopsy, it can be evaluated within a 60 day period.
6. Receive first dose of investigational product after 7 days after the kidney transplant procedure and within 7 days after the qualifying renal allograft biopsy procedure that was positive for AMR.
7. Be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.
8. If female and of child-bearing potential, must have a negative urine pregnancy test confirmed by a negative serum beta human chorionic gonadotropin (beta-HCG) pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Day 1 visit.
9. Agree to comply with any applicable contraceptive requirements of the protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Have received pediatric en bloc kidney transplant.
2. Have primary Focal Segmental Glomerulosclerosis, rapidly progressive glomerulonephritis, membrano-proliferative glomerulonephritis type 1 (including C3 glomerulopathy), "dense deposit disease", or thrombotic microangiopathy as the cause of native kidney failure.
3. Have prior or concurrent non-renal solid organ transplant or hematopoietic stem cell transplant (HSCT) or have more than 2 completed kidney transplant procedures (note: 1 double kidney transplant procedure is considered to be 1 procedure).
4. Have a known neoplastic lesion in the transplanted allograft
5. Have, any ongoing infection that causes hemodynamic compromise or as determined by the investigator, any surgical or medical condition that could interfere with the administration of investigational product, interpretation of study results, or could compromise patient safety, including (as determined by the transplanting surgeon and documented in the operative report) any major technical complications of the renal artery, renal vein, or ureteral anastomosis
6. Have ongoing treatment for HCV infection.
7. Have had a recent myocardial infarction (MI) within the past 6 months and/or at the time of screening are treated with anticoagulants and/or antiplatelet agents (excluding aspirin) for a previous myocardial infarction.
8. Have a history of:
   - abnormal bleeding,
   - clotting events or disorders (excluding a history of clotted hemodialysis access or superficial thrombophlebitis in the absence of medically confirmed coagulopathy),
   - any coagulopathy (documented or clinically suspected)

   For example, patients should be excluded if they have a history of renal allograft arterial or venous thrombosis, deep vein thrombosis, pulmonary embolism, ischemic cerebrovascular accident (stroke) or transient ischemic attack (TIA), any large vessel thrombosis.
9. Have a history of allergic reaction to CINRYZE or other blood products.
10. Have had any change in androgen therapy (eg, danazol, oxandrolone, stanozolol, testosterone), tranexamic acid, epsilon-aminocaproic acid, or other fibrinolytics within 3 months before the first dose of investigational product.
11. Have participated in the active dosing phase of any other investigational drug study within 30 days prior to dosing with investigational product.
12. Have any of the following local laboratory values reported prior to dosing with investigational product:
    - Within 24 hours prior to subject dosing, white blood cell (WBC) count $<0.5\times10^9$/L or $>20\times10^9$/L (the value of $>20\times10^9$/L should be excluded if obtained during steroid treatment)
    - Within 24 hours prior to subject dosing platelet count $< 25\times10^9$/L or $>600\times10^9$/L

13. Be pregnant or breastfeeding.
14. Have received any of the following agents within 1 month prior to the first dose of investigational product:
    - Sucrose-containing IVIg
    - Any C1 INH (plasma-derived [eg, CINRYZE®, Berinert®, Cetor®] or recombinant [eg, Rhucin®])
    - Eculizumab (Soliris®)
    - Ecallantide (Kalbitor®)

4.3 Restrictions

There will be no special restrictions for subjects participating in this study. Subjects are to maintain their normal or recommended renal diets per standard of care, medications (with the exception of those listed in Section 5.4), and activities of daily living as determined by the investigator.

4.4 Reproductive Potential

4.4.1 Female Contraception

Sexually active females of child-bearing potential should be using an acceptable form of contraception, as described below. Females of child-bearing potential must be advised to use acceptable contraceptives from the time of screening and through 3 months following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study from the time of screening and for 3 months following the last dose of investigational product.

Female subjects should be either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea)
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Females of child-bearing potential with a negative urine pregnancy test (confirmed by a negative serum beta-HCG pregnancy test) at the Screening Visit and a negative urine pregnancy test at the Day 1 Visit. Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms

- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the Screening Visit, plus condoms. Note: if subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.4.2 Male Contraception

Male subjects will be required to use a condom in conjunction with spermicidal gel, foam, cream, film, or suppository from time of dosing until 3 months after the last dose of investigational product. Child-bearing female partners of male study participants will be required to follow the acceptable methods of contraception for this study (described in Section 4.4.1) from the time of first dosing until 3 months after the last dose of investigational product. For male subjects, sexual intercourse with pregnant partners should also be avoided during the course of the study unless condoms are used from the time of the first dose until 3 months after the last dose of investigational product. Male subjects must not donate sperm until 3 months after the last dose of investigational product.

4.5 Discontinuation or Withdrawal of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from the study with the medical monitor when possible.

If a subject is discontinued from the study (not only from treatment) for any reason prior to the Month 6 follow-up Visit, every effort will be made to obtain AEs, serum BUN and Cr results, $eGFR_{MDRD}$, and a biopsy to send 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 from treatment for any reason for the remainder of a treatment cycle for before receiving 7 doses, the subject will continue in the study and no Early Discontinuation Visit will be performed. In this instance, the next scheduled treatment visit in the treatment cycle should be conducted and all procedures for that visit should be performed other than those related to study drug administration, and the scheduled Day 25 post-treatment visit will follow (any remaining treatment visits for that cycle are not required). If a subject is discontinued from the study for any reason after the Month 6 visit and 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 (see Table 2 for End of Study Visit procedures).

Whenever possible and with the consent of the subject, the investigator will attempt to obtain information on graft and subject survival status from discontinued subjects at remaining scheduled assessment times through Month 48. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded in the case report form (CRF) and source documents.

Subjects who discontinue will not be replaced. Approximately 112 eligible subjects with biopsy-proven AMR will be randomized to provide 56 subjects per treatment arm. Additional eligible subjects may be enrolled based on the interim data analysis of the first 30 subjects who complete the Month 6 TG assessment (Section 9.5.1).

4.5.1 Reasons for Discontinuation and/or Withdrawal

The reason for investigational product early discontinuation and/or withdrawal from the study must be determined by the investigator and recorded in the subject's medical record and in the CRF. In the case of early discontinuation of the medicinal product and/or withdrawal from the study for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered in the CRF.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol violation
- Consent withdrawal by subject
- Other, specify (e.g., pregnancy, etc.)

4.5.2 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any timepoint prior to the last scheduled study visit (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations.

4.5.3 Stopping Rules

If any of the clinically significant thrombotic or thromboembolic events listed below (exclusive of superficial thrombophlebitis, dialysis access clotting, or catheter-related thrombotic events) is reported as a study-drug-related SAE in any subject, as defined by the Principal Investigator at the site and confirmed through a diagnostic examination as indicated in section 8.2.4, enrollment of new subjects will be halted.

- Renal allograft arterial or venous thrombosis
- Deep vein thrombosis
- Myocardial infarction
- Pulmonary embolism
- Ischemic cerebrovascular accident (stroke), or transient ischemic attack (TIA), exclusive of cerebrovascular hemorrhage (subarachnoid or subdural hemorrhage)
- Any large vessel thrombosis (exclusive of the presence of an indwelling catheter)

Study procedures for subjects already randomized will continue, including treatment according to their assigned dosing regimen.

The DMC will perform a safety review of this specific event and of the patient population included in the study and will forward its recommendation to the Sponsor about the opportunity, in terms of patient safety, of restarting enrollment. Enrollment may be restarted by the Sponsor in consultation with the DMC.

Please see Section 8.2.4 and Appendix 4 for further information on thrombotic and thromboembolic events.

5. CONCOMITANT AND POST-TREATMENT MEDICATIONS

5.1 Concomitant Medications

All prescription and over-the-counter medications will be recorded in the CRF as concomitant medications from 2 weeks prior to 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). Medications used to treat AEs or SAEs, regardless of relatedness of the AEs/SAEs to investigational product, will be recorded through 30 days after the last dose of investigational product for each treatment period. AEs of special interest and the medications listed in Section 5.3 and 5.5 will be recorded for the duration of the study. Topical medications will be recorded only if used for treatment of an AE. Prophylactic treatment for deep vein thrombosis (DVT) (including mechanical treatment, eg, compression) will also be collected through the duration of the study.

Administration of the following will not be recorded unless the investigator considers this important to the assessment of an AE:

- Intravenous fluids
- Enteral or parenteral nutrition
- Vitamins or other dietary supplements
- Electrolyte supplementation
- Oxygen

5.2 Concomitant Blood Products

The dates and amount of the following blood products will be recorded in the CRF if administered from 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):

- Albumin
- Packed red blood cells
- Whole blood
- Fresh frozen plasma
- Cryoprecipitate
- Platelets

5.3 Immunosuppressive Agents or Treatments

From the day of the first dose of investigational product (Day 1) through Year 4, the following concomitant medications will be collected in the CRF:

- Any IV or oral steroids

- Rituximab
- Bortezomib
- Muromonab-CD3
- Alemtuzumab
- Anti-thymocyte globulin (rabbit)
- Lymphocyte immune globulin, anti-thymocyte globulin (equine)
- Any sucrose-free IVIg preparation
- Plasmapheresis, plasma exchange, or immune adsorption treatments
- Daclizumab or basiliximab
- Tacrolimus and Cyclosporine
- Mycophenolate mofetil and mycophenolic acid
- Azathioprine
- Other immunosuppressive agents (specify)

5.4 Prohibited Medications

Use of the following agents is prohibited from Day 1 through the EOS evaluation:

- Sucrose-containing IVIg
- Any C1 INH: plasma-derived (eg, Berinert®, Cetor®) or recombinant (eg, Rhucin®)
- Eculizumab (Soliris®)
- Ecallantide (Kalbitor®)
- Any unapproved/investigational biologic agent or drug

5.5 Other Medications

From the day of the first dose of investigational product (Day 1) through Year 4, the following concomitant medications will be collected in the CRF:

- Ace-inhibitors (eg, Capoten, Vasoten, Lotensin), sartans (eg, Diovan, Micardis), renin inhibitors (eg, Tekturna)
- Antiplatelet medications (eg, ASA, Plavix, Ticlid)
- Anticoagulant agent (eg, Comadin, Xarelto)

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is CINRYZE, which will be provided by the sponsor as a lyophilized powder of 500 U C1 INH/vial. Vials of CINRYZE also contain the following inactive ingredients: trisodium citrate, sodium chloride, L-Valine, L Alanine, L-Threonine, and sucrose. Each vial of CINRYZE will be reconstituted with sterile water for IV injection and administered with 0.9% sodium chloride solution for infusion.

The placebo product is 0.9% sodium chloride solution for infusion.

Additional information is provided in the pharmacy manual.

6.1.1 Blinding the Treatment Assignment

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, IRT) 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 (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.

6.1.2 Commercially Obtained Investigational Product

CINRYZE product approved for commercial distribution in the US and sterile water for injection will be labeled for clinical use and supplied by the sponsor.

Mix 2 transfer devices for reconstitution will also be supplied by the sponsor.

Sites will be responsible for sourcing 0.9% sodium chloride solution for infusion of either the active drug or the placebo.

6.2 Administration of Investigational Product(s)

Reconstitution and administration instructions for CINRYZE will be provided as a separate document to investigative sites.

6.2.1 Interactive Voice/Web Response System Technology for Investigational Product Management

An IV/WRS (IRT) will be employed in this study to manage the tracking and confirmation of shipment, supply, inventory, ordering, expiration, and site-assignments of the investigational product. The IV/WRS provider will provide a user manual and training to each site, with detailed instruction on the use of the IV/WRS.

6.2.2 Allocation of Subjects to Treatment

This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule automatically assigned by the IV/WRS (IRT).

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each level of the severity of AMR and donor characteristic (as defined in the paragraph below) across sites, the subject number is assigned to subjects according to the sequence of presentation for study participation. Subject number is unique within a protocol.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. A randomization number will be assigned by the IV/WRS at the Baseline Visit (Day 1) after subject eligibility has been confirmed using the randomization criteria. The randomization schedule will be stratified for (1) living vs deceased donor and (2) severity of acute AMR as defined by the screening period $eGFR_{MDRD}$ $\leq$15 mL/min/1.73m^2 (severe) or >15 ml/min/1.73m^2 (mild to moderate).

6.2.3 Dosing

Eligible subjects in this study will receive a total of 7 doses of investigational product over a 13-day period: an initial 100 mL IV infusion containing 5000 U CINRYZE or placebo (100 mL 0.9% sodium chloride for infusion) on Day 1, followed by 2500 U of CINRYZE in 100 mL of IV infusion or placebo (100 mL 0.9% sodium chloride for infusion) IV on Days 3, 5, 7, 9, 11, and 13 (Table 4). If DSA reduction therapy occurs on the same day as investigational product dosing, investigational product will be administered after completion of the plasmapheresis, plasma exchange or immune adsorption treatment session and dosing of the sucrose-free IVIg.

Table 4 Investigational Product Dosing Day, Volume and Amount

	Volume	CINRYZE	Placebo
Day 1	100 mL	5000 Units of CINRYZE (50 mL of CINRYZE/ 50 mL of normal saline)	100 mL of normal saline
Day 3, 5, 7, 9, 11, and 13	100 mL	2500 Units of CINRYZE (25 mL of CINRYZE/ 75 mL of normal saline)	100 mL of normal saline

Note: All doses must be brought up to 100 mL

Additionally, if a study subject has resolution of their qualifying episode of acute AMR and, during the first 180 days after the biopsy of the qualifying episode of AMR, has a new episode of AMR as defined in Section 3.1, the subject may be retreated with investigational product per the same randomization assignment per protocol.

6.2.4 Unblinding the Treatment Assignment

The treatment assignment must not be broken during the study except in the following situations:

1. Emergency situations where the identification of the investigational product is required for further treatment of the subject. The investigator should contact the Sponsor's representative(s) not affiliated with the core team as soon as possible after the subject has been unblinded.
2. The first interim analyses for sample size re-estimation after the first 30 subjects complete the Month 6 TG assessment. Only the DMC members will be unblinded for this interim analysis.
3. The second interim analysis is conducted when an adequate number of subjects complete the Month 6 TG assessment for the primary endpoint. The adequate number of subjects will be determined based on the first interim analysis. 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.
4. When approximately 50% (~26 events), 75% (~39 events), and 100% (~51 events) of the study information (ie, total number of subjects with all-cause graft failure) is collected. Only the DMC members will be unblinded for the 50% and 75% time points in these interim analyses.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded on the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the contract research organization (CRO) and the Sponsor's representative(s). Code-break information is held by the pharmacist/designated person at the site and by the CRO Medical Monitor for the study or designee.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information are applied to the investigational product(s) container. All investigational product is labeled with a minimum of the protocol number, dosage form, directions for use, storage conditions, expiry date and batch number/packaging reference, the statements 'For clinical trial use only', and/or 'CAUTION: New Drug - Limited by Federal (or US) Law to Investigational Use', Keep out of reach of children', and the sponsor's name and address. Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label.

Space is allocated on the label so that the site representative can record a unique subject identifier.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name.
- Additional labels may not be added without the sponsor's prior full agreement

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

CINRYZE will be supplied as open-label material in labeled cartons containing 1 labeled vial.

Sterile water will also be supplied as open-label material in labeled cartons containing 1 labeled vial.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject number on the investigational product labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a study nurse) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered medication will be documented in the CRFs and/or other investigational product record.

No investigational product stock or returned inventory from a Shire ViroPharma, Inc.-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

If the investigational product is to be destroyed by the study sites, sites must follow their own process/policy that describes such activities. All drug destruction processes will be documented and the sites must retain copies of these documents within the site regulatory binder. The sites must ensure that the clinical trial material accountability and destruction log is complete, accurate, and ready for review and/or audit at each monitoring visit.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor’s satisfaction.

6.5 Subject Compliance

All doses of investigational product will be administered to subjects at the investigational site. The pharmacist/nominated person will record details of dispensed product on the drug accountability form and the clinical staff will record details of administration of product in the subject’s medical record.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1, Table 2, and Table 3 for study procedures. Screening procedures and timing are listed below. For detailed descriptions of each procedure, see Section 7.2 Study Evaluations and Procedures. See Section 7.2.3.5 for details on which laboratory tests are required locally in addition to those sent to the central laboratory.

7.1.1 Screening Period

Screening will occur after the biopsy diagnosis of the qualifying AMR episode and before the first dose of investigational product. Investigational product may not be administered within 7 days of kidney transplant. Submission of pathology slides/images will occur to confirm the qualifying AMR episode. Local laboratory testing at screening will be used to determine subject eligibility.

- Informed consent
- Screening registration in the IV/WR (IRT) system
- Medical history including the presence/absence of diabetes, pre-AMR creatinine and $eGFR_{MDRD}$
- Inclusion/exclusion eligibility
- Physical examination, including height and body weight
- Lower extremity examination, including a determination of presence or absence of unilateral calf tenderness or leg swelling; a diagnostic exam will be performed if a DVT is suspected
- Vital signs
- 12-lead electrocardiogram (ECG)
- Central Pregnancy testing (also local lab serum and urine) for female subjects of child-bearing potential
- Central Virology screen
- Central Hematology (also local hematology lab results will be used to assess subject eligibility at screening)
- Central Clinical chemistry (includes central lab testing for creatinine and BUN)
- Local Serum BUN, creatinine and $eGFR_{MDRD}$ (at screening the first local laboratory creatinine value obtained after the biopsy that is diagnostic of AMR should be used to determine AMR severity for stratification)
- Central Proteinuria: spot urine protein, urine creatinine, and urine protein to urine creatinine ratio
- Renal allograft assessment, including: function, and failure

- Central Anti-C1 INH antibodies
- Donor-specific antibody identification. In addition to the central laboratory, per protocol this test is required to be performed locally only at screening. Eligibility will be based on the local results. If it is anticipated that the local screening DSA results will not be available within the screening period, previously obtained local DSA results, if available, can be used to assess eligibility if obtained after kidney transplant and within 30 days prior to the qualifying biopsy that is diagnostic of an AMR episode. In any instance, a local DSA test should still be performed at the time of AMR diagnosis.
- Donor-specific antibody reduction treatment and sucrose-free IVIg (plasmapheresis, plasma exchange, or immune adsorption treatments/sucrose-free IVIg may be provided as part of standard of care prior to study entry). All blood sample collections for laboratory analysis should be performed prior to receiving DSA reduction therapy, except as otherwise specified for PK/PD samples.
- Concomitant medications
- Adverse event monitoring
- EuroQoL Group 5-Dimension 5-Level Self–report Questionnaire
- Healthcare resource utilization

Once eligibility for participation in the study is determined, the subject should be randomized or registered as screen failure, as applicable, via IV/WRS (IRT). A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been randomized or administered investigational product(s). Subjects cannot be rescreened once they have been designated as a screen failure.

Note: In the event of new biopsy-proven acute AMR allowing retreatment, screening procedures will be completed as detailed in the screening retreatment column of Table 1.

7.1.2 Investigational Product Administration Period

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 or sucrose-free IVIg may be administered at the discretion of the investigator per 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. See Section 7.2.3.5 for details on which laboratory tests are required locally in addition to those sent to the central laboratory.

7.1.2.1 Day 1

The first dose of investigational product on Day 1 should be administered as soon as possible and within 7 days after the qualifying biopsy procedure.

All blood sample collection for laboratory testing should be collected prior to receiving DSA reduction therapy (if given) except as specified for PK/PD samples.

- Inclusion/exclusion eligibility prior to first dose of investigational product
- Randomization via IV/WRS (IRT) prior to first dose of investigational product
- Physical examination, including body weight prior to first dose of investigational product
- Lower extremity examination prior to first dose of investigational product, including a determination of presence or absence of unilateral calf tenderness or leg swelling; a diagnostic exam will be performed if a DVT is suspected
- Vital signs (obtained within 30 minutes prior to investigational product administration and then between 30 minutes and 1 hour after completion of investigational product infusion)
- Pregnancy testing (with local urine test) prior to first dose of investigational product for female subjects of child-bearing potential
- Central Hematology prior to first dose of investigational product
- Central Clinical chemistry, local BUN and serum creatinine with $eGFR_{MDRD}$ prior to first dose of investigational product
- Central lab blood collection for pharmacokinetic/pharmacodynamic analysis prior to the start of DSA reduction therapy (if done), within 15 minutes prior to the start of investigational product infusion, and 1 hour (+5 minutes) after the start of investigational product infusion
- Donor-specific antibody reduction treatment and sucrose-free IVIg (plasmapheresis, plasma exchange, or immune adsorption treatments/sucrose-free IVIg may be provided as part of standard of care prior to study entry)
- Investigational product administration (after DSA reduction therapy and sucrose-free IVIg, if done)
- Concomitant medications
- AE monitoring
- Renal allograft assessment including: function, and failure
- Subject survival status
- Healthcare resource utilization

7.1.2.2 Days 3, 5, 7, 9, and 11

- Lower extremity examination, including a determination of presence or absence of unilateral calf tenderness or leg swelling; a diagnostic exam will be performed if a DVT is suspected
- Body weight
- Vital signs (obtained within 30 minutes prior to investigational product administration and then between 30 minutes and 1 hour after completion of investigational product infusion)

- Serum BUN and creatinine with $eGFR_{MDRD}$ (central and local laboratories) prior to investigational product administration
- For Day 7 only: Central lab blood collection for pharmacokinetic/pharmacodynamic analysis prior to the start of DSA reduction therapy (if done), within 15 minutes prior to the start of investigational product infusion, and 1 hour (+5 minutes) after start of investigational product infusion
- Donor-specific antibody reduction treatment and sucrose-free IVIg (plasmapheresis, plasma exchange, or immune adsorption treatments/sucrose-free IVIg may be provided as part of standard of care prior to study entry)
- Investigational product administration (after DSA reduction therapy and sucrose-free IVIg, if done)
- Concomitant medications
- AE monitoring
- Renal allograft assessment including: function and failure
- Subject survival status
- Healthcare resource utilization

7.1.2.3 Day 13

- Lower extremity examination including a determination of presence or absence of unilateral calf tenderness or leg swelling; a diagnostic exam will be performed if a DVT is suspected
- Body weight
- Vital signs (obtained within 30 minutes prior to investigational product administration and then between 30 minutes and 1 hour after completion of investigational product infusion)
- Central Hematology prior to administration of investigational product
- Central Clinical chemistry (includes BUN and creatinine) and local BUN and serum creatinine with $eGFR_{MDRD}$ prior to administration of investigational product
- Central lab blood collection for pharmacokinetic/pharmacodynamic analysis prior to the start of DSA reduction therapy (if done), within 15 minutes prior to the start of investigational product infusion, and 1 hour (+5 minutes) after start of investigational product infusion
- Donor-specific antibody reduction treatment and sucrose-free IVIg (plasmapheresis, plasma exchange, or immune adsorption treatments/sucrose-free IVIg may be provided as part of standard of care prior to study entry)
- Investigational product administration (after DSA reduction therapy and sucrose-free IVIg, if done)
- Concomitant medications
- Adverse event monitoring
- Renal allograft assessment including: function and failure
- Subject survival status
- Healthcare resource utilization

7.1.3 Post-Treatment Follow-Up Period

See Section 7.2.3.5 for details on which laboratory tests are required locally in addition to those sent to the central laboratory.

7.1.3.1 Day 25 (±48 hours)

- Lower extremity examination including a determination of presence or absence of unilateral calf tenderness or leg swelling; a diagnostic exam will be performed if a DVT is suspected
- Body weight
- Vital signs
- Central lab Hematology
- Serum BUN and creatinine with $eGFR_{MDRD}$ (local and central laboratories)
- Central lab Proteinuria: spot urine protein, urine creatinine, and urine protein to urine creatinine ratio
- Central lab Anti-C1 INH antibodies
- Central lab Donor-specific antibody identification
- Concomitant medications
- Adverse event monitoring
- Renal allograft assessment including: function and failure
- Subject survival status
- EuroQoL Group 5-Dimension 5-Level Self–report Questionnaire
- Healthcare resource utilization
- Submission of pathology slides/images from screening qualifying AMR biopsy (if not submitted earlier, after randomization)

7.1.3.2 Month 3 (±21 days)

- Body weight
- Serum BUN and creatinine with $eGFR_{MDRD}$ (local and central laboratories)
- Central lab Proteinuria: spot urine protein, urine creatinine, and urine protein to urine creatinine ratio
- Central lab Anti-C1 INH antibodies
- Central lab Donor-specific antibody identification
- Concomitant medications
- Adverse event monitoring
- Renal allograft assessment including: function and failure

- Subject survival status
- EuroQoL Group 5-Dimension 5-Level Self–report Questionnaire
- Healthcare resource utilization

7.1.3.3 Month 6 (±21 days)

- Presence/absence of diabetes
- Body weight
- Serum BUN and creatinine with $eGFR_{MDRD}$ (local and central laboratories)
- Central lab Proteinuria: urine protein, urine creatinine, and urine protein to urine creatinine ratio
- Kidney allograft biopsy and submission of pathology slides/images
- Central lab Anti-C1 INH antibodies
- Central lab Donor-specific antibody identification
- Concomitant medications
- Adverse event monitoring
- Renal allograft assessment including: function and failure
- Subject survival status
- EuroQoL Group 5-Dimension 5-Level Self–report Questionnaire
- Healthcare resource utilization

7.1.3.4 Months 12 (±21 days), Months 18, 24, 30, 36, 42 (all ±28 days)

- Body weight
- Serum BUN and creatinine with $eGFR_{MDRD}$ (local and central laboratories)
- Central lab Proteinuria: spot urine protein, urine creatinine, and urine protein to urine creatinine ratio
- Central lab Anti-C1 INH antibodies (only if antibodies are detected at the previous time point)
- Central lab Donor-specific antibody identification
- Concomitant medications
- Adverse event monitoring
- Renal allograft assessment including: function and failure
- Subject survival status
- EuroQoL Group 5-Dimension 5-Level Self–report Questionnaire
- Healthcare resource utilization

7.1.3.5 EOS Visit/Month 48 [±28 days] or at patient discontinuation if after Month 6 Visit

- Presence/absence of diabetes
- Body weight
- Serum BUN and creatinine with $eGFR_{MDRD}$ (local and central laboratories)
- Central lab Proteinuria: spot urine protein, urine creatinine, and urine protein to urine creatinine ratio
- Central lab Anti-C1 INH antibodies
- Central lab Donor-specific antibody identification
- Concomitant medications
- Adverse event monitoring
- Renal allograft assessment including: function and failure
- Subject survival status
- EuroQoL Group 5-Dimension 5-Level Self–report Questionnaire
- Healthcare resource utilization

All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Section 8.1).

7.1.3.6 Early Discontinuation Visit: Discontinuation between End of Investigational Product Dosing (Day 13) and Month 6 (not applicable if discontinuation is from treatment only)

- Body weight
- Serum BUN and creatinine with $eGFR_{MDRD}$ (local and central laboratories)
- Proteinuria: spot urine protein, urine creatinine, and urine protein to urine creatinine ratio
- Renal allograft biopsy and submission of pathology slides/images
- Donor-specific antibody identification
- Concomitant medications
- Adverse event monitoring
- Renal allograft assessment including: function and failure
- Subject survival status

7.1.4 Additional Care of Subjects After the Study

No after care is planned for this study.

7.2 Study Evaluations and Procedures

Subjects meeting the eligibility criteria listed in Section 4 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily granted by the subject. All subjects will have a screening evaluation performed after the qualifying biopsy such that the first dose of investigational product can be administered within 7 days from the biopsy that is diagnostic of the qualifying AMR episode. The schedules of study procedures and blood sample collection for pharmacokinetic/pharmacodynamic assessments are provided in Table 1, Table 2, and Table 3, respectively.

7.2.1 Demographic and Other Baseline Characteristics

Age and/or birth date, sex, race, and ethnicity will be recorded for all subjects.

7.2.2 Efficacy

7.2.2.1 Donor-specific Antibody Identification

A histocompatibility screen for DSA identification and specificity by solid phase immunoassays will be performed by the local and central laboratories at Screening, and per-protocol only by the central laboratory at Day 25, and subsequent study visits as specified in Table 2. DSA identification is mandatory for the local lab at Screening and may be performed at other time points by the local laboratory at the discretion of the investigator as part of standard of care. Clinical decisions will be based on local laboratory analysis.

Samples will be sent to a central laboratory at Screening, Day 25, Month 3, 6, 12, 18, 24, 30, 36, 42, and 48. Panel reactive antibody will also be assessed. Additional antibody and titer testing may be performed in the future.

All results will be recorded.

7.2.2.2 Renal Allograft Biopsies

Qualifying Biopsy

The qualifying renal allograft biopsy will have been performed as standard of care between 72 hours and 12 months after transplant and prior to screening for this study. The qualifying biopsy will be used to establish the diagnosis of AMR. Biopsy slides and a representative micrograph images (including, but not limited to EM) will be sent, within 30 days after the biopsy, to the Sponsor's designee, and then to the independent, blinded pathology EAC for confirmation of acute AMR and as a baseline for comparison with the Month 6 biopsy. It is recommended that at least 2 separate cores containing cortex be obtained for the qualifying biopsy.

Month 6 (Post-treatment) Biopsy

The Month 6 (post-treatment) biopsy is required by this protocol. At least 2 separate cores containing cortex must be obtained (this requirement must be applied for subjects who discontinue prior to 6 months as well).

The biopsy slides and representative micrographs (including, but not limited to EM images) will be sent within 30 days after the Month 6 biopsy, to the Sponsor's designee, and then to the independent, blinded pathology EAC for comparison with the qualifying biopsy to assess changes in histopathology.

Additional Biopsies

Subjects may have additional "for-cause" or scheduled biopsies as part of their standard-of-care treatment. For biopsies obtained at any time from enrollment through the study follow-up period, pathology slides and representative micrographs (including, but not limited to EM images) will be sent, within 30 days after the biopsy, to the Sponsor's designee, and then to the pathology EAC. Biopsies that demonstrate evidence of infiltrating neutrophils and/or monocytes with or without the presence of C4d, following resolution of the prior AMR episode, will qualify as new biopsy-proven acute AMR, and retreatment may be given with the same investigational product to which the subject was originally randomized as well as plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free IVIg per protocol. The retreatment qualifying biopsy slides and representative micrographs (including, but not limited to EM images) will be sent, within 30 days after the biopsy, to the Sponsor's designee, and then to the pathology EAC for confirmation of acute AMR. Available biopsy slides and micrographs used to determine AMR episode resolution must also be sent to the pathology EAC for confirmation of acute AMR resolution. Additionally, any subject that discontinues from the study after receiving dosing for the qualifying episode of AMR and prior to the Month 6 follow-up Visit, will have a biopsy (±2 weeks from discontinuation) and its slides and EM images sent to the pathology EAC for determination of TG.

Histopathology

Additional instruction outside of this protocol will be provided to all sites regarding details on slides and image requirements.

Representative histopathology sections of each renal allograft biopsy (qualifying and all post-treatment biopsies) will be sent for processing to the investigative site's pathologist. Glass slides are required for Periodic acid Schiff, hematoxylin and eosin, trichrome and silver stains. If possible, glass slides for CD34 and CD68 must also be provided. The pathologist will process sections: (1) for hematoxylin and eosin stain and Periodic acid Schiff, trichrome, and silver stains and (2) for C4d presence by immunofluorescence (C4d images are required even if negative). If immunofluorescence images are not available, immunohistochemical glass slides must be provided instead. Whenever possible, sections will also be processed for immunoperoxidase stain for CD34 and CD68. Additionally, biopsy tissue remaining after the qualifying biopsy assessment should be preserved in paraffin or another method appropriate for EM processing. Electron microscopy images will be obtained locally for patients enrolled in the study. Biopsy tissue from the Month 6 biopsy will be also obtained for EM processing. Representative EM images obtained locally will be sent to the pathology EAC for determination of the presence of early GBM and/or endothelial damage not seen on light microscopy. This will be used for an exploratory analysis of long-term outcomes associated with such early changes seen only on EM.

Further details on glass slides and images required for submission to the pathology EAC will be provided in a separate document.

Biopsy slides and representative micrographs (including, but not limited to EM images) will be sent by the sites to the Sponsor's designee within 30 days after the biopsy, and will be provided to an independent, blinded pathology EAC for determination of the presence of new or worsening TG at 6 months of initiation of treatment. Furthermore, any additional biopsy that qualifies the subject for retreatment per protocol or that will be used to define AMR episode resolution will also be sent to the pathology EAC. Acute AMR confirmation will be according to published Banff criteria. These data will be recorded.

Electron Microscopy

Tissue specimens will be processed locally for EM. EM images for the qualifying biopsy are required if EM was performed as standard of care, or if biopsy tissue remaining after the qualifying biopsy assessment is available for EM processing. EM images are required for the Month 6 visit, or if a patient discontinues the study after initial treatment and prior to the Month 6 visit (if possible to obtain). Representative images will be sent to the independent, blinded pathology EAC to assess new or worsening TG at 6 months of initiation of treatment. In addition, the pathology EAC will use the EM images to determine the extent of GBM disease and endothelialitis consistent with early TG, and to determine the association of such early changes not yet evident on light microscopy with long-term outcomes to support an exploratory analysis.

Determination of Antibody-Mediated Rejection on Biopsy

The independent, blinded pathology EAC will record categorical information using the Banff criteria from the qualifying biopsies, Month 6 biopsies, and any other biopsies processed for light microscopy (and EM) and sent for their evaluation according to the EAC Charter.

7.2.2.3 Resolution of Qualifying and Recurrent AMR Episodes

Serum creatinine may be tested locally outside of the protocol-mandated time points at the discretion of the investigator as part of standard of care, in order to assess resolution of AMR.

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. 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 the absence of significant decline (≥20%) eGFR from pre-AMR baseline, a follow-up biopsy within 3 months is recommended in order to assess resolution. Resolution is defined initially by the local pathologist according to histological findings and later confirmed by the pathology EAC, and should be based on improvement from previous biopsy and characterized by Banff criteria as: (g + ptc) <2 if C4d-negative; (g + ptc) = 0 if C4d-positive.

The investigator will record the applicable $eGFR_{MDRD}$ values and the date of resolution of the qualifying and recurrent AMR episodes in the CRF, when applicable, including the criteria used for determination of resolution (clinically and/or through histopathology).

7.2.2.4 Recurrence of AMR During the First 180 days of the Study

Recurrence is defined as biopsy evidence of AMR after resolution of a previous AMR episode. The investigator will record the date of recurrence of AMR episode in the CRF, when applicable. During the first 180 days after the qualifying biopsy, if the qualifying AMR episode resolves and there is new biopsy-proven acute AMR per protocol 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. Prior to the first retreatment dose of investigational product, subjects will complete a subset of the screening procedures as indicated in the Screening Retreatment column in Table 1 and then will follow subsequent study treatment visits and procedures as noted in Table 1 and Table 2. Inclusion criteria 1 and 5 are not applicable for retreatment eligibility and signing of a new consent form is not required for retreatment. Retreatment should occur as soon as possible within 7 days of the biopsy that defined the new AMR episode. Retreatment may not occur for recurrent AMR episodes diagnosed through biopsies done after the first 180 days after the qualifying biopsy date. Biopsies at 6 months following retreatment are not required. The only biopsy follow-up mandated by the study will be at Month 6 after initial treatment. With the exception of the Month 6 biopsy, completion of follow-up biopsies after the qualifying AMR episode is at the discretion of the study sites per local standard of care. Biopsy slides and images for unscheduled standard of care biopsies will also be submitted to the EAC.

7.2.2.5 Allograft Failure

Allograft failure due to AMR is determined by the presence of the following criteria: institution of permanent dialysis (defined as dialysis treatment >30 days), current renal allograft nephrectomy, and/or a clinical determination that the allograft irreversibly and irrevocably ceases functioning and $eGFR_{MDRD} \leq 15$ mL/min/1.73m^2. Renal allograft function will be assessed and an $eGFR_{MDRD}$ and recorded at all timepoints. If the subject returns to or permanent dialysis is initially instituted in the case of pre-emptive kidney transplant recipients, the date of return or institution of permanent dialysis will be recorded. All cause graft failure may occur due to causes other than chronic ongoing AMR and include the following: (1) chronic cellular rejection, (2) heart disease, (3) hypertension, (4) diabetes, (5) drug toxicity, and (6) recurrent native kidney disease. The independent blinded nephrology EAC will assess graft failure events to determine and document the cause.

7.2.2.6 Splenectomy

The date of splenectomy (if necessary) performed any time from Screening through the EOS Visit will be recorded in the CRF.

7.2.2.7 Subject Survival Status

Subject survival status (yes/no) will be determined at all timepoints. The date and cause of death will be recorded in the CRF.

7.2.2.8 Donor-specific Antibody Reduction Treatments and Intravenous Immunoglobulin

To reduce DSA, subjects will be required to receive a minimum of 5 plasmapheresis, plasma exchange, or immune adsorption treatments (the choice of any of these procedure(s) will be based on standard-of-care at each study site) from the time of diagnostic biopsy for qualifying episode of acute AMR through Study Day 13. Each DSA reduction treatment will be followed by no less than 100 mg/kg sucrose-free IVIg. Protocol-mandated plasmapheresis, plasma exchange, or immune adsorption treatments should be completed by Day 13. Additional DSA reduction treatments and sucrose-free IVIg may be administered at the discretion of the investigator as part of 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 treatment session and dosing of sucrose-free IVIg. Blood collection for laboratory assessments, other than those specified on Table 3, should be performed prior to the DSA reduction treatments. Investigators will record details of each DSA reduction treatment and each sucrose-free IVIg dose in the CRF.

7.2.3 Safety

The name and address of each third party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

7.2.3.1 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.

In addition, the following information will be recorded:

- Primary cause of native renal failure: diabetes (type 1 or type 2); hypertension; diabetes and hypertension; any glomerulonephritis (eg, focal sclerosing segmental glomerulosclerosis, rapidly progressing glomerulonephritis, membrano-proliferative glomerulonephritis); any autoimmune nephropathy (eg, systemic lupus erythematosus, Goodpasture's syndrome, Immunoglobulin A nephropathy); drug toxicity (eg, lithium, non-steroidal anti-inflammatory abuse); congenital defect (eg, posterior urethral valves); Polycystic Kidney Disease or other
- Diabetes (yes/no)
- Onset date of AMR and pre-AMR $eGFR_{MDRD}$ that qualifies the subject to the study
- Total number of lifetime kidney transplants (one bilateral kidney transplant procedure counts as one procedure)
- Other transplants (eg, 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 of 2 weeks before through 2 weeks after the current transplant, including the date of 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

Refer to Section 5.3 and 5.5 for additional requirements on medication history.

7.2.3.2 Physical Examination (Including Height and Weight)

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 (Section 7.2.3.3). Changes after the Physical Examination of the Screening Visit will be captured as AEs on the AE CRF page, as deemed by the investigator.

The investigator or designee will perform physical examinations at time points specified in Table 1. Physical examinations will be performed in accordance with standard practices at the investigational site. Body weight and height will also be measured at time points specified in Table 1 and Table 2.

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 (Section 8.2.4).

7.2.3.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). 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 (does not include abnormalities identified during the Physical Examination at the Screening Visit, that are not directly caused by an event that occurred after signing informed consent and before the Screening Physical Examination), 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 PVRM via SAE form throughout the study, regardless of relationship to investigational product: any thrombotic or thromboembolic event (Section 8.2.4), any hypersensitivity reaction, any new episode of kidney allograft rejection (excluding AMR), and any kidney allograft failure as defined by Section 7.2.2.5. Refer to Section 8, Adverse and Serious Adverse Events Assessment.

7.2.3.4 Vital Signs

Vital signs include blood pressure and pulse. Any deviations from Screening in vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE. 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.

7.2.3.5 Clinical Laboratory Evaluations

7.2.3.5.1 Central Laboratory Testing

Clinical laboratory safety tests will be performed by a central laboratory at the time points on Table 1 and Table 2. Eligibility will be determined based on local laboratory DSA values. On investigational product dosing days, blood samples for clinical safety laboratory testing should be collected prior to the administration of investigational product. All clinical laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges will be supplied by the central laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values that are unexpected or not explained by the subject's clinical condition may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed by the central laboratory:

DSA Identification
Please see Section 7.2.2.1. Collection for the Central laboratory will be performed at all timepoints according to Table 1 and Table 2.

Chemistry

- albumin
- alanine aminotransferase
- alkaline phosphatase
- aspartate aminotransferase
- blood urea nitrogen
- calcium
- bicarbonate
- chloride
- creatinine (including $eGFR_{MDRD}$ calculation)
- direct bilirubin
- gamma-glutamyl transferase
- glucose
- lactate dehydrogenase
- phosphorus
- potassium
- sodium
- spot urine protein
- total bilirubin
- total cholesterol
- total protein
- uric acid

BUN and serum creatinine with $eGFR_{MDRD}$ calculation (for time points that do not include the above chemistry panel)

Hematology

- complete blood count with differential
- hematocrit
- hemoglobin
- platelet count
- red blood cell count
- white blood cell count with differential

Virology Screen

- Hepatitis (Hepatitis B Surface Antigen, Hepatitis C Antibody)

Anti-C1 INH Antibodies

Blood samples will be collected at screening (pre-dose sample should always be collected at screening), on Day 25, and at Months 3 and 6 for determination of anti-C1 INH antibodies. If sucrose-free IVIg is administered at the screening visit, a sample for anti-C1 INH will be collected before (pre-dose sample) and after sucrose-free IVIg administration (post-dose sample). Subjects with anti-C1 INH antibodies will be followed at the time points specified in Table 2, to measure titers. For 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. For Months 3 and 6 the test will be performed for each subject. See Table 2.

Pharmacokinetic/Pharmacodynamic Assessments

See section 7.2.4.1

Urinalysis

A urine sample will be collected at the visits specified on Tables 1 and 2 for the assessment of proteinuria, to include spot urine protein, urine creatinine, and urine protein to creatinine ratio.

7.2.3.5.2 Local Laboratory Testing

Local laboratory testing will be used to determine subject eligibility and for all clinical decisions. The following tests will be performed by the local laboratory:

DSA Identification

Please see Section 7.2.2.1. DSA testing at the local laboratory is only required at screening. If it is anticipated that the local DSA results will not be available within the screening period, previously obtained local DSA results can be used to assess eligibility, if obtained after kidney transplant and between 30 days prior to the biopsy that is diagnostic of the qualifying AMR episode and the time of obtaining informed consent. In any instance, a screening local DSA test should be performed after obtaining informed consent. Additional DSA tests may also be done locally at other time points at the discretion of the investigator according to local standard of care.

Safety Laboratories

Safety local laboratory values including white blood cell (WBC) count and platelets from the local laboratory will be used to determine eligibility.

BUN, Creatinine and eGFR Calculation

BUN and Serum Creatinine will be tested locally at all protocol-required study visits, and creatinine can be tested outside of the protocol-required study visits at the discretion of the investigator as part of standard of care in order to calculate eGFR and assess pre-AMR and resolution of AMR for all AMR episodes (qualifying and recurrent).

Pre-AMR eGFR values are required for all episodes of AMR in order to assess eligibility for enrollment into the study and for re-treatment of recurrent AMR episodes occurring within the first 180 days after the qualifying biopsy. The $eGFR_{MDRD}$ need to also be obtained at screening (or screening for retreatment), using the first creatinine value available after the qualifying (or recurrent) biopsy that is diagnostic for AMR. At screening, this will be used for the purpose of assessing AMR severity for stratification. Pre-AMR and Resolution of AMR eGFR values are also required for all AMR episodes when AMR resolution is assessed clinically. Otherwise, resolution can only be assessed through histopathology (see Section 7.2.2.3).

Clinical sites will calculate the eGFR, including the pre-AMR eGFR baseline for each episode of AMR as well as their clinical resolution, using the local serum creatinine results and the appropriate MDRD equation as follows:

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.

Coagulopathy Panel
In the event that a subject experiences an unexplained clinically significant thrombotic or thromboembolic event (Section 8.2.4), a coagulopathy panel will be performed at the site's local laboratory when clinically feasible to obtain, which may include at the discretion of the investigator some of the following test parameters:

- Activated protein C resistance ratio
- Alpha 2 Antiplasmin functional
- Anti-phospholipid antibody
- Antithrombin III antigenic level
- Antithrombin III functional
- Factor V, VIII, IX, XI levels
- Homocysteine level
- Plasminogen Activator Inhibitor-1
- Protein C activity
- Protein C antigen
- Protein S activity
- Protein S antigen

7.2.3.6 Pregnancy Test

A urine pregnancy test and a confirming serum beta-HCG pregnancy test (central and local laboratories) will be performed on females of child-bearing potential at the Screening Visit, and a urine pregnancy test will be performed on females of child-bearing potential on Day 1 of each AMR episode prior to investigational product administration.

7.2.3.7 Electrocardiogram

A 12-lead ECG will be performed at the Screening visit and at any additional time during the study if clinically indicated per standard of care. Each ECG will include heart rate, RR Duration, PR duration, QT duration, QRS duration. QTcF will be programmatically derived. The investigator will be responsible for providing the interpretation for all ECGs in terms of clinical significance to the subject.

7.2.4 Others

7.2.4.1 Pharmacokinetic/Pharmacodynamic Assessments

Blood samples for the determination of plasma concentrations of functional and antigenic C1 INH and complement components C3a and C5a will be collected at time points shown in Table 3. "Time of dose" is defined as the start of the investigational product infusion.

Of note, if plasmapheresis, plasma exchange, or immune adsorption treatments are performed on a dosing day, blood samples for pharmacokinetic/ pharmacodynamic testing will be obtained before the DSA reduction and sucrose-free IVIg treatments, as well as prior to investigational product administration (ie, post-DSA reduction treatment), and at time points relative to the start of the investigational product infusion, as outlined in Table 3. The actual date and time of each sample collection will be recorded. Plasma samples for the determination of antigenic and functional C1 INH concentrations and complement C3a and C5a levels will be analyzed according to validated methodology.

In addition, plasma samples will be stored and may be used to investigate additional complement or cytokine levels that might correlate with response to treatment.

7.2.4.2 Health Outcomes and Outcomes Research Assessments

The validated quality of life EQ-5D-5L questionnaire will be administered to subjects at the time points on Table 1 and Table 2.

7.2.4.3 Healthcare Resource Utilization

Healthcare resource utilization will be assessed at the time points on Table 1 and Table 2.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs 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 as well as the events of special interest regardless of relationship to investigational product (any thrombotic or thromboembolic event, any hypersensitivity reaction, any new episode of kidney allograft rejection [excluding AMR] - Section 8.1.4) 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. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae

- Recovering/Resolving
- Unknown

8.1.4 Adverse Events of Special Interest

In addition, the following events of special interest, both serious and non-serious, will be closely monitored and reported to Shire PVRM via SAE form throughout the study, regardless of relationship to investigational product:

- Any thrombotic or thromboembolic event: thrombotic or thromboembolic events will be assessed for relatedness to investigational product. Stopping rules related to thrombotic or thromboembolic events are described in Section 4.5.3.
- Any hypersensitivity reaction
- Any new episode of kidney allograft rejection (excluding AMR)
- Kidney allograft failure as defined in Section 7.2.2.5

AESIs reported via SAE form that do not meet the serious criteria definition (Section 8.2.3) should be reported on the SAE form as being non-serious.

8.1.5 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. Please note that AMR should not be classed as an AE.

8.1.6 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pre-treatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.7 Pregnancy

All pregnancies are to be reported from the time informed consent is signed and throughout the defined post-treatment follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Pharmacovigilance Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Trial Serious Adverse Event Form. NOTE: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Trial Serious Adverse Event Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine beta-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.8 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 125 U/kg of the product.

- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors. Medication errors should be reported for all products under investigation. The administration and/or use of the unassigned treatment is/are always reportable as a medication error. The administration and/or use of an expired investigational product should be considered as a reportable medication error.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information (RSI) for this study is located in the Investigator's Brochure, which the sponsor has provided under separate cover to all investigators.

There is limited clinical experience with CINRYZE in kidney transplant patients with acute AMR at the dose intended for clinical use (ie, 9 subjects in the Phase 2 pilot study 0624-201). Safety data from these 9 patients were reviewed, and it has not been possible to define any expected adverse reactions (ADRs) to date.

Therefore, there is currently not enough information to establish a list of expected AEs in this population.

8.2.2 Reporting Procedures

All initial and follow-up SAE and AESI reports must be reported by the investigator to the Shire Pharmacovigilance Department and the PPD Clinical Study mailbox within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (Section 8.1.8) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Trial Serious Adverse Event Form and verify the accuracy of the information recorded on the form with the corresponding source documents (NOTE: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Pharmacovigilance Department and the PPD Clinical Study mailbox. A copy of the Shire Clinical Trial Serious Adverse Event Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor / PPD Medical Monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A ***Serious Adverse Event*** **(SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.
- ***For the purposes of this study***: clinically significant thrombotic or thromboembolic event (Section 8.2.4)

8.2.4 Thrombotic or Thromboembolic Events

Evaluation of any suspected thrombotic or thromboembolic events will follow the algorithm outlined in Appendix 4. Clinically significant thrombotic or thromboembolic events (except superficial thrombophlebitis, dialysis access clotting, or catheter-related thrombotic events, unless these meet serious criteria as defined in Section 8.2.3) will be reported via SAE form as SAE and will include established diagnoses of any of the following:

- Renal allograft arterial or venous thrombosis
- Deep vein thrombosis
- Myocardial infarction
- Pulmonary embolism
- Ischemic cerebrovascular accident (stroke), or transient ischemic attack (TIA), exclusive of cerebrovascular hemorrhage (subarachnoid or subdural hemorrhage)
- Any large vessel thrombosis (exclusive of the presence of an indwelling catheter)

Diagnosis must be established with a confirmatory diagnostic examination that, at the discretion of the investigator, may include but is not limited to: ultrasound or angiography of the allograft consistent with absence of flow in the renal vein or renal artery; ultrasound of the deep veins suggesting non-compressibility and/or a venography confirming occlusion of the vessel (DVT); coronary arteriography confirming occlusion of the vessel within the distribution of the ECG deficit (myocardial infarction); pulmonary angiography confirming pulmonary artery occlusion or definitive defect on nuclear medicine lung V/Q scan (pulmonary embolism); cerebral angiogram confirming occlusion of a major cerebral artery (ischemic cerebrovascular accident); or any other angiogram confirming thrombotic or thromboembolic occlusion of any large artery or vein.

Evaluation of subjects with unexplained clinically significant thrombotic or thromboembolic events should include a coagulopathy panel when clinically feasible to obtain (Section 7.2.3.5).

8.2.5 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 8.1, and must be reported to the Shire Pharmacovigilance Department and the CRO/Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event.

8.2.6 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.7 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product).

8.2.8 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and the clinical CRO are responsible for notifying the relevant regulatory authorities US institutional review boards (IRBs) and EU central ethics committees (ECs) of related, unexpected SAEs.

In addition the clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP616 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data will be entered into a clinical database as specified in PPD's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data will be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, treatment allocation, and investigational product preparation/ accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513).

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed. The SAP will be finalized prior to the first interim analysis to preserve the integrity of the statistical analysis and study conclusions.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

9.5.1 Interim Analysis and Adaptive Design

The study is designed to have 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) 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.

For the first interim analysis, the EACs, sponsor, investigator, as well as the subject 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 subjects will be blinded to the EACs, investigator, and subjects during the conduct of the study.

The purpose of the first interim analysis is to allow early stopping of the study for futility, to assess safety of the treatment, and potentially to adjust the sample size. This analysis will be performed when 30 subjects complete 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. Alternatively, as appropriate, the trial may be stopped for futility at the interim analysis or the sample size of the study may be adjusted up using the CHW method (Cui et al. 1999). 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. The pre-defined conditional power lower limit (CP_{LL}) and upper limit (CP_{UL}) will be used for decision making and are documented in the Statistical Analysis Plan for the interim analysis (IA).

The purpose of the second interim analysis is to allow early stopping if the primary endpoint is not met or for claiming of efficacy based on new or worsening TG within at 6 months of initiation of treatment. This analysis will be done when a required number of subjects (based on the first interim analysis) complete the Month 6 TG assessments. If the result of the second interim analysis is statistically significant at 0.0249, the primary null hypothesis will be rejected. The test statistic at the second interim stage will be derived using CHW method and specified in the interim SAP.

The efficacy boundary of TG at 6 months of initiation of treatment will be pre-specified by Haybittle-Peto boundary (Haybittle 1971; Peto et al. 1976). 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 of initiation of treatment. The overall significance level for the efficacy analysis of TG at 6 months of initiation of treatment will be preserved at 0.025 (1-sided test) by using a significance level of 0.0249 for the second interim analysis.

If the result of the second interim analysis of the primary endpoint 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 (ie, proportion of subjects with all-cause graft failure).

For the key secondary endpoint, the study information is event based. The study will continue until approximately 51 confirmed clinical events are reached unless stopped prematurely based on findings at an interim analysis or the last enrolled subject has been followed for 4 years. There will be 3 analyses (2 interim and 1 final) of proportions of subjects with all-cause graft failure, at approximately 50% (~26 events), 75% (~39 events), and 100% (~51 events) of the study information. The purpose of the 2 interim analyses is to allow early stopping of the study for overwhelming efficacy and assessing safety of the treatment. An alpha spending function approximating the O'Brien-Fleming boundary shape (O'Brien and Fleming 1979) will be employed to maintain an overall significance level at 0.025. The test statistics and boundary values for decision making at the 3 analyses (2 interim and 1 final) will be specified in the SAP.

The actual stopping boundaries for this sequential design will be predetermined so that the overall significance level for the comparison of proportions of subjects with all-cause graft failure is maintained at α=0.025. Further details regarding the sequential monitoring plan and decision rules will be prepared before the start of data monitoring and documented in the interim SAP.

The alpha-spending boundaries represent guidelines for further evaluation of the endpoints and other data. Excursions across the boundaries do not constitute stopping rules, per se. Decisions to alter the study conduct will be based on other information, as well.

If serious safety concerns are noted at the time of either interim analysis, the sponsor will communicate with the regulatory authorities and clinical sites as appropriate regarding stopping the clinical trial. If the 3rd or 4th interim analysis indicates the study can be stopped early for efficacy, the Sponsor will communicate with appropriate regulatory authorities to obtain agreement on the decision.

Full details of the analysis will be provided in the SAP.

9.5.2 Data Monitoring Committee

An independent 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 will monitor ongoing data generated by the study at defined intervals, as specified in the DMC charter, for the duration of the study including, but not limited to, after 30 subjects complete the Month 6 TG assessment; after the re-estimated number of subjects, based on the first interim analysis recommendation, complete the Month 6 TG assessment; and after approximately 50% (~26 subjects) and 75% (~39 subjects) targeted subjects have experienced all-cause graft failure. Their role is to protect the interests of the subjects in the study and of those still to be entered, by review of accumulating data generated in the study.

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 the independence, confidentiality, formal communication, and outline of the content of reports that will be provided by the DMC.

For each interim analysis, the p-values, CP, 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.

In addition, the DMC will review reported SAE cases of specific drug-related thrombotic and thromboembolic events in the context of study stopping rules (Section 4.5.3), and will also evaluate interim efficacy data and make recommendations regarding study continuation, stopping or sample size adjustment based on observed results of the study. The recommendations made by the DMC to alter the conduct of the study will be forwarded to Shire. Shire will review the results with regulatory authorities, as appropriate, prior to any decisions regarding stopping the study or publically discussing interim results.

9.5.3 Endpoint Adjudication Committee

9.5.3.1 Pathology Endpoint Adjudication Committee

An independent (no members employed by the sponsor or participating as an investigator in the study), blinded pathology EAC will be established to assess biopsy slides and images for confirmation of AMR for qualifying diagnoses and for determination of the presence of new or worsening TG at 6 months of initiation of treatment (Section 7.2.2) and for any additional biopsies evaluated. In addition, they will also assess graft failure events to determine the cause. The roles, responsibilities and rules governing operation of the pathology EAC are discussed in full in the pathology EAC charter.

9.5.3.2 Nephrology Endpoint Adjudication Committee

An independent (no members employed by the sponsor or participating as an investigator in the study), blinded nephrology EAC will be established to assess the outcomes of kidney allografts. This committee will confirm that the most current kidney allograft has failed to function and determine the primary cause of allograft (ie, AMR-related, recurrent kidney disease, drug toxicity, cardiac disease, diabetes, other-cause failure). The roles, responsibilities and rules governing operation of the nephrology EAC are discussed in full in the nephrology EAC charter.

9.6 Sample Size Calculation and Power Considerations

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.

9.7 Study Population

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

The **Intent-to-Treat Population** 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.

The **Full Analysis Set (FAS)** 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.

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.

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.

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.

The **Pharmacokinetic (PK) and Pharmacodynamic (PD) Analysis Set** is defined as all subjects who received at least 1 dose of CYNRIZE and have at least 1 evaluable post-dose PK/PD concentration value.

9.8 Efficacy Analyses

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the proportion of subjects with new or worsening TG at 6 months post-treatment as determined by Banff criteria. The FAS set is the primary set for efficacy analysis. Subjects who do not have the primary efficacy endpoint assessed at 6 months post-dose will be assigned as failures.

The primary endpoint will be presented as the proportion of subjects with new or worsening TG occurring at 6 months post-treatment, 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 $\Pi_{Placebc}$ 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 (1-sided test) to test null hypothesis:

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

Against the 1-sided alternative:

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

In the initial plan, the statistical difference between treatments will be evaluated by the CHW weighted test statistic Z_{CHW} when the first 60 subjects complete the assessments for the primary endpoint (second interim analysis). If the $Z_{CHW} \geq Z_{0.0249}$ (equivalent to p-value from the test is ≤0.0249 [1-sided test]), it will be concluded that CINRYZE is efficacious based on the proportion of subjects with new or worsening TG at 6 months after initiation of treatment and the result will serve as evidence of efficacy based on these 60 subjects. However, the number of subjects might be changed (increased) depending on the results of the first interim analysis in which the sample size will be re-estimated (Section 9.5.1).

Design features are in place to protect the study-wise error level at 0.025 (1-sided test) for testing the hypotheses related to primary and key secondary endpoints. In order to declare a successful study, statistical significance must be met successively on the surrogate endpoint of proportions of subjects with new or worsening TG at 6 months of initiation of treatment and on the endpoint of all-cause graft failure. No adjustment for multiple co-primary endpoints is needed. The alpha spent at each endpoint will be controlled by sequential testing boundaries assuring that no more than 0.025 alpha (1-sided test) is expended in the multiple analyses across time for each of the primary and key secondary endpoints.

A number of sensitivity analyses will be performed to assess any impact on the primary endpoint results, inference, and conclusions due to missing data. In addition, descriptive analyses on the primary endpoint will be provided in selected subgroups.

9.8.2 Secondary Efficacy Endpoints

9.8.2.1 Key Secondary Efficacy Endpoint

The key secondary endpoint is defined as the proportion of subjects with all-cause graft failure (ie, return to permanent dialysis and/or removal of the transplanted kidney and/or clinical determination of cessation of graft function) at 4 years following treatment of the initial qualifying AMR episode. The FAS population will be used to report the efficacy data for all-cause graft failure. Subjects who do not have the key secondary efficacy endpoint assessed post-dose will be assigned as failures.

The proportion of subjects with all-cause graft failure will be summarized by treatment group. Subjects with an assessment of all-cause graft failure or who drop out due to graft failure will be included in the hypothesis testing.

The test statistics and boundary values for decision making at the 3 analyses (2 interim and 1 final) will be specified in the SAP.

The null hypothesis for the proportion of subjects with all-cause graft failure post-treatment will be tested at the overall accumulative alpha level of 0.025 (1-sided test). This hypothesis will only be tested if testing for the primary endpoint of new or worsening TG at 6 months of initiation of treatment is statistically significant.

A number of sensitivity analyses will be performed to assess any impact on the key secondary endpoint results, inference, and conclusions due to missing data. In addition, descriptive analyses on the key secondary endpoint will be provided in selected subgroups.

9.8.2.2 Secondary Efficacy Endpoints

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 screening to 6 months
- Change in histopathology per Banff criteria from pre-AMR to 6 months
- Proportion of subjects with all-cause graft failure at 6 months

9.8.2.3 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
- Proportion of subjects with graft failure due to AMR at 4 years
- Time to all-cause graft failure
- Time to graft failure due to AMR
- Proportion of subjects with resolution of the qualifying AMR episodes
- Time to resolution of AMR episodes
- Proportion of subjects alive at 4 years
- Time to all-cause mortality

Time to all-cause graft failure, time to graft failure due to AMR, time to resolution of AMR after initial treatment, and time to overall survival for both treatment groups will be summarized by Kaplan-Meier estimates, and the difference between treatments will be assessed by proportional hazard regression. The FAS population will be used in these analyses.

The proportion of subjects with graft failure due to AMR, with resolution of the qualifying AMR episodes, and overall survival will be assessed by treatment group. The FAS population will be used in these analyses.

Graft function, defined as eGFR ≥40 mL/min/1.73m^2 at 3 months post-transplant, will be estimated by the MDRD formula shown below:

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

Histopathology, graft function, and other secondary endpoints will be evaluated at the specified time-points or as change from the corresponding baseline value. Summary statistics will be provided by treatment group.

9.8.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are defined as:

[redacted]

9.9 Safety Analyses

Safety endpoints include TEAEs, vital signs measurements, antibodies to C1 INH, and clinical safety laboratory testing. The safety analysis set will be used to report the safety data.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, by treatment group, and and/or by AMR episode. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Clinical laboratory tests, vital signs, and anti-C1 INH antibodies will be summarized. Potentially clinically significant values will also be summarized and listed.

9.10 Pharmacokinetic/Pharmacodynamic Endpoints

Pharmacokinetic and pharmacodynamic endpoints include:

- Analysis of serum complement factors (anaphylatoxin split product of C3 activation important in chemotaxis [C3a] and anaphylatoxin split product of C5 activation important for histamine release and chemotaxis [C5a]) and their potential relationship to C1 INH concentrations
- Analysis of the pharmacokinetics of CINRYZE and the effect of plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free IVIg for the treatment of AMR on C1 INH levels

The pharmacokinetic and pharmacodynamic Analysis Set will be used to report C1 INH and complement data.

The PK parameters will be summarized by descriptive statistics at each collection timepoint by treatment.

Plasma samples at pre-DSA reduction and 1 hour post investigational product administration will be assessed for C1 INH (antigen and functional binding). Concentrations of C1 INH (antigen and functional binding) will be summarized by treatment using descriptive statistics for each nominal collection time, including concentrations corrected by baseline.

Complement C3a and C5a levels in those plasma samples will be measured. Results will be summarized using descriptive statistics for values at the designated time points and change from pre- to post-infusion of investigational product will be evaluated.

9.11 Health Economics and Outcomes Endpoints

The health economic and outcomes endpoints include:

- Measurement of the EuroQoL Group 5 Dimension 5-Level Self-report Questionnaire (EQ-5D-5L)
- Measurement of healthcare resource utilization (HRU)

The effect on quality of life will be measured by the change from baseline in the EQ-5D-5L by treatment per results in 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 timepoint for FAS.

The effect on HRU will be measured by treatment. Results of the HRU will be summarized at each timepoint by treatment.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996) and any updates, EU Directive 2001/20/EC and its updates, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP.

This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and any updates, EU Directive 2001/20/EC and its updates, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the coordinating principal investigator, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the sponsor (or designee) and should be handled in accordance with instructions from the sponsor. The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the CRF. All data sent to the sponsor must be endorsed by the investigator. The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor, the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally-authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor (or designee) has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives will review their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market CINRYZE; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results / Publication Policy

Shire ViroPharma, Inc. will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire ViroPharma, Inc. adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire ViroPharma, Inc. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire ViroPharma, Inc. products or projects must undergo appropriate technical and intellectual property review, with Shire ViroPharma, Inc. agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire ViroPharma, Inc., the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results.

If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	01 Apr 2015	Global
Amendment 1	28 May 2015	Global
Amendment 2	25 Jun 2015	Global
Amendment 3	01 Sep 2016	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Sep 2016**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Updated the title page to indicate the study is multicenter		Title page
Updated the Shire signatory to Andrea Vergani, MD, PhD		Protocol Signature page
Added a high-level amendment summary and rationale to provide a general overview and justification of amendment revisions		Amendment Summary and Rationale
Updated the emergency contact information and removed contract research organization contact information as this information will be provided in a separate document		Emergency Contact Information Section 8.2.2.
Updated the contact information for quality complaints		Product Quality Complaints
Clarified that intravenous immunoglobulin (IVIg) is to be sucrose-free to avoid potential renal toxicity and dosed at no less than 100 mg/kg to allow more flexibility and adhere to site standard of care		Throughout protocol
Removed the limit for a maximum enrollment to add greater flexibility		Synopsis Section 3.1. Section 4.5. Section 9.5.1
Combined the US and EU sites to include approximately 40 sites in 6 countries		Synopsis Section 3.3
Clarified the primary objective as follows: • Removed dosing details from the primary and secondary objectives as they are included in protocol dosing Section 6.2.3 • Added text to the primary objective to clarify that measurement of transplant glomerulopathy (TG) is at 6 months after "initiation of" treatment Clarified secondary objectives as follows: • Revised the key secondary objective text to clarify that subjects will be assessed for all-cause graft failure at 4 years following treatment initiation • Reorganized the secondary objectives into study entry to 6 months and study entry to 4 years to provide increased structure and clarity to the protocol • Revised the secondary and exploratory objectives to eliminate details for measurements that are included in the endpoints and to broaden scope		Synopsis Section 2.2 Throughout protocol

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Sep 2016**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
• Added change in proteinuria as a secondary objective to better assess graft function • Added time to AMR resolution as a secondary objective to better assess CINRYZE effect • Moved assessment of recurrence from secondary to exploratory objectives in order to reprioritize study goals • Combined pharmacokinetic (PK) and pharmacodynamic (PD) analyses and moved from secondary to exploratory objectives to reprioritize study goals • [redacted]		
Revised the stratification for severity to specify estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease ($eGFR_{MDRD}$) (ie. ≤15 mL/min/1.73m^2 or >15 mL/min/1.73m^2)		Synopsis Section 3.1 Section 6.2.2
Removed the details about how the Endpoint Adjudication Committees (EACs) will conduct assessments as this information will be in their Charters		Synopsis Section 3.1 Section 7.2.2.2
Revised the definition of graft failure to specify that permanent dialysis is defined as dialysis treatment >30 days, current transplant nephrectomy, or clinical determination of cessation of kidney graft ($eGFR_{MDRD}$ ≤15 mL/min/1.73m^2)		Synopsis Section 3.1
Added a definition of adequate kidney function using $eGFR_{MDRD}$ values and timing in relation to transplant for clarity Clarified definitions of pre-AMR baseline and resolution of qualifying and recurrent AMR episodes Clarified that treatment should be started as soon as possible after screening and within 7 days of the qualifying biopsy procedure to assure treatment of the acute phase of the AMR episode		Synopsis Section 3.1 Section 7.1.1 Section 7.1.2.1 Section 7.2.2.3
Clarified that recurrence is defined as biopsy evidence of AMR after resolution of the previous episode		Synopsis Section 3.1 Section 7.2.2.4
Revised study methods including: • Clarified that AMR will be defined using the most recent Banff 2013 criteria • Clarified that biopsy slides will be required for most staining and to send to a central image core for scanning in order to improve homogeneity • Clarified that during the screening period, the first $eGFR_{MDRD}$ value obtained after the qualifying biopsy should be used • Clarified that the EACs will be blinded and independent • Clarified that collection of blood samples will be done prior to DSA reduction treatment and after investigational product (CINRYZE or placebo) administration in order to avoid confounding factors • Clarified that timing for the 5 required DSA treatments or sucrose-free IVIg is at investigator discretion within the study dosing period to allow more flexibility and adhere to site standard of care • Clarified general assessments to be completed by both EACs		Synopsis Section 3.1 Section 3.2 Section 4.1 Section 4.5 Section 6.2.4 Section 7.1.2 Section 7.2.2.2 Section 9.5.3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Sep 2016**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
• Clarified that in the event of early discontinuation by a subject, every effort will be made to obtain adverse events (AEs), biopsy if applicable, serum blood urea nitrogen (BUN) and creatinine (Cr) and $eGFR_{MDRD}$ results for EAC evaluation as collection of this information will strengthen study conclusions		
Clarified that pregnancy tests are required only for women of child-bearing potential		Synopsis Section 4 Section 7.1 Section 7.2.3.6
Revised the inclusion/exclusion criteria as follows: • Added an age limit for enrollment to ensure subject safety (≤70 years of age) • Revised weight requirements: Change from ≥40 kg to ≥45 kg to assure patient safety • Added that if DSA cannot be promptly identified during screening, that previously obtained data can be used if obtained after kidney transplant and within 30 days of the qualifying AMR episode to allow for greater enrollment flexibility • Specified that the qualifying episode of AMR must occur between 72 hours and 12 months after transplant to improve patient homogeneity • Added criteria for adequate kidney function defined as having a pre-AMR baseline $eGFR_{MDRD}$ ≥20 mL/min/1.72m^2 if the qualifying AMR episode occurs ≤21 days after transplant or pre-AMR baseline $eGFR_{MDRD}$ ≥30 mL/min/1.72m^2 if the qualifying AMR episode occurs >21 days after transplant • Separated the criteria for contraception from the pregnancy test criteria per protocol standards • Added the exclusion of subjects having C3 Glomerulopathy or Thrombotic microangiopathy as the cause of native kidney failure and updated "focal sclerosing glomerulosclerosis" to "primary Focal Segmental Glomerulosclerosis" to limit the risk of recurrence of glomerular diseases that could make TG assessment difficult • Added the exclusion of subjects having received organ transplants other than kidneys, hematopoietic stem cell transplant (HSCT), or more than 1 completed kidney re-transplant procedure to prevent confounding influences on study data • Added the exclusion of subjects with any ongoing infection or surgical or medical condition that could compromise patient safety or confound efficacy assessment • Added the exclusion criteria of subjects being actively treated for hepatitis C virus (HCV) infection to ensure subject safety and avoid confounding influences on study data • Added the exclusion of subjects with an existing neoplastic lesion in the allograft to ensure subject safety and avoid confounding influences on study data		Synopsis Section 4. Section 7.2.3.1 Section 7.2.3.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Sep 2016**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
• Added the exclusion of subject with a change in androgen therapy to ensure subject safety and avoid confounding influences on study data • Added the exclusion of a subject with a history of transient ischemic attack (TIA) or myocardial infarction (MI) within 6 months of study entry to ensure subject safety and avoid confounding influences on study data • Added the exclusion for subject receiving sucrose-containing IVIg within a month of the first dose in order to avoid the risk of sucrose-containing IVIg kidney toxicity in this patient population • Removed the criterion for exclusion of Bortezomib as a prohibited medication 1 month prior to the first dose in order to provide greater enrollment flexibility • Clarified that local laboratory results should be used for enrollment eligibility in order to avoid delays in investigational product administration • Clarified the exclusion criterion for white blood cell count during steroid treatment, in order to avoid this confounding factor		
Updated the endpoints to reflect the changes in the objectives including details on specific measurements to be done		Synopsis Section 9.8.2 Section 9.8.3
Clarified that the adverse events of special interest (AESI) of new kidney allograft rejection exclude AMR		Synopsis Section 7.2.3.3 Section 8.1 Section 8.1.4 Section 8.1.5
Added language requiring the reporting of non-serious AESI to Shire Pharmacovigilance and Risk Management (PVRM) Department using serious adverse event (SAE) forms to ensure subject safety		Synopsis Section 3.1 Section 7.2.3.3 Section 8.1.4
Updated the study schedules and study procedures to reflect the changes to the protocol		Table 1 and Table 2 Section 7.1
Added a column to Table 1 to clarify which procedures are to be completed prior to retreatment		Table 1
Moved the column for early discontinuation assessments from Table 1 to Table 2 in order to separate it from the dosing period in Table 1		Table 1 and Table 2
Revised the window for subject assessments from ±14 days to ±21 days for months 3 through 12 and to ±28 days for months after Month 12 to allow greater flexibility to subjects and sites		Table 2
Removed analysis of PK/PD samples for a subset of patients at Day 2-12 as this information is not required		Table 3 Section 9.10
Clarified that CINRYZE, in doses utilized to treat hereditary angioedema (HAE), does not require pre-administration medications such as antihistamines or acetaminophen		Section 1.3.1
Added information about the collection of healthcare resource utilization to ensure subject safety and to obtain additional information on quality of life		Section 3.1 Section7.2.4.3
Updated Figure 1 to reflect changes in protocol, including a decrease in the retreatment period to the first 6 months		Figure 1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Sep 2016**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
Removed use of prohibited or experimental drugs from reasons for discontinuation in order to allow data capture for these patients as well		Section 4.5.1
Specified that concomitant medications and AEs will be collected through 30 days after the last dose of investigational product for each treatment period to ensure adequate information is collected for analysis of safety		Section 5.1 Section 7.2.3.3 Section 8.1
Specified prophylactic treatment for deep vein thrombosis (DVT) will be collected throughout the study to ensure comprehensive safety data collection		Section 5.1
Added a table to clarify dosing		Table 4
Clarified that sites will be responsible for sourcing 0.9% sodium chloride solution for infusion of either the active drug or the placebo		Section 6.1
Clarified that dosing with investigational product cannot be administered within the 7 days after transplant based on data monitoring committee (DMC) recommendation and must be administered within 7 days after the qualifying biopsy to provide adequate screening time to sites and to ensure subjects receive prompt treatment		Synopsis Section 3.1 Section 4.1. Section 7.1 Section 7.2
Revised text to clarify destruction of investigational product		Section 6.4
Indicated that when the criterion to conduct the second interim analysis is met, treatment assignment for those subjects may be unblinded for analysis to designated sponsor representatives and to clarify that the treatment assignments for all other subjects will be blinded to the EACs, investigator, and subjects to ensure the study blind		Section 6.1.1 Section 6.2.4 Section 9.5.1
Clarified the requirements for sites to provide slides and images to ensure that sites understand this is required and not optional and indicated that instructions will be provided separately to further describe details for the requirements		Section 7.2.
Clarified DSA identification as follows: • Clinical decision will be based on local laboratory analysis of DSA, including additional time points done at the discretion of the investigator as part of standard of care • DSA testing will be done by the central laboratory at Screening, Day 25, Months 3, 6, 12, 18, 24, 30, 36, 42, and 48 • Added serum collection for DSA titer testing		Section 7.2.2.1
Specified that immunohistochemical staining is acceptable if immunofluorescence is not available in order to collect needed data and allow more flexibility to sites		Section 7.2.2.2
Indicated that whenever possible, biopsy tissue remaining after the qualifying biopsy assessment will be preserved in paraffin or another method appropriate for electron microscopy (EM) processing to allow for additional information to be obtained as needed		Section 7.2.2.2
Added the following for biopsies during the study to allow better tissue sampling and analysis: • The recommendation to provide at least 2 separate cores containing cortex for the qualifying biopsy • The requirement for at least 2 separate cores containing cortex at the 6 month biopsy and for subjects who discontinue prior to 6 months		Section 7.2.2.2
• Added the definition of resolution: Resolution will be achieved when, after treatment, the local $eGFR_{MDRD}$ value increases to at least within		Section 7.2.2.3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **01 Sep 2016**	**Global/Country/Site Specific** **Global**
Description and Rationale for Change		**Section(s) Affected by Change**
20% or above the $eGFR_{MDRD}$ value collected as a pre-AMR baseline. • Added that if an AMR episode is diagnosed per a standard of care biopsy, in absence of significant (≥20%) eGFR decline from pre-AMR baseline, a follow-up biopsy is recommended within 3 months in order to assess resolution and to ensure subject safety		
Clarified which assessments are required by local and central laboratories		Section 7.2.3.5
Added in details on how to calculate eGFR from creatinine values		Section 7.2.3.5
Clarified that the choice of plasmapheresis, plasma exchange, or immune adsorption treatments will be based on the standard of care at the study site to allow more flexibility and adhere to site standard of care		Section 7.2.2.8
Added additional chemistry laboratories and specified that subjects where anti-C1-inhibitor (C1 INH) antibodies are detected will be followed until negative to ensure subject safety		Section 7.2.3.5
Removed the appendix describing the collection of plasma samples and cross references to this appendix as this information will be provided in a separate document		Section 7.2.4.1 Appendix 4
Removed Section 7.2.5 and information about the volume of blood to be drawn from each subject as this information will be provided in a separate document		formerly Section 7.2.5
Revised the reference safety information location to the Investigator's Brochure to prevent duplication of source information location		Section 8.2.1
Added that AESI must be reported within 24 hours by the investigator to the Shire Pharmacovigilance Department and the Shire Medical Monitor within 24 hours of the first awareness of the event to ensure subject safety		Section 8.2.2
Removed details about the interim analysis as this information will be included in the interim analysis statistical plan		Section 9.5.1 Section 9.8.2.1
Specified that the study will not be stopped for efficacy until the Sponsor has received confirmation of the decision from the appropriate regulatory agency per the request from regulatory agencies		Section 9.5.2
Study population analysis sets have been redefined to ensure data collected is fully analyzed		Section 9.7
Specified that a number of sensitivity analyses will be performed to assess any impact on the key endpoint results, inference, and conclusions due to missing data and that selected analyses on the key endpoint will be provided in selected subgroups		Section 9.8.1 Section 9.8.2.1
Clarified the correct $eGFR_{MDRD}$ formula		Section 9.8.2.2
Added the analysis for the results of the EM to clarify rationale on the images requirement		Section 9.8.3
Clarified the analysis for C1 INH, C3a, and C5a		Section 9.10
Added new health economics endpoints and a section to describe and clarify the analysis of the health economic and outcome endpoints		Section 9.11
Added in the 2013 updated criteria for Banff classification		Appendix 2

Protocol Amendment		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **25 Jun 2015**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Shire signatory was updated to Marc E. Uknis, MD, FACS		Protocol Signature page
Since ultrastructural analysis (electron microscopy; EM) may not be available for all Month 6 biopsies and since early pathology evident only on EM has not been validated with diminished long-term graft survival, the definition of TG was revised from chronic glomerulopathy (cg) score >0 to cg score ≥1b (ie, evident changes on light microscopy)		Synopsis Section 1.1, Section 1.2.3, Section 2.1.2, Section 3.1, Section 7.2.2.2
[redacted]		Synopsis Section 2.2.3, Section 7.2.2.2, Section 9.8.3
Updated a background statement regarding TG with more recent references		Section 1.1, Section 11

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **28 May 2015**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Name of sponsor was changed to Shire ViroPharma, Inc for consistency among study documents.		Global
Shire signatory was updated to Arian Pano, MD.		Protocol Signature page
Contact information was updated for CINRYZE quality complaints.		Product Quality Complaints page
Added the following secondary objective that was inadvertently omitted in Version 1: "To assess the overall subject survival status (proportion and time-to-event)" for consistency with endpoints and analyses.		Synopsis Section 2.2.2, Section 9.8.2.2
Clarified that time to overall survival for both treatment groups will also be summarized by Kaplan-Meier estimates.		Section 9.8.2.2
Removed the secondary objective/endpoint of frequency of AMR: "To assess the number of acute AMR episodes treated per protocol during the follow-up period."		Synopsis Section 2.2.2, Section 9.8.2.2
Changed EQ-5D-5L from a secondary objective/endpoint to an exploratory objective/endpoint.		Synopsis Sections 2.2.3, Section 9.8.3
Footnote added to clarify that the screening blood samples for immunogenicity should be obtained prior to and following administration of IVIg if administered on the same day as screening.		Table 1
Added recording presence/absence of diabetes at screening, Month 6, and end of study.		Table 1, Table 2 Section 7.1.1, Section 7.1.3.3 Section 7.1.3.5
Added the following to be recorded for medical history: • Diabetes (yes/no) • Onset date of AMR that qualifies the subject to the study • "Other: specify" for medications administrated for immunosuppression within 2 weeks of current transplant.		Section 7.2.3.1
Total blood volume was adjusted to 244 mL to include samples required for serum BUN/Cr (75 mL) and DSA identification and titer (55 mL).		Section 7.2.5, Table 4
Corrected equation for definition of pooled proportion for the first interim analysis.		Section 9.5.1
DMC meeting frequency was updated to align with interim analyses: after 30 subjects complete the Month 6 TG assessment; after the re-estimated number of subjects (based on the first interim analysis recommendation) complete the Month 6 TG assessment; and after approximately 50% (~26 subjects) and 75% (~39 subjects) targeted subjects have experienced all-cause graft failure.		Section 9.5.2

Appendix 2 Banff Classification of Renal Allograf Biopsy (2013 Update)

In 2007 Banff classification of renal allograft; C4d deposition was as essential feature of antibody mediated rejection (ABMR). But with the growing evidence of ABMR (with evidence of microvascular injury and donor specific antibody [DSA]) in the absence of C4d deposition, classification is revised in 2013 focusing mainly on redefining ABMR. Additionally, electron microscopic (EM) findings are incorporated in to cg (chronic glomerulopathy) scoring. Now suggestion is made for EM to be considered in all biopsies done ≥6 months post-transplant and ≥3 months in for-cause post-transplant allografts to assess early changes of transplant glomerulopathy. There is also recognition of overlap between ABMR and TCMR as mild to moderate arteritis (v1) and severe arteritis (v2) which was solely part of TCMR in 2007 classification also features in acute/active ABMR in the latest Banff 2013 classification.

In the revised classification, ABMR has been classified as acute/active ABMR and chronic, active ABMR. For the diagnosis of acute/active ABMR all three features are required which include **histologic evidence of acute tissue injury** (microvascular inflammation, intimal or transmural arteritis, acute thrombotic microangiopathy or acute tubular injury (*in the absence of any other cause*)], **evidence of current/recent antibody interaction with vascular endothelium** (linear C4d staining in peritubular capillaries, at least moderate microvascular inflammation or increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury) and **serologic evidence of DSA.**

Similarly for the diagnosis of chronic, active ABMR all three features are required for diagnosis including **morphologic evidence of chronic tissue injury** (transplant glomerulopathy [*if no evidence of chronic thrombotic microangiopathy*] or severe peritubular capillary basement membrane multilayering [*requires electron microscopy*] or arterial intimal fibrosis of new onset [*excluding other causes*]), e**vidence of current/recent antibody interaction with vascular endothelium** (*similar to acute/active ABMR criterion*) and **serologic evidence of DSA**

SCORING AND CLASSIFICATION OF HISTOLOGIC FINDINGS ON ALLOGRAFT BIOPSY

Glomerulitis score

g0	No glomerulitis
g1	Glomerulitis in less than 25% of glomeruli
g2	Segmental or global glomerulitis in 25 to 75% of glomeruli
g3	Glomerulitis (mostly global) in more than 75% of glomerul

Criterion for allograft glomerulopathy

cg0	No GBM double contours by LM or EM
cg1	1a: no GBM double contours by LM but GBM double contours (incomplete or circumferential) in at least 3 glomerular capillaries by EM with associated endothelial swelling and/or subendothelial electronlucent widening 1b: ≥1 glomerular capillaries with GBM double contours in 1 nonsclerotic glomerulus by LM. EM confirmation is recommended if available.

cg2	Double contours affecting 26 to 50% of peripheral capillary loops in the most affected of nonsclerotic glomeruli
cg3	Double contours affecting more than 50% of peripheral capillary loops in the most affected of nonsclerotic glomeruli

Tubulitis score

T0	No mononuclear cells in tubules
T1	Foci with 1 to 4 cells/tubular cross section (or 10 tubular cells)
T2	Foci with 5 to 10 cells/tubular cross section
T3	Foci with > 10 cells/tubular cross section, or the presence of at least two areas of tubular basement membrane destruction accompanied by i2/i3 inflammation and t2 tubulitis elsewhere in the biopsy

Intimal arteritis score

V0	No arteritis
V1	Mild-to-moderate intimal arteritis in at least one arterial cross section
V2	Severe intimal arteritis with at least 25% luminal area lost in at least arterial cross section
V3	Transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel

Classification of peritubular capillaritis (PTC)

ptc0	No significant cortical ptc, or <10% of PTCs with inflammation
ptc1	≥ 10% of cortical peritubular capillaries with capillaritis, with max 3 to 4 luminal inflammatory cells
ptc2	≥ 10% of cortical peritubular capillaries with capillaritis, with max 5 to 10 luminal inflammatory cells
ptc3	≥ 10% of cortical peritubular capillaries with capillaritis, with > 10 luminal inflammatory cells

one comment on the composition (mononuclear cells vs. neutrophils) and extent (focal, ≤50% vs. diffuse, >50%) of peritubular capillaritis is recommended

Interstitial Inflammation score

i0	No or trivial interstitial inflammation
i1	10 to 25% of parenchyma inflamed
i2	26 to 50% of parenchyma inflamed
i3	More than 50% of parenchyma inflamed

Appendix 3 Scales and Assessments

The following scale/assessment will be utilized in this study:

Full Title of Scale/Assessment	Version Number	Date Issued
EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L)	2009	25 March 2015

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.

Appendix 4 Recommended Procedures for Suspected Thrombotic or Thromboembolic Events