# CLINICAL STUDY PROTOCOL
# SUBSTANTIAL STUDY PROTOCOL AMENDMENT NO. 3

## A Double-blind, Randomized-withdrawal, Placebo-controlled Study to Evaluate the Efficacy and Safety of Human Plasma-derived C1-esterase Inhibitor as Add-on to Standard of Care for the Treatment of Refractory Antibody Mediated Rejection in Adult Renal Transplant Recipients

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| **Study Number:** | CSL842_3001 |
| **Study Product:** | C1-esterase Inhibitor, Human (500 IU/mL) |
| **Development Phase:** | Phase 3 |
| **Sponsor:** | CSL Behring LLC<br>1020 First Avenue<br>King of Prussia, PA 19406<br>United States |
| **EudraCT Number:** | 2017-000348-17 |
| **Protocol Version:** | Amendment 3 |
| **Protocol Date:** | 31 Jan 2020 |
| **Compliance:** | This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations. |

# List of Personnel and Organizations Responsible for Conduct of the Study

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator's Study File. This list will be updated by CSL (or delegate) and provided to the study sites as needed.

# Revision History

| Date | Version | Summary of Significant Changes |
|---|---|---|
| 01 March 2017 | Original | Not applicable |
| 27 June 2017 | Country-specific Amendment 1 (United Kingdom) | 1. Addition of pregnancy testing monthly during the Treatment Period 1 and Treatment Period 2, and Retreatment Period.<br>2. Section 6.1.3.2, clarification of unblinding procedure. |
| 28 November 2017 | Substantial Amendment 1 | 1. A Non-responder Follow-up Period is added for subjects who are non-responders after Treatment Period 1. These subjects will be followed until graft failure or up to 48 months after enrollment. Statistical analyses are amended to reflect this change.<br>2. Pregnancy tests are added at monthly intervals.<br>3. Additional timepoints are added for C1-esterase inhibitor activity/antigen and collection of retention samples in Treatment Period 1.<br>4. Administration of IVIg is tailored to current standard of care practice and may be given when DSA is ≥ 2000 MFI during Treatment Period 2 and the Retreatment Period.<br>5. A provision is added to enroll up to 136 subjects in Treatment Period 1.<br>6. Exclusion criterion 3 is deleted, ie, subjects with evidence of chronic changes on biopsy (interstitial fibrosis [ci], arterial fibrointimal, arterial hyalinosis [ah], or chronic glomerulopathy [cg] scores of 3), ongoing dialysis, active infection, coagulopathy disorder, or hepatobiliary disease are now permitted to participate in the study. |

| Date | Version | Summary of Significant Changes |
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| 28 November 2017 | Substantial Amendment 1 (continued) | 7. Inclusion criterion 5 is amended to add that subjects must achieve steady-state eGFR within 60 days post-transplant, and that subjects with slow or delayed graft function must have a 50% increase in urine output with a 50% decrease in serum creatinine 7 days post-transplant.<br>8. Exclusion criterion 4a (previously 5a) amended to include HBV as part of the viral hepatitis criterion. The criterion now includes instructions for confirmed HCV or HBV, ie subjects must be receiving or have received antiviral therapy and have no history of cirrhosis.<br>9. New exclusion criterion 5 includes a history of HIV as collected in medical history at Screening<br>10. Procedures for breaking the blind are clarified.<br>11. Dry body weight measured at Screening is changed to body weight and date of biopsy is added to medical history.<br>12. The criteria used to determine frequency of blood draws for creatinine measurement is changed from an increase of 20% to 10% above the previous value in Treatment Period 2.<br>13. Secondary endpoints are clarified to reduce redundancy.<br>14. The statistical plan is revised to address the change to the study design.<br>15. Study durations are changed from years to months<br>16. Virus testing is clarified.<br>17. Language on Banff criteria for AMR diagnosis is clarified and made consistent throughout the protocol.<br>18. Baseline eGFR is clarified.<br>19. Blood sample collection and recording is clarified.<br>20. Banff Scoring System is updated in Appendix 3. |
| 23 January 2019 | Substantial Amendment 2 | 1. Plasmapheresis is no longer mandatory if DSA is ≥ 5000 MFI<br>• Plasmapheresis should be performed if a subject has DSA with clinical significance based on the investigator's medical judgement<br>2. Dosing at Week 13 is clarified<br>• The dose administered at the Week 13 visit will be the first dose of Treatment Period 2 for responders (ie blinded)<br>• The 2nd dose at Week 12 is the final open label dose for Treatment Period 1 for both responders and non-responders |

| Date | Version | Summary of Significant Changes |
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| | Substantial Amendment 2 (continued) | 3. The first dose of IVIg will occur on Week 4 if the subject received high dose IVIg within 4 weeks of Study Day 1 as standard of care.<br>4. Mean corpuscular hemoglobin concentration and mean corpuscular volume are not required safety assessments but can be collected if available.<br>5. Week 13 visit is clarified as the end of Treatment Period 1 for nonresponders and start of Treatment Period 2 for responders.<br>6. The order of Visit 13 assessment is changed to align with the end of Treatment Period 1 assessments verses start of Treatment Period 2 assessments and a header is added to highlight the Treatment Period 1 early withdrawal assessments. |
| 31 January 2020 | Substantial Amendment 3 | 1. The responder definition is revised.<br>2. Definition of loss-of-response is changed.<br>3. The primary endpoint is changed from time to loss-of-response to loss-of-response status (binary yes / no).<br>4. The secondary endpoints are revised.<br>5. The number of planned subjects and sites are increased.<br>6. A schedule of assessments is added for the Non-responder Follow-up Period.<br>7. Development of recurrent or persistent AMR is added as an efficacy assessment.<br>8. Timing for collecting serum creatinine is amended.<br>9. Monitoring of kidney function is added during the Responder Follow-up Period.<br>10. Potential risks and benefits are updated based on the most recent periodic reports and Investigator Brochure updates.<br>11. CCI [redacted]<br>12. Study design rationale is revised to support changes to the primary endpoint.<br>13. Inclusion criteria 5, 6, and 7 are amended.<br>14. Exclusion criterion 8 is amended.<br>15. Dosing of C1-INH and placebo based on body weight is clarified.<br>16. Shipping of investigational product to subjects is added<br>17. Diagnosis of AMR based on inclusion biopsy is clarified.<br>18. Measured eGFR timing is clarified.<br>19. Re-screening after screen failure instructions are amended. |

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| | | 20. Assessment of biopsy-confirmed AMR is added during the Responder Follow-up Period.<br>21. Assessments during the Non-responder Follow-up Period are amended.<br>22. The adverse event observation period is amended.<br>23. Statistical analyses are amended to support changes implemented by Amendment 3.<br>24. New literature references are added. |

# Protocol Synopsis

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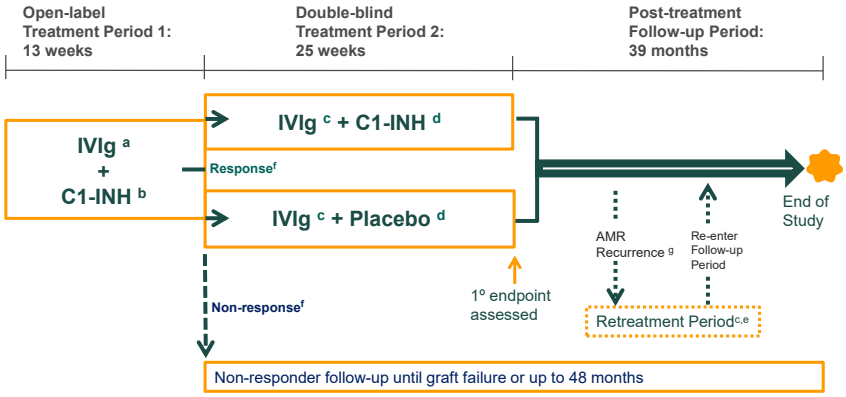
| **Title** | A Double-blind, Randomized-Withdrawal, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Human Plasma-derived C1-esterase Inhibitor as Add-on to Standard of Care for the Treatment of Refractory Antibody Mediated Rejection in Adult Renal Transplant Recipients |
| **Study Number** | CSL842_3001 |
| **Sponsor** | CSL Behring LLC (CSL) |
| **Development Phase** | Phase 3 |
| **Study Product** | C1-esterase Inhibitor, Human (500 IU/mL); throughout the protocol, the study product will be abbreviated as C1-INH. |
| **Indication** | Chronic treatment of refractory antibody-mediated rejection (AMR) in adult kidney transplant recipients in combination with intravenous immunoglobulin (IVIg) containing regimens. |
| **Study Summary and Overview** | This is a double-blind, randomized-withdrawal, placebo-controlled study consisting of 2 treatment periods, a Responder Follow-up Period and Retreatment Period(s) (if needed).<br><br>Eligible subjects will enter into the open-label Treatment Period 1 (TP1), during which all subjects will receive C1-INH. Subjects who respond to treatment with C1-INH by Week 12 as assessed by pre-defined responder criteria will be randomized into Treatment Period 2 (TP2) of the study; those subjects who do not respond to treatment will enter a Non-responder Follow-up Period (up to 48 months). Subjects who are responders will be randomized to receive either C1-INH or placebo during TP2. All subjects will receive standard of care throughout TP1 and TP2 (IVIg 2 grams/kg once every 4 weeks in TP1 and at investigator discretion in TP2; plasmapheresis, as needed in TP1 and TP2). At the End-of-TP2 at Week 38, subjects will then enter a 39-month Responder Follow-up Period. Subjects will receive treatment consistent with their local standard of care during the Responder Follow-up Period, and their allograft status, kidney function, and survival will be monitored.<br><br>During the Responder Follow-up Period, subjects with biopsy proven AMR (recurrent or persistent disease) may receive retreatment with blinded investigational product (in combination with standard of care) as a part of the Retreatment Period.<br><br>An illustrated overview of the study is presented on the next page. |

**Study Overview:**




AMR = antibody-mediated rejection; C1-INH = C1-esterase inhibitor, human; DSA = donor-specific antibody; eGFR = estimated glomerular filtration rate; IV = intravenous; IVIg = intravenous immunoglobulin; TP1 = Treatment Period 1; TP2 = Treatment Period 2

Note: Post-treatment Follow-up Period is for responders.

[a] Intravenous immunoglobulin (IVIg) will be administered every 4 weeks to all subjects at a dose of 2 grams/kg. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days. Plasmapheresis may be administered based on local DSA results and Principal Investigator's judgement.

[b] Intravenous C1-INH (60 IU/kg) will be administered to each subject over the first 13 days of TP1 for a total of 5 doses. Thereafter, subcutaneous C1-INH (60 IU/kg twice weekly) will be administered to each subject for the remainder of TP1.

[c] If DSA ≥ 2000 MFI in local lab in TP2 or Retreatment Period, IVIg may be administered to subjects at a dose of 2 grams/kg every 4 weeks. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days. Plasmapheresis may be administered based on local DSA results and Principal Investigator's judgement.

[d] During the TP2, eligible subjects will be randomized 1:1 to receive treatment with investigational product (C1-INH [60 IU/kg]) or placebo] subcutaneously twice weekly.

[e] Retreatment period(s) are blinded and subjects will receive the same investigational product treatment assignment as received during TP2.

[f] Response is defined as an End-of-TP1 eGFR (mean of Week 11 and Week 12 eGFR) that is ≥ 20 mL/min/1.73 $m^2$ and ≥ 90% of the baseline eGFR (mean of Screening and the Day 1 eGFR) (Section 10.3.1).

[g] AMR Recurrence or persistence in Follow-up Period is proven by biopsy, evidenced by infiltrating neutrophils and/or monocytes with or without the presence of C4d (g > 0, v > 0, and/or ptc > 0; if C4d is negative, g + ptc ≥ 2 (Section 8.1.3.3).

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| **Primary Objective** | The primary objective of the study is to evaluate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients. |
| **Primary Endpoint** | Proportion of subjects with loss-of-response at the End-of-TP2. Loss-of-response is defined as any 1 of the following 3 conditions:<br>• End-of-TP2 glomerular filtration rate (eGFR) (mean of Week 36 and Week 38 eGFR) that is not stable, defined as:<br>  ○ End-of-TP2 eGFR that is < 90% of the End-of-TP1 eGFR for subjects whose End-of-TP1 eGFR (mean of Week 11 and Week 12 eGFR) is ≥ 100% of baseline;<br>  ○ End-of-TP2 eGFR that is < 90% of baseline for subjects whose End-of-TP1 eGFR is ≥ 90% of baseline and < 100% of baseline |

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| | • Allograft failure (defined by allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first)<br>• Subject death by any cause. |
| **Secondary Objectives** | The secondary objectives of the study are:<br>1. To further evaluate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients.<br>2. To evaluate the safety of C1-INH in the treatment of refractory AMR in renal allograft recipients.<br>3. To evaluate the pharmacokinetics of C1-INH during the treatment of refractory AMR in renal allograft recipients. |
| **Secondary Endpoints** | • Proportion of subjects with all-cause allograft failure status through the Responder Follow-up Period (ie, within 48 months after enrollment). Allograft failure is defined as 1 of the following:<br>o Allograft nephrectomy, institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first, OR<br>o Subject death by any cause.<br>• The difference in eGFR from the End-of-TP1 eGFR and baseline eGFR.<br>• The difference between the End-of-TP2 eGFR and the End-of-TP1 eGFR.<br>• The rate of change of eGFR during TP2, ie, the slope of the mean regression line in TP2.<br>• Time (weeks) to all-cause allograft failure through the Responder Follow-up Period (within 48 months after enrollment).<br>• Proportion of responders at the End-of-TP1. Response is defined as an End-of-TP1 eGFR that is ≥ 20 mL/min/1.73 $m^2$ and ≥ 90% of the baseline eGFR.<br>• Proportion of subjects surviving through the Responder Follow-up Period.<br>• Proportion of subjects with any adverse event assessed as related to investigational product.<br>• Mean pre-dose C1-esterase inhibitor functional activity at Day 1, Week 12, and Week 38.<br>• C1-esterase inhibitor functional activity $C_{max}$ and $AUC_{0-t}$ for IV and SC administration. |
| **Number of Subjects** | Approximately 120 subjects (and up to 175) are planned to participate in the open-label TP1 in order to randomize 60 subjects into the double-blind TP2. |
| **Study Duration** | The duration of the study for an individual subject is expected to be approximately 210 weeks, or 48 months). This estimation is based on:<br>• A 2-week Screening Period.<br>• A 13-week Open-label Treatment Period (TP1).<br>• A 25-week Double-blind Treatment Period (TP2).<br>• Follow-up Periods: |

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| | ○ 39-month (170 weeks) Responder Follow-up Period (up to 48 months following enrollment), or<br>○ 45-month Non-responder Follow-up period (up to 48 months following enrollment).<br><br>The overall study duration (ie, first subject's Screening Visit to last subject's final study visit) is anticipated to be approximately 6 years. |
| **Study Population and Main Criteria for Eligibility** | Adult renal allograft recipients with biopsy confirmed acute antibody-mediated rejection as defined by Banff 2015 criteria that is clinically unresponsive to an IVIg-containing regimen given as standard of care. |
| **Investigational Product Dose, Dosing Regimen, and Administration** | C1-esterase inhibitor is a lyophilized powder (1500 IU C1-INH per single-use vial) reconstituted with 3 mL water for injection. After reconstitution, C1-INH is available at a concentration of 500 IU/mL.<br><br>The comparator product, placebo, which contains the excipients of C1-INH plus albumin, will be reconstituted with 3 mL water for injection.<br><br>The terminology 'Investigational Product' is inclusive of both C1-INH and placebo. |

| Timeframe | Intravenous Administration | Subcutaneous Administration |
|---|---|---|
| **Treatment Period 1:** [a] The Day 1 Visit to the Day 13 Visit | 60 IU/kg C1-INH | Not applicable |
| **Treatment Period 1:** [a] The Day 14 Visit to the Week 12 2nd dose | Not Applicable | 60 IU/kg C1-INH |
| **Treatment Period 2:** [b] Week 13 to the Week 38 Visit | Not Applicable | 60 IU/kg C1-INH<br>OR<br>0.12 mL/kg placebo |
| **Retreatment Period:** [c] The Retreatment Day 1 Visit to the Retreatment Week 26 Visit | Not Applicable | 60 IU/kg C1-INH<br>OR<br>0.12 mL/kg placebo |

[a] Treatment Period 1 is open-label and all subjects will receive C1-INH. C1-INH (60 IU/kg) will be administered IV to each subject over the first 13 days of Treatment Period 1 for a total of 5 doses. Thereafter, C1-INH (60 IU/kg twice weekly) will be administered SC to each subject for the remainder of Treatment Period 1.

[b] Treatment Period 2 is blinded and subjects will be randomized 1:1 to treatment with investigational product (C1-INH [60 IU/kg] or placebo) subcutaneously twice weekly.

[c] Retreatment Period(s) are blinded and subjects will receive the same investigational product treatment assignment subcutaneously as received during Treatment Period 2.

Note: Week 13 is the final visit of Treatment Period 1 for non-responders and the first visit of Treatment Period 2 for responders.

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| **Efficacy Assessments** | Efficacy assessments conducted during the study will include:<br>• eGFR.<br>• Responder status (ie, response/loss-of-response).<br>• Biopsy histopathology.<br>• Splenectomy.<br>• Donor-specific antibodies (DSA).<br>• CCI [redacted]<br>• Allograft failure.<br>• Subject survival.<br>• CCI [redacted]<br>• Development of recurrent or persistent AMR |
| **Safety Assessments** | Safety assessments conducted during the study will include:<br>• Physical examination.<br>• Vital signs.<br>• Adverse events.<br>• Hematology.<br>• Serum biochemistry, including creatinine.<br>• Immunogenicity to C1-INH.<br>• Virus testing.<br>• Pregnancy test. |
| **Pharmacokinetics** | Blood samples will be taken for the assessment of C1-esterase inhibitor functional activity, C1-esterase inhibitor antigen concentrations, and immunoglobulin concentrations. |
| CCI [redacted] | CCI [redacted] |
| **Other Assessments** | The EQ-5D-3L health-related quality of life questionnaire will be administered to subjects who participate in the study. |
| **Statistical Analyses** | Determination of the sample size is based on the following assumptions:<br>• The proportions of subjects experiencing loss-of-response at the End-of-TP2 will be 0.75 with placebo and 0.30 with C1-INH.<br>• There will be at least 90% power to detect a statistically significant effect with two-sided test with alpha = 0.05.<br>• Logistic regression model with treatment effect will be used for the primary efficacy analysis. Wald test statistic for treatment effect from Logistic regression has approximately same distribution as chi-square [Fleiss et al, 2003]. Therefore, the sample size calculation based on chi-square test is used to ensure similar power for hypothesis testing.<br>• Treatment allocation will be 1:1.<br>• The planned interim analysis for futility will not impact the type 1 error for the final analysis.<br>Under these assumptions, a total of 60 subjects (30 randomized to C1-INH and 30 randomized to placebo) will provide approximately 95% power. The study will |

enroll a sufficient number of subjects to ensure that 60 subjects are randomized.

The primary analysis of the primary efficacy endpoint of loss-of-response status at the End-of-TP2 will be based on the proportion of subjects with loss-of-response between the randomized treatment groups (C1-INH or placebo) using a logistic regression model.

The key secondary efficacy endpoint of all-cause allograft failure at the end of 48 months after enrollment will be analyzed between the randomized treatment groups (C1-INH or placebo) using a logistic regression model.

All efficacy analyses will be conducted based on the Modified Intent-to-Treat analysis set. Sensitivity analyses for efficacy endpoints will be based on the Intent-to-Treat analysis set.

Safety will be analyzed for all subjects who receive at least 1 dose of the investigational product. The extent of exposure to open-label C1-INH, and to double-blind C1-INH or placebo will be summarized using descriptive statistics. Treatment-emergent adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Clinical laboratory parameters will be summarized using descriptive statistics, or frequency counts and percentages.

## Table 1 Schedule of Assessments: Screening and Open-label Treatment Period 1

| Study Period | Screening | Treatment Period 1 (Open-label) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Visit | Screening | | | | | | | | | | | | | | | | | EoTP1 [a] |
| Study Week | - 2 to 0 | 1 | | | 2 | | | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| Study Day | -14 to 1 | 1 [b] | 4 | 7 | 10 | 13 | 14 | 21 | 28 | 35 | 42 | 49 | 56 | 63 | 70 | 77 | 84 | 91 |
| Window in Days | | | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 |
| Informed Consent/IRT Registration | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | | | | |
| Demographics/Medical History [c] | X | | | | | | | | | | | | | | | | | |
| Physical Examination [d] | X | X | | X | | | X | | X | | | | X | | | | | X |
| Vital Signs [e] | X | X | | X | | | X | | X | | | | X | | | | | X |
| Blood Draws: Pregnancy Test [f] | X | X | | | | | | | X | | | | X | | | | X | |
| Blood Draws: HBV /HCV | X | | | | | | | | | | | | | | | | | |
| Blood Draws: Retention Sample [g] | X | | | | | | | | | | | | | | | | X[a] | |
| Blood Draws: Creatinine [CL] [h] | X | X | | X | | | X | X | X | X | X | X | X | X | X | X | X [a] | |
| Blood Draws: Serum Biochemistry Panel [h] | X | X | | X | | | X | X | X | X | X | X | X | X | X | X | X [a] | |
| Blood Draws: Hematology | X | X | | X | | | X | | | | | | | | | | X [a] | |
| Blood Draws: CCI and DSA [i] | | X | | | | | | | X | | | | X | | | | X [a] | |
| Blood Draws: C1-esterase Inhibitor Activity/Antigen | | X | X | X | X | | X | | X | | | | X | | X | | X [a] | |
| Blood Draws: Immunoglobulin Concentration | | X | | | | | | | X | | | | X | | | | X [a] | |
| CCI | | | | | | | | | | | | | | | | | | |
| Blood Draws: PK CCI Sampling Subset [j] | | | | | X | | | | | | | | | | | X | | |
| Blood Draws: Antibodies to C1-esterase Inhibitor | | X | | | | | | | | | | | | | | | CCI | |
| Intravenous C1-INH [k] | | X | X | X | X | X | | | | | | | | | | | | |
| Subcutaneous C1-INH [l] | | | | | | | ← | | | | | | | | | | → | |
| Intravenous Immunoglobulin (IVIg) [m] | | X | | | | | | | X | | | | X | | | | X | |
| CCI | | | | | | | | | | | | | | | | | | |
| Responder Status/Randomization [o] | | | | | | | | | | | | | | | | | | X |
| EQ-5D-3L Questionnaire | | X | | | | | | | | | | | | | | | X | |
| Dispense C1-INH [p] | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X |
| Subjects Return Used C1-INH [q] | | | | | | | | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events | ← | | | | | | | | | | | | | | | | | → |
| Prior/Concomitant Therapies | ← | | | | | | | | | | | | | | | | | → |

C1-INH = C1-esterase Inhibitor, Human (500 IU/mL); [CL] = central laboratory; DSA = donor-specific antibodies; eCRF = electronic case report form; EoTP1 = End of Treatment Period 1; eCRF = electronic case report form; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; IRT = interactive response

technology; IVIg = intravenous immunoglobulin; MFI = mean fluorescence intensity; CCI [redacted]; PK = pharmacokinetic; TP1 = Treatment Period 1; TP2 = Treatment Period 2.

**Note:** All procedures should be completed before the administration of C1-INH, except for the administration of IVIg, unless otherwise noted.

**Footnotes to the Schedule of Assessments (Screening and Treatment Period 1):**

[a] If a subject is withdrawn/discontinued from the study for any reason during Treatment Period 1, then the investigator should make every effort to perform the assessments scheduled for the Week 13 Visit, in addition to selected blood draws (see Section 8.5.3.14). In addition, investigators should also contact these subjects by telephone approximately 30 days after the End-of-TP1 Visit to collect follow-up safety information. Screening and Day 1 assessments can occur on the same day. Note: Week 13 is the End-of-TP1 for non-responders and the start of TP2 for responders.

[b] All procedures scheduled for the Day 1 Visit should be completed before the first doses of C1-INH and IVIg are administered.

[c] Medical history will include documentation of date of biopsy, creatinine at time of inclusion biopsy, thrombotic microangiopathy and the Banff category scores (Appendix 3) from the pre-enrollment kidney biopsy that was used to qualify for participation.

[d] A physical examination will be conducted per the investigator's standard procedure, and will also include assessment of unilateral pain and/or swelling of the lower extremities for the purpose of screening for deep vein thrombosis.

[e] Vital signs assessments will include blood pressure, pulse rate, body temperature, and body weight (used to determine the volume of C1-INH to be administered). Height will also be measured at Screening (only).

[f] A pregnancy test will be conducted for women of childbearing potential, only. Serum pregnancy test will be conducted at Screening and Week 12. Urine or serum pregnancy tests will be conducted at all other timepoints. If the screening pregnancy test is conducted within 24 hours of Day 1, then an additional pregnancy test is not needed on Day 1.

[g] A blood sample will be retained for potential future serology assessments.

[h] Creatinine will be measured by the central laboratory ([CL]) and as a part of the serum biochemistry panel by the local laboratory. The complete list of assessments included as a part of the biochemistry panel is presented in Table 13.

[i] Donor-specific antibodies will be measured in both the central and local laboratories. Central laboratory results will be used for analyses. Local laboratory results will be used by the investigator to make treatment decisions, including the initiation of plasmapheresis. Donor-specific antibodies should be tested in the local laboratory within between 24 and 72 hours after completing plasmapheresis.

[j] Sequential PK CCI [redacted] sampling from a subset of subjects will occur on the Day 10 and Week 11 Visits. See Table 6 for additional details.

[k] Intravenous C1-INH will be administered at a dose of 60 IU/kg at the study site. Intravenous C1-INH should be administered with a minimum of 48 hours between each dose.

[l] Subcutaneous C1-INH will be administered at a dose of 60 IU/kg every 3 or 4 days (ie, twice weekly) at the study site, at home by a medical professional, or at home by the subject under the supervision of a medical professional. The first dose of subcutaneous C1-INH should be administered between 24 and 48 hours after the last dose of intravenous C1-INH.

[m] Intravenous immunoglobulin will be administered at a dose of 2 grams/kg. Administration of the dose will begin at the visit. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days (see Section 5.4.1 for details).

[n] CCI [redacted]

[o] Responders will be randomized to treatment with blinded investigational product during Treatment Period 2. The definition of response is provided in Section 10.3.1. Non-responders will enter a 45-month Non-responder Follow-up Period.

[p] If investigational product will be administered off-site after the completion of the visit, then it will be dispensed to the subject. Only subjects who are randomized may receive blinded investigational product at the Week 13 Visit.

[q] Throughout Treatment Period 1, subjects will return any used or partially used vials of C1-INH. Subjects should then return all vials (ie, used, partially used, and unused) of C1-INH at the Week 13 Visit.

## Table 2 Schedule of Assessments: Blinded Treatment Period 2

| | Study Period | Treatment Period 2 (Blinded) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Study Visit | Non-visit weeks | | | | | | | EoTP2 [a] |
| | Study Week | 14 | 15 | 16 | 20 | 24 | 28 | 32 | 38 |
| | Study Day | | | 112 | 140 | 168 | 196 | 224 | 266 |
| | Window in Days | | | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 |
| Physical Examination [b] | | | | | | X | | | X |
| Vital Signs [c] | | | | | | X | | | X |
| Blood Draws | Creatinine [CL] [d] | ← | | | | | | | → |
| | Serum Biochemistry [d, e] | | | | X | | X | | X |
| | Hematology | | | | X | | X | | X |
| | CCI and DSA [f] | | | X | X | X | X | X | X |
| | Pregnancy Test [g] | | | X | X | X | X | X | X |
| | Retention Sample [h] | | | | | | | | X |
| | C1-esterase Inhibitor Activity/Antigen | | | X | | | | X | X |
| | Immunoglobulin Concentration | | | | | | | X | |
| | CCI | | | | | | | | |
| | Antibodies to C1-esterase Inhibitor | | | | | | | | X |
| Subcutaneous Investigational Product [i] | | ← | | → | | | | | |
| Intravenous Immunoglobulin (IVIg) [j] | | | | X | X | X | X | X | |
| CCI | | | | | | | | | |
| Kidney Allograft Biopsy | | | | | | | | | X |
| EQ-5D-3L Questionnaire | | | | | | | | | X |
| Dispense Investigational Product [l] | | | | X | X | X | X | X | |
| Subjects Return Used Investigational Product [m] | | | | X | X | X | X | X | X |
| Adverse Events | | ← | | → | | | | | |
| Concomitant Therapies | | ← | | → | | | | | |

C1-INH = C1-esterase Inhibitor, Human (500 IU/mL); [CL] = central laboratory; DSA = donor-specific antibodies; eCRF = electronic case report form; EoTP2 = End of Treatment Period 2; GFR = glomerular filtration rate; IVIg = intravenous immunoglobulin; MFI = mean fluorescence intensity; CCI ; PK = pharmacokinetic.

**Note 1:** All procedures should be completed before the administration of C1-INH, except for the administration of IVIg, unless otherwise noted.

**Note 2:** Between the Week 13 Visit and the Week 16 Visit, each subject who is eligible to participate in Treatment Period 2 will administer investigational product (C1-INH or placebo) as per the randomization schedule (Footnote I, below) and will have blood drawn for creatinine measurement (Footnote D, below).

**Footnotes to the Schedule of Assessments (Treatment Period 2):**

[a] If a subject is withdrawn from the study for any reason during Treatment Period 2, then the investigator should make every effort to perform the assessments scheduled for the Week 38 Visit. In addition, investigators should contact these subjects by telephone approximately 30 days after the Week 38 Visit (ie, the End of Treatment Period 2 Visit) to collect follow-up safety information.

[b] A physical examination will be conducted per the investigator's standard procedure, and will also include assessment of unilateral pain and/or swelling of the lower extremities for the purpose of screening for deep vein thrombosis.

[c] Vital signs assessments will include blood pressure, pulse rate, body temperature, and body weight.

[d] Beginning during Treatment Period 2, a blood sample for creatinine measurement at the central laboratory [CL] will be drawn once every 14 days (± 7 days) at the study site or at home by a medical professional. Blood draws for creatinine measurements may occur more frequently at the investigator's discretion.

[e] The biochemistry panel includes assessment of creatinine; the complete list of assessments included as a part of the biochemistry panel is presented in Table 13.

[f] Donor-specific antibodies will be measured in both the central and local laboratories. Central laboratory results will be used for analyses. Local laboratory results will be used by the investigator to make treatment decisions, including the initiation of IVIg and plasmapheresis. Additional blood draws for assessment of DSA will occur after plasmapheresis, as described in Section 5.4.2.

[g] A pregnancy test will be conducted for women of childbearing potential, only. Serum pregnancy test will be conducted at Week 16 and EoTP2. Urine or serum pregnancy tests will be conducted at all other timepoints.

[h] A blood sample will be retained for potential future serology assessments.

[i] Throughout Treatment Period 2, subcutaneous investigational product (C1-INH or placebo) will be administered as per the randomization schedule every 3 or 4 days (ie, twice weekly) at the study site, at home by a medical professional, or by the subject under the supervision of a medical professional. The first dose of randomized investigational product will be administered at the week 13 visit.

[j] If DSA ≥ 2000 MFI, intravenous immunoglobulin may be administered at a dose of 2 grams/kg. Administration of the dose will begin at the visit. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days.

[k] CCI .

[l] If investigational product will be administered off-site after the completion of the visit, then it will be dispensed to the subject.

[m] Throughout Treatment Period 2, subjects should return any used or partially used vials of investigational product. Subjects should then return all vials (ie, used, partially used, and unused) of investigational product at the Week 38 Visit.

## Table 3 Schedule of Assessments: Responder Follow-up Period

| | Study Period | Responder Follow-up Period | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Study Visit | [redacted] | | | | | | EoS [a] |
| | Study Month | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
| | Study Week | 52 | 78 | 104 | 130 | 156 | 182 | 208 |
| | Window in Days | ± 28 | ± 28 | ± 28 | ± 28 | ± 28 | ± 28 | ± 28 |
| Blood Draws | Creatinine [CL] [b] | X | X | X | X | X | X | X |
| | Antibodies to C1-esterase Inhibitor | CCI [redacted] | | | | | | |
| | C1-esterase Inhibitor Activity/Antigen | X | | | | | | |
| | CCI [redacted] | | | | | | | |
| Biopsy-confirmed AMR (yes/no)[c] | | X | X | X | X | X | X | X |
| EQ-5D-3L Questionnaire | | X | | X | | X | | X |
| Allograft Failure [d] | | X | X | X | X | X | X | X |
| Subject Survival | | X | X | X | X | X | X | X |

AMR = antibody-mediated rejection; [CL] = central laboratory; eCRF = electronic case report form; EoS = End of Study; CCI [redacted].

**Note:** Assessment of DSA and/or allograft biopsy will be conducted as per local standard of care.

**Footnotes to the Schedule of Assessments (Responder Follow-up Period):**

[a] If a subject is withdrawn from the study for any reason during the Follow-up Period, then the investigator should make every effort to perform the assessments scheduled for the Month 48 Visit.

[b] Creatinine will be measured by the central laboratory.

[c] Occurrence of biopsy-confirmed AMR (Section 8.1.3.3) since the last visit, based on documentation in the subject's medical record. Responses will be recorded in the eCRF.

[d] The definition of allograft failure is presented in Section 8.1.3.7.

## Table 4 Schedule of Assessments: Non-responder Follow-up Period

| Study Period | Non-responder Follow-up Period | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Study Visit | | | | | | | | EoS [a] |
| Study Month | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
| Window in Days | ± 28 | ± 28 | ± 28 | ± 28 | ± 28 | ± 28 | ± 28 | ± 28 |
| Creatinine [CL] [b] | X | X | X | X | X | X | X | X |
| Biopsy-confirmed AMR (yes/no)[c] | X | X | X | X | X | X | X | X |
| EQ-5D-3L Questionnaire | | X | | X | | X | | X |
| Allograft Failure [d] | X | X | X | X | X | X | X | X |
| Subject Survival | X | X | X | X | X | X | X | X |

AMR = antibody-mediated rejection; [CL] = central laboratory; DSA = donor-specific antibodies; eCRF = electronic case report form; EoS = End of Study.

**Note 1:** Assessment of DSA and/or allograft biopsy will be conducted as per local standard of care.

**Note 2:** Data for subjects entering the Non-responder Follow-up period prior to Amendment 3 can be collected from medical history within 60 days of study entry. Data for subjects who enter after Amendment 3 will be collected prospectively.

**Footnotes to the Schedule of Assessments (Non-responder Follow-up Period):**

[a] If a subject is withdrawn from the study for any reason during the Non-responder Follow-up Period, then the investigator should make every effort to perform the assessments scheduled for the Month 48 Visit.

[b] Creatinine will be measured by the central laboratory for prospectively collected samples from subjects who enter the Non-responder Follow-up Period after Amendment 3. Creatinine values may be obtained retrospectively from medical records if samples cannot be drawn prospectively.

[c] Occurrence of biopsy-confirmed AMR (Section 8.1.3.3) since the last visit, based on documentation in the subject's medical record. Responses will be recorded in the eCRF.

[d] The definition of allograft failure is presented in Section 8.1.3.7.

## Table 5 Schedule of Assessments: Blinded Retreatment Period

| Study Period | | Retreatment Period (Blinded) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Study Visit | | | | | | | | | EoRP [a] |
| Retreatment Week | | 1 | | 4 | 8 | 12 | 16 | 22 | 26 |
| Retreatment Day | | 1 | 7 | 28 | 56 | 84 | 112 | 154 | 182 |
| Window in Days | | | ± 2 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 | ± 7 |
| Physical Examination [b] | | X | | | | X | | | X |
| Vital Signs | | X | | | | X | | | X |
| Blood Draws | Pregnancy Test[c] | X | | X | X | X | X | X | X |
| | Retention Sample [d] | X | | | | | | | X |
| | Creatinine [CL] [e] | X | X | X | X | X | X | X | X |
| Subcutaneous Investigational Product [f] | | ← | | | | | | | → |
| Intravenous Immunoglobulin (IVIg) [g] | | X | | X | X | X | X | X | |
| Dispense Investigational Product [h] | | X | X | X | X | X | X | X | |
| Subjects Return Used Investigational Product [i] | | | X | X | X | X | X | X | X |
| Adverse Events | | ← | | | | | | | → |
| Concomitant Therapies | | ← | | | | | | | → |

AMR = antibody-mediated rejection; C1-INH = C1-esterase Inhibitor, Human (500 IU/mL); [CL] = central laboratory; DSA = donor-specific antibodies; EoRP = End of Retreatment Period; GFR = glomerular filtration rate; IVIg = intravenous immunoglobulin; MFI = mean fluorescence intensity.

**Note 1:** Subjects may undergo retreatment during the Responder Follow-up Period with the blinded investigational product in Treatment Period 2. Retreatment may occur following a diagnosis of recurrent or persistent AMR by biopsy, evidenced by infiltrating neutrophils and/or monocytes with or without the presence of C4d ($g > 0$, $v > 0$, and/or $ptc > 0$; if C4d is negative, $g + ptc \geq 2$ ). Retreatment may start at any time during the Responder Follow-up Period, and will last for 25 weeks or until the Month 48 Visit, whichever occurs first. The Retreatment Period may also be shorter than 25 weeks at the investigator's discretion. Following blinded retreatment, subjects will enter the Responder Follow-up Period.

**Note 2:** All procedures conducted during a Retreatment Period should be completed before the administration of C1-INH, except for the administration of IVIg, unless otherwise noted.

**Note 3:** Assessment of DSA will be conducted as per local standard of care.

**Footnotes to the Schedule of Assessments (Retreatment Period):**

[a] If a subject is withdrawn from the study for any reason during a Retreatment Period, then the investigator should make every effort to perform the assessments scheduled for the Retreatment Week 26 Visit. In addition, investigators should contact these subjects by telephone approximately 30 days after the Retreatment Week 26 Visit (the End of Retreatment Period Visit) to collect follow-up safety information.

[b] A physical examination will be conducted per the investigator's standard procedure, and will also include assessment of unilateral pain and/or swelling of the lower extremities for the purpose of screening for deep vein thrombosis.

[c] Serum pregnancy tests will be conducted at Retreatment Day 1 and Week 26 (EoRP). Urine or serum pregnancy tests should be conducted at all other timepoints.

[d] A blood sample will be retained for potential future serology assessments.

[e] Creatinine will be measured by the central laboratory.

[f] Subcutaneous investigational product (C1-INH or placebo) will be administered as per the randomization schedule every 3 or 4 days (ie, twice weekly) at the study site, at home by a medical professional, or by the subject under the supervision of a medical professional.

[g] If DSA ≥ 2000 MFI, intravenous immunoglobulin may be administered at a dose of 2 grams/kg. Administration of the dose will begin at the visit. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days.

[h] If investigational product will be administered off-site after the completion of the visit, then it will be dispensed to the subject.

[i] Throughout a Retreatment Period, subjects should return any used or partially used vials of investigational product. Subjects should then return all vials (ie, used, partially used, and unused) of investigational product at the Week 26 Retreatment Visit.

**Table 6 Schedule of Assessments: Sequential Pharmacokinetic / CCI Sampling Conducted in a Subset of Subjects**

| Activity | Timepoint | Timepoint Window |
|---|---|---|
| **Day 10 Visit (Day 10 ± 1 Day)** | | |
| Blood Draw | - 30 minutes | ± 30 minutes |
| Intravenous Administration of C1-INH 60 IU/kg | 0 minutes | NA |
| Blood Draw | 15 minutes | ± 5 minutes |
| Blood Draw | 3 hours | ± 30 minutes |
| Blood Draw | 8 hours | ± 1 hour |
| Blood Draw | 24 hours | ± 6 hours |
| Blood Draw | 48 hours | ± 6 hours |
| Blood Draw | 72 hours | ± 6 hours |
| **Week 11 Visit (Day 77 ± 2 Days)** | | |
| Blood Draw | - 30 minutes | ± 30 minutes |
| Subcutaneous Administration of C1-INH 60 IU/kg | 0 minutes | NA |
| Blood Draw | 24 hours | ± 6 hours |
| Blood Draw | 48 hours | ± 6 hours |
| Blood Draw | 72 hours | ± 6 hours |

C1-INH = C1-esterase Inhibitor, Human (500 IU/mL).

**Note 1:** All blood draws will be timed relative to the start of C1-INH administration.

**Note 2:** CCI [redacted]

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# List of Abbreviations

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| AMR | Antibody-mediated Rejection |
| C1-INH | CSL Behring's C1-esterase Inhibitor, Human (500 IU/mL) |
| CI | Confidence Interval |
| [CL] | Central Laboratory |
| CSL | CSL Behring LLC |
| DSA | Donor-specific Antibody |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| g | Glomerulitis [Banff Category Score] |
| GBM | Glomerular basement membrane |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| HAE | Hereditary angioedema |
| HCV | Hepatitis C Virus |
| HLA | Human Leukocyte Antigen |
| HR | Hazard Ratio |
| ICH | International Council for Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ITT | Intent-to-Treat |
| IU | International Units |
| IV | Intravenous |
| IVIg | Intravenous Immunoglobulin |
| MDRD | Modification of Diet in Renal Disease |
| MFI | Mean fluorescence intensity |
| CCI [redacted] | |
| CCI [redacted] | |
| PK | Pharmacokinetic |
| ptc | Peritubular Capillaritis [Banff Category Score] |
| PTC | Peritubular Capillary |
| RiS | Run-in Safety |
| RWS | Randomized Withdrawal Safety |

| Abbreviation | Term |
|---|---|
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| $S_{cr}$ | Serum Creatinine |
| TEE | Thromboembolic Events |
| TG | Transplant glomerulopathy |
| TP1 | Treatment Period 1 |
| TP2 | Treatment Period 2 |
| U | Units |

**Note:** Throughout this document, abbreviations are used for all units of measure. These abbreviations are not defined at the first appearance in the text.

# Conventions

- Throughout the protocol, the active study product "C1-esterase Inhibitor, Human (500 IU/mL)" will be abbreviated "C1-INH". Where referenced, other C1-esterase inhibitor products will be specified by their branded names (eg, Berinert, Cinryze) or using the terminology "C1-esterase inhibitor product".

- The terminology 'Investigational Product' is inclusive of both C1-INH and placebo, and excludes intravenously administered immunoglobulin.

- Nomenclature for study visits will use the following conventions:
  - Scheduled study visits occurring during the first 2 weeks of the open-label Treatment Period 1 (TP1) will be referenced using days (eg, the Day 1 Visit, the Day 14 Visit, etc).
  - Scheduled study visits occurring after the first 2 weeks of the open-label TP1 and during the blinded Treatment Period 2 (TP2) will be referenced using weeks (eg, the Week 3 Visit, the Week 12 Visit, the Week 38 Visit, etc).
  - Scheduled study visits occurring during the Responder Follow-up Period will be referenced using months (eg, the Month 12 Visit, the Month 48 Visit, etc).
  - Scheduled study visits occurring during the first week of a Retreatment Period will be referenced using days and will be designated as retreatment visits (ie, the Day 1 Retreatment Visit and the Day 7 Retreatment Visit). Scheduled study visits occurring after the first week of a Retreatment Period will be referenced using weeks and will be designated as retreatment visits (eg, the Week 2 Retreatment Visit, the Week 22 Retreatment Visit, etc).

- For the purposes of the conduct of this study, the following equivalencies will be used:
  - 24 hours is equal to 1 day.
  - 1 week is equal to 7 days.
  - 1 month is equal to 28 days.
  - 52 weeks is equal to 1 year.

- In this protocol, the term 'therapy' (eg, prior and/or concomitant therapy) is inclusive of any intervention, medication, or other treatment that a subject may receive.

# 1 Introduction

## 1.1 Background

Antibody-mediated rejection (AMR) is associated with poor long-term allograft and patient survival [Takemoto et al, 2004; Dalla Vecchia et al, 1997; Emonds et al, 2000; Fine et al, 1979; Stegall et al, 2011; Montgomery et al, 2011b]. Antibody-mediated rejection is mediated primarily by donor-specific antibody (DSA) directed against the human leukocyte antigen (HLA) class I and/or class II molecules present on the vascular endothelium and tubules of the transplanted kidney [Miller et al, 2004; Montgomery et al, 2011a; Pascual et al, 2008; Stegall et al, 2012; Gulleroglu et al, 2013]. This antibody-antigen interaction activates the classical complement pathway, resulting in direct cellular damage and initiation of an inflammatory response which results in further damage to the allograft [Burns et al, 2008; Grafals and Akalin, 2009; Stegall et al, 2011; Stegall et al, 2012]. Left unchecked, the endothelial damage caused by complement activation can result in allograft thrombosis, tissue necrosis, and endothelial cell detachment from the basement membrane, which is all characteristic histological features of AMR [Nguyen and Butani, 2013]. This early injury is later complicated by the proliferation of myofibroblasts leading to progressive scarring of the kidney graft [Gulleroglu et al, 2013]. This process eventually leads to transplant glomerulopathy (TG), as evidenced by double contouring of the glomerular basement membrane. These irreversible anatomical lesions, including intimal thickening of the peritubular capillaries (PTCs), permanently compromise allograft function [Colvin, 2007; Cornell et al, 2008; Kittleson and Kobashigawa, 2012; Nankivell and Alexander, 2010; Crespo et al, 2001; Loupy et al, 2017; Stites et al, 2015].

Clinically, patients with AMR may have fever, fatigue, irritability, pain over the allograft site, and rapid onset of renal dysfunction (decrease in urine output and estimated glomerular filtration rate [eGFR]). Several risk factors have been associated with the occurrence of acute AMR; the patients at greatest risk are sensitized (DSA positive) to their donors after exposure to human HLA proteins through a prior transplant, blood transfusion, and/or pregnancy [Stegall et al, 2011; Lefaucheur et al, 2010; Eurotransplant, 2013]. Patients may also develop AMR post-transplant via (de novo) production of DSA in response to the allograft HLA proteins. Renal failure patients with DSA are generally excluded from receiving a transplant; therefore, AMR is a rare (5 to 7%), but serious and morbid complication of kidney transplantation.

There are no approved therapies for AMR; however, intravenous immunoglobulin (IVIg) therapy with plasmapheresis can successfully treat 50 to 75% of cases on the short term [Montgomery et al, 2016]. If ongoing AMR is inadequately treated, or is refractory to treatment, transplant glomerulopathy occurs. Concurrently, there is a progressive decline in renal function [Djamali et al, 2014] manifested by decline in glomerular filtration rate (GFR) until the allograft is lost and dialysis and/or re-transplantation is necessary.

Since DSA activates the classical complement pathway which results in inflammation and eventual TG, complement inhibition should prevent the damage which is associated with early graft loss. CCI [redacted] study of complement inhibition showed that long-term suppressive therapy with a C1-esterase inhibitor product could be used to rescue patients with AMR refractory to IVIg and plasmapheresis [Viglietti et al, 2016a]. This protocol seeks to study complement inhibition by C1-esterase inhibitor in a placebo-controlled manner as a treatment for refractory AMR in renal transplant recipients.

## 1.2 Background Information on C1-esterase inhibitor

### 1.2.1 Overview

C1-esterase inhibitor belongs to the family of serine protease inhibitors. It has important inhibiting potential on several of the major cascade systems of the human body, including the coagulation, complement, and contact cascades, as well as the fibrinolytic system. In the complement cascade system C1-esterase inhibitor inactivates its substrates by covalently binding to the active sites preventing the actions of C1r (subcomponent of complement component C1), C1s (activated form of complement component C1), and manose-associated serine proteases.

C1-esterase inhibitor is a soluble, single chain glycoprotein containing 478 amino acid residues organized into three beta sheets and eight or nine alpha helices. The heavily glycosylated molecule has an apparent molecular weight of 105 kD, of which the carbohydrate chains comprise 26% to 35%.

CSL Behring's C1-esterase inhibitor product ("C1-esterase Inhibitor, Human [500 IU/mL]", abbreviated as "C1-INH") is human plasma-derived, and available at a concentration of 500 IU/mL after reconstitution. A detailed description of the chemistry, pharmacology,

efficacy, and safety of C1-INH is provided in the Investigator's Brochure [C1-INH (500 IU/mL) Investigator's Brochure, 2019].

### 1.2.2 Nonclinical Evaluation

Nonclinical studies of C1-esterase inhibitor products have demonstrated an acceptable safety profile and pharmacokinetic (PK) properties.

In nonclinical studies with the currently marketed C1-esterase inhibitor product Berinert (CSL Behring), C1-esterase inhibitor was well tolerated and no toxicity was observed in single-dose intravenous (IV) toxicity studies in rats and mice at doses up to 6000 IU/kg, and in a repeated-dose IV toxicity study in rats at a dose of 200 IU/kg for 14 days [C1-INH (500 IU/mL) Investigator's Brochure, 2019].

Local tolerance studies in rabbits were conducted with Berinert, investigating IV and subcutaneous (SC) routes of administration [C1-INH (500 IU/mL) Investigator's Brochure, 2019]. No treatment-related local reactions were observed at IV Berinert injection sites; erythema and edema were observed at SC Berinert injection sites with a slightly higher incidence and/or intensity when compared to control sites. Overall, a single IV, intra-arterial, SC, or intramuscular injection of Berinert was locally well-tolerated in rabbits.

To investigate the thrombogenic potential of C1-esterase inhibitor products (Berinert and C1-INH), thrombogenicity studies based on the established Wessler rabbit model of venous stasis-induced thrombosis were conducted [C1-INH (500 IU/mL) Investigator's Brochure, 2019]. Potential pro-thrombotic effects of C1-esterase inhibitor were studied following IV administration, as this route of administration leads to higher peak plasma levels, which are considered most relevant for potential pro-thrombotic effects. Following single IV administration of doses up to 800 IU/kg to rabbits, no thrombus formation could be observed.

### 1.2.3 Clinical Experience with C1-INH in Transplant

C1-esterase inhibitor products have been studied in kidney transplant patients for the treatment of acute AMR, prevention of AMR, and for the treatment of refractory AMR. Case reports and small clinical trials have been conducted, CCI [redacted]

C1-esterase inhibitor has been evaluated for the prevention of AMR in HLA-sensitized kidney transplant recipients. A phase 1/2, exploratory, randomized, placebo-controlled, single center trial using Berinert was conducted in 20 desensitized (prior to transplant) subjects for

the prevention of AMR following renal allograft transplantation [Vo et al, 2015]. Subjects received either 20 IU/kg Berinert or placebo intra-operatively (intravenously), then twice weekly for 7 doses. No subjects developed AMR in the Berinert group; 1 (10%) developed AMR in the placebo group at 1 month following treatment. At 6 months, 2 (20%) subjects developed AMR in the Berinert group; 3 (30%) developed AMR in the placebo group. Berinert was generally well tolerated in this population, with no study drug related serious adverse events (SAEs).

Another C1-INH product (Cinryze; Shire Viropharma Incorporated) was evaluated as treatment in subjects with AMR. A phase 2b, multicenter, double-blind, randomized, placebo-controlled pilot study was conducted to evaluate the use of Cinryze as add-on therapy to standard of care (ie, IVIg/plasmapheresis) in 18 subjects with acute AMR [Montgomery et al, 2016]. Subjects received IV Cinryze (n = 9) or placebo (n = 9); treatment was 5000 U (approximately 60 U/kg) IV on Day 1 then 2500 U (approximately 30 U/kg) IV every other day (6 doses) for 2 weeks for a total of 20,000 units. Both groups showed similar improvements in histopathology parameters on biopsies (Banff Classification) obtained one week after cessation of study drug (Day 20). Seven of 9 (78%) subjects receiving Cinryze and 6 of 9 (67%) receiving placebo had resolution of their AMR; the most prominent feature of the improvement on biopsy was seen as a decrease in C4d staining. Cinryze-treated subjects achieved supra-physiologic C1-esterase inhibitor levels of a median 1.73-fold above normal, and Cinryze was considered to be generally well tolerated without any serious safety concerns.

A prospective, historically matched controlled single-arm pilot study was conducted to evaluate the efficacy and safety of Berinert added to high-dose IVIg for the treatment of refractory AMR (nonresponsive to standard of care) in 6 subjects [Viglietti et al, 2016a]. Subjects received 20 IU/kg Berinert intravenously on Days 1, 2, and 3 and then twice weekly and 2 grams/kg IVIg (Privigen; CSL) every month for 6 months. All Berinert-treated subjects showed an improvement in eGFR after 6 months of treatment. At Month 6, study subjects with positive C4d staining in peritubular capillaries decreased from 83% (5/6) at baseline to 17% (1/6) with treatment, and anti-HLA DSA C1q binding decreased from 100% (6/6) to 17% (1/6). No death or allograft loss was observed in patients treated with Berinert. One SAE (gastrointestinal bleeding) occurred in 1 subject, which was considered not related to the study drug. One subject experienced an adverse event (AE) of an episode of deep vein thrombosis of a lower limb 5 months after inclusion in the study, which led to discontinuation

of Berinert. The episode was subsequently determined to be caused by local venous compression due to a popliteal cyst, and was considered not related to study drug.

## 1.3 Study Overview

Eligible subjects will enter into the open-label TP1, during which all subjects will receive C1-esterase Inhibitor, Human (500 IU/mL) (C1-INH) at a dose of 60 IU/kg (Table 1). Subjects who respond to treatment with C1-INH by Week 12 as assessed by pre-defined responder criteria (Section 8.1.3.2) will be randomized into TP2 of the study; those subjects who do not respond to treatment will enter a Non-responder Follow-up Period during which they will be followed up to 48 months following enrollment. Subjects who are responders will be randomized to receive either C1-INH or placebo during TP2 (Table 2). All subjects will receive standard of care treatment for AMR throughout TP1 and TP2, including IVIg 2 grams/kg once every 4 weeks for at least the first 12 weeks of treatment, with plasmapheresis as needed. At the End-of-TP2 at Week 38, subjects will then enter a 39-month Responder Follow-up Period (Table 3). Subjects will receive treatment consistent with their local standard of care during the Responder Follow-up Period, and their allograft status, kidney function, and survival will be monitored. During the Responder Follow-up Period, recurrence or persistence of biopsy proven AMR recurrences may receive retreatment with blinded investigational product (in combination with standard of care) as part of Retreatment Period(s) (Table 5).

While recognizing the need for a randomized placebo-controlled study to confirm the efficacy of C1-INH in this patient population, it would be unethical to withhold C1-INH therapy from patients already determined to be refractory to standard of care. Upfront randomization to placebo or cross over designs would not be appropriate, as subjects in the placebo cohort would continue to receive therapy deemed ineffective. A randomized withdrawal design allows for all study subjects to receive active treatment for a pre-determined period of time and randomization of subjects with a positive response at the end of the open label run-in allows for enrichment of the study population that would most benefit from complement inhibition. Randomization of responders to C1-INH or placebo would then confirm the efficacy of C1-INH as placebo subjects would be hypothesized to lose their response to investigational product over time. Any difference that emerges between the group receiving continued treatment and the group randomized to placebo would demonstrate the effect of the active treatment [International Conference on Harmonisation, 2000]. Hence, this is a multicenter, double-blind, randomized-withdrawal, placebo-controlled

study to investigate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients.

## 1.4 Potential Risks and Benefits

Consistent safety of Berinert administered intravenously for the on-demand, acute treatment of hereditary angioedema (HAE) attacks has been observed in over 30 years of use. Since 1985 to 04 August 2019, 1,506,583,576 IU of Berinert IV have been sold worldwide, corresponding to 1,004,389 standard doses and an estimated exposure of 83,699 patient years. Cumulatively since 2017 to 04 Aug 2019, 596,094,000 IU of Berinert SC have been sold worldwide, corresponding to 132,465 standard doses and an estimated exposure of 1274 patient years. Post-marketing surveillance has shown that Berinert is safe and well tolerated when used at the recommended dosage for the treatment of acute HAE attacks. No case reports concerning proven Hepatitis A Virus, Hepatitis B Virus, Hepatitis C Virus (HCV), or Human Immunodeficiency Virus-1 or -2 infections resulting from the use of Berinert have been received.

The PK of CSL Behring's current formulation of C1-INH (500 IU/mL) and Berinert after IV and SC administration have been investigated in Phase 1 healthy volunteer studies and a Phase 2 study in HAE patients. An acceptable safety and local tolerability profile was demonstrated for C1-INH (500 IU/mL) in healthy and HAE subjects. Following IV and SC administrations of C1-INH (500 IU/mL) (1500 IU) and Berinert (1500 IU), there were no severe AEs, no SAEs, no clinically significant laboratory parameters, no thromboembolic events (TEEs), and no anti-C1-INH antibodies (including inhibitory antibodies). In two Phase 3 studies in HAE subjects, subcutaneous administration of 40 and 60 IU/kg of C1-INH (500 IU/mL) was well tolerated. No inhibitory antibodies to C1-INH, cases of anaphylaxis, or seroconversions for human immunodeficiency virus, hepatitis B virus, or HCV were identified during the study. Although noninhibitory antibodies to C1-INH were detected during the study, there was no apparent association between treatment and the detection of these antibodies. Injection site reactions and injection site pain occurred frequently and were the most commonly reported AEs in these studies.

Risks associated with C1-esterase inhibitor products include hypersensitivity/anaphylactic-type reactions, TEEs, and potential virus transmission:

- **Hypersensitivity/Anaphylactic-type Reactions:** Hypersensitivity and anaphylactic-type reactions have been reported rarely with the use of C1-esterase inhibitor products in

patients with HAE. Hypersensitivity or anaphylactic reactions in this study population are expected to be rare because the subjects have normal, physiologic C1-esterase inhibitor, as opposed to in the HAE population. Nonetheless, anaphylaxis will be specifically monitored during this study.

- **Thromboembolic Events:** Thromboembolic events have been occasionally reported following the use of C1-esterase inhibitor products, in particular in patients receiving off-label high doses of up to 500 IU/kg IV in the context of cardiac surgery and extracorporeal circulation [Arzteblatt, 2000]. At the doses to be used in this clinical study (60 IU/kg IV; 60 IU/kg SC), a causal relationship between TEEs and the use of C1-esterase inhibitor has not been established. Nonetheless, TEEs will be specifically monitored during this study.
- **Potential Virus Transmission:** C1-INH contains human plasma-derived C1-esterase inhibitor and, therefore, has the potential for virus transmission to recipients. However, Berinert and C1-INH has a very high margin of virus safety with the risk of virus transmission minimized by donor selection and screening criteria, and by reducing enveloped and non-enveloped viruses using pasteurization, nanofiltration methods, and chromatography in the manufacturing process [De Serres et al, 2003]. Each subject will provide a retention sample before and after treatment with the investigational product for potential future serology assessments.

Additional information on C1-INH can be found in the C1-INH investigator's brochure [C1-INH (500 IU/mL) Investigator's Brochure, 2019].

Without treatment, up to 90% of study subjects with refractory AMR would otherwise go on to lose their kidney graft and have associated mortality risk [Viglietti et al, 2016b]. Given the low probability of potential risks and the implementation of study procedures that will closely monitor the safety of study subjects, the associated benefit/risk assessment is acceptable for subjects who participate in the study.

# 2 Study Objectives and Endpoints

## 2.1 Primary Objective and Endpoint

### 2.1.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients.

### 2.1.2 Primary Endpoint

**Table 7 Primary Endpoint**

| Endpoint | Summary Measure |
|---|---|
| Loss-of-response during TP2. | Proportion of subjects with loss-of-response at the End-of-TP2.<br>Loss-of-response at the End-of-TP2 is defined as any 1 of the following 3 conditions:<br>• End-of-TP2 eGFR (mean of Week 36 and Week 38 eGFR) that is not stable, defined as:<br>o End-of-TP2 eGFR that is < 90% of the End-of-TP1 eGFR for subjects whose End-of-TP1 eGFR (mean of Week 11 and Week 12 eGFR) is ≥ 100% of baseline;<br>o End-of-TP2 eGFR that is < 90% of baseline for subjects whose end-of- TP1 eGFR is ≥ 90% of baseline and < 100% of baseline<br>• Allograft failure (defined by allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first)<br>• Subject death by any cause |

eGFR = estimated glomerular filtration rate; TP1= Treatment Period 1; TP2 = Treatment Period 2

## 2.2 Secondary Objectives and Endpoints

### 2.2.1 Secondary Objectives

The secondary objectives of the study are:

1. To further evaluate the efficacy of C1-INH in the treatment of refractory AMR in renal allograft recipients.
2. To evaluate the safety of C1-INH in the treatment of refractory AMR in renal allograft recipients.

3. To evaluate the PK of C1-INH during the treatment of refractory AMR in renal allograft recipients.

### 2.2.2 Secondary Endpoints

**Table 8 Secondary Endpoints**

| Secondary Objective | Endpoints | Summary Measure |
|---|---|---|
| 1 | All-cause allograft failure through the Responder Follow-up Period (key secondary). | Proportion of subjects with all-cause allograft failure through the Responder Follow-up Period (ie, within 48 months after enrollment). Allograft failure is defined as 1 of the following (see also Section 8.1.3.7):<br>• Allograft nephrectomy, institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first, OR<br>• Subject death by any cause. |
| 1 | Change in eGFR from baseline to TP1 | The difference between the End-of-TP1 eGFR and baseline eGFR. |
| 1 | Change in eGFR from TP1 to the End-of -TP2. | The difference between the End-of-TP2 eGFR and the End-of-TP1 eGFR. |
| 1 | The rate of change of eGFR. | The rate of change of eGFR during TP2 as defined by the slope of the mean regression of eGFR over time in TP2. |
| 1 | Time (weeks) to all-cause allograft failure through the Responder Follow-up Period (key secondary). | Time (weeks) to all-cause allograft failure through the Responder Follow-up Period (ie, within 48 months after enrollment). |
| 1 | Responder status at the End-of-TP1. | Proportion of responders at the End-of-TP1. Response is defined as End-of-TP1 eGFR that is ≥ 20 mL/min/1.73 $m^2$ and ≥ 90% of the baseline eGFR. |
| 1 | Subject death through the Responder Follow-up Period. | Proportion of subjects surviving through the Responder Follow-up Period. |

| Secondary Objective | Endpoints | Summary Measure |
|---|---|---|
| 2 | Any AE assessed as related to investigational product during TP1 and during TP2. | Proportion of subjects with any AE assessed as related to investigational product. |
| 3 | Pre-dose C1-esterase inhibitor functional activity at Day 1, Week 12, and Week 38. | Mean pre-dose C1-esterase inhibitor functional activity at Day 1, Week 12, and Week 38. |
| 3 | For the subset of subjects with sequential PK sampling, C1-esterase inhibitor functional activity $C_{max}$, and $AUC_{0-t}$ after IV and/or SC administration of C1-INH. | C1-esterase inhibitor functional activity $C_{max}$ and $AUC_{0-t}$ for IV and SC administration. |

AE = adverse event; $AUC_{0-t}$ = area under the plasma-concentration time curve 0 to a definite time; $C_{max}$ = maximum concentration; eGFR = estimated glomerular filtration rate; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous; TP1 = Treatment Period 1; TP2 = Treatment Period 2

## 2.3 CCI [redacted]

### 2.3.1 CCI [redacted]

CCI [redacted]

### 2.3.2 CCI [redacted]

CCI [redacted]

CCI

[redacted]

# 3 Study Overview

## 3.1 Study Design

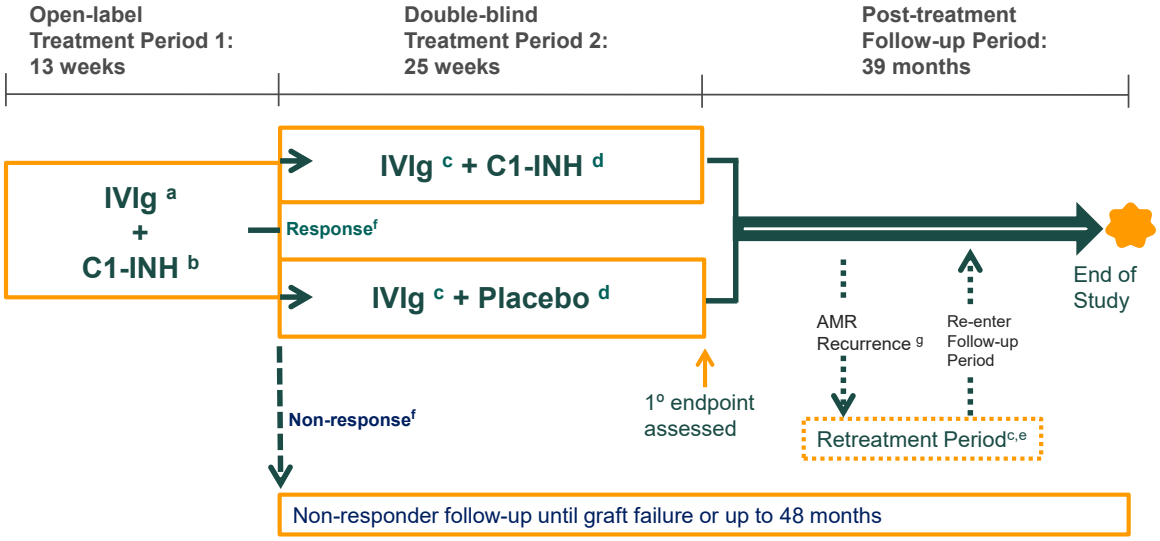
This is a double-blind, randomized-withdrawal, placebo-controlled study consisting of 2 treatment periods, and a Responder Follow-up Period during which retreatment is permitted if needed:

- During open-label TP1, all eligible subjects will receive treatment with C1-INH (60 IU/kg) in combination with standard of care for 13 weeks. At the conclusion of TP1, subjects who demonstrate a treatment response (see Section 8.1.3.2) will be randomized to continue in the study in TP2. Subjects who are considered non-responders will enter the Non-responder Follow-up Period during which they will be followed for up to 48 months.
- During the blinded TP2, randomized subjects will either continue treatment with C1-INH (60 IU/kg) or begin treatment with placebo (both in combination with IVIg and plasmapheresis) for 25 weeks, according to the randomization schedule.
- At the conclusion of TP2, randomized subjects will enter the Responder Follow-up Period, where they will be observed for approximately 39 months until Study Month 48.

Randomized subjects who experience a biopsy-proven AMR recurrence or who have persistent AMR during the Reponder Follow-up will be permitted to undergo blinded retreatment with either C1-INH or placebo (both in combination with standard of care treatment). Subjects who participate in a Retreatment Period will receive blinded investigational product (C1-INH or placebo) according to their TP2 treatment assignment, in combination with standard of care.

The rationale for this study design is presented in Section 3.3.1.

## Figure 1 Study Overview




AMR = antibody-mediated rejection; C1-INH = C1-esterase inhibitor; human;IVIg = intravenous immunoglobulin; MFI = mean fluorescence intensity; TP1 = Treatment Period 1; Treatment Period 2

Note: Post-treatment Follow-up Period is for responders.

[a] Intravenous immunoglobulin (IVIg) will be administered every 4 weeks to all subjects at a dose of 2 grams/kg. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days. Plasmapheresis may be administered based on local DSA results and Principal Investigator's judgement (Section 5.4.2).

[b] Intravenous (IV) C1-INH (60 IU/kg) will be administered to each subject over the first 13 days of TP1for a total of 5 doses. Thereafter, subcutaneous (SC) C1-INH (60 IU/kg twice weekly) will be administered to each subject for the remainder of TP1.

[c] If DSA ≥ 2000 MFI in local lab in TP2 or Retreatment Period, IVIg may be administered to subjects at a dose of 2 grams/kg every 4 weeks. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days. Plasmapheresis may be administered based on local DSA results and Principal Investigator's judgement (Section 5.4.2).

[d] During the TP2, eligible subjects will be randomized 1:1 to receive treatment with investigational product (C1-INH [60 IU/kg] or placebo) subcutaneously twice weekly.

[e] Retreatment Period(s) are blinded and subjects will receive the same investigational product treatment assignment as received during Treatment Period 2.

[f] Response is defined as an End-of-TP1 eGFR (mean of Week 11 and Week 12 eGFR) that is ≥ 20 mL/min/1.73 $m^2$ and ≥ 90% of the baseline eGFR (mean of Screening and the Day 1 eGFR) (Section 10.3.1).

[g] AMR Recurrence or persistence in Responder Follow-up Period is proven by biopsy, evidenced by infiltrating neutrophils and/or monocytes with or without the presence of C4d (g > 0, v > 0, and/or ptc > 0 (if C4d is negative, g + ptc ≥ 2, Section 8.1.3.3).

## 3.2 Dose and Dosing Regimen

**Table 10 Summary of Administration of Investigational Product**

| Timeframe | Intravenous Administration | Subcutaneous Administration |
|---|---|---|
| **Treatment Period 1:** The Day 1 Visit to the Day 13 Visit [a] | 60 IU/kg C1-INH | Not applicable |
| **Treatment Period 1:** The Day 14 Visit to the Week 12 2nd dose [a] | Not Applicable | 60 IU/kg C1-INH |
| **Treatment Period 2:** Week 13 to the Week 38 Visit [b] | Not Applicable | 60 IU/kg C1-INH OR 0.12 mL/kg placebo |
| **Retreatment Period:** The Retreatment Day 1 Visit to the Retreatment Week 26 Visit[c] | Not Applicable | 60 IU/kg C1-INH OR 0.12 mL/kg placebo |

IV = intravenous; SC = subcutaneous

[a] Treatment Period 1 is open-label and each subject will receive C1-INH. C1-INH (60 IU/kg) will be administered IV to each subject over the first 13 days of Treatment Period 1 for a total of 5 doses. Thereafter, C1-INH (60 IU/kg twice weekly) will be administered SC to each subjects for the remainder of Treatment Period 1. The first dose of randomized investigational product will be administered to responders at the Week 13 Visit.

[b] Treatment Period 2 is blinded and subjects will be randomized 1:1 to treatment with investigational product (C1-INH [60 IU/kg] or placebo) subcutaneously twice weekly.

[c] Retreatment Period(s) are blinded and subjects will receive the same investigational product treatment assignment as received during Treatment Period 2.

Note: Week 13 is the final visit of Treatment Period 1 for non-responders and the first visit of Treatment Period 2 for responders.

### *Treatment Period 1*

C1-INH will be administered to all subjects during TP1 in an open-label manner.

C1-INH will be administered intravenously to subjects at the Day 1, 4, 7, 10, and 13 Visits for a total of 5 doses. Intravenous C1-INH will be administered at the study site during site visits.

Subcutaneous C1-INH will be administered every 3 to 4 days (ie, twice weekly) beginning at the Day 14 Visit and for the remainder of TP1. Subcutaneous C1-INH is required to be administered at the study site during site visits, but at other times may instead be administered at home by a medical professional (eg, a home visit nurse) or by the subject under the supervision of a medical professional.

***Treatment Period 2***

Investigational product (ie, C1-INH or placebo) will be administered to all subjects during TP2 in a double-blind manner.

Subcutaneous investigational product will be administered every 3 to 4 days (ie, twice weekly) during TP2. Subcutaneous C1-INH is required be administered at the study site during site visits, but at other times may instead be administered at home by a medical professional (eg, a home visit nurse) or by the subject under the supervision of a medical professional.

***Retreatment Period***

Subjects may undergo retreatment during the Responder Follow-up Period with the blinded investigational product to which they were randomized in TP2. Retreatment may occur following a diagnosis of recurrent or persistent AMR by biopsy, evidenced by infiltrating neutrophils and/or monocytes with or without the presence of C4d (glomerulitis [g] > 0, intimal arteritis [v] > 0, and/or peritubular capillaritis [ptc] > 0; if C4d is negative, g+ptc ≥ 2). Retreatment may start at any time during the Responder Follow-up Period, and will last for 26 weeks or until the Month 48 Visit, whichever occurs first. The Retreatment Period may also be shorter than 26 weeks at the investigator's discretion.

During the Retreatment Period, SC investigational product will be administered twice weekly (approximately every 3 to 4 days). During the Retreatment Period (if needed), SC C1-INH will be administered either at the site or may be dispensed to the subject and administered SC at home either by a medical professional or by the subject under the supervision of a medical professional.

***Subcutaneous Administration of the Investigational Product***

Subcutaneous administration of the investigational product should be via a single SC injection in the abdomen, thigh, upper arm, or other appropriate location. The injection site should be changed for each new administration and should be at least 5 cm (2 inches) away from the previous injection site.

The twice weekly administration of investigational product beginning at the Day 14 Visit and during any Retreatment Period (if applicable) should ideally be scheduled on fixed days of the week (eg, Monday and Thursday). The suggested interval between each administration of investigational product is 3 or 4 days (ie, twice weekly). In addition, the investigational product should ideally be administered at approximately the same time on each day. A missed

injection should be administered as soon as possible, unless within 24 hours of the next scheduled injection; in this situation, the missed injection should be omitted, and the administration of investigational product should occur at the next scheduled day and time.

The volume of investigational product to be administered will be based on each subject's body weight (from the Screening physical examination) and will not be adjusted during the study.

## 3.3 Scientific Rationale

### 3.3.1 Study Design Rationale

Antibodies directed against a transplanted donor organ (ie, DSA) activate the complement system, resulting in direct and indirect damage to the allograft. Complement-mediated damage as a result of AMR is recognized as an important cause of poor long-term allograft and patient survival.

Although no therapies have been approved for the treatment of AMR, the current standard of care most commonly consists of intravenously administered immunoglobulin (IVIg) with or without plasmapheresis and/or rituximab. These regimens can result in acceptable short-term allograft survival for kidney transplant patients with AMR. However, approximately 25% of patients with AMR are refractory to standard therapies, and eGFR continues to decline despite first-line treatment [Viglietti et al, 2016a]. Approximately 20% of patients with active AMR have simultaneous chronic active AMR [Viglietti et al, 2018, Aubert et al, 2019], which is generally not amenable to treatment and whose natural history is progressive loss of function [Loupy and Lefaucheur, 2018]. In addition, approximately 50% of patients with active AMR have simultaneous chronic active T-cell mediated rejection [Viglietti et al, 2018]. Not surprisingly, therefore, up to 90% of grafts in these patients fail within 4 years of the diagnosis of refractory AMR. The addition of complement inhibition therapy to standard of care has been reported in the literature to successfully treat acute AMR that is unresponsive to treatment with a standard of care regimen [Viglietti et al, 2016a].

In that study, all subjects showed an improvement in eGFR as the key indicator of clinical response to complement inhibitor therapy. Estimated GFR is a functionally important, therapeutically relevant, and clinically accepted surrogate marker of allograft survival. In a recent AMR workshop sponsored by the FDA, GFR was considered as a potentially acceptable surrogate marker for pivotal clinical trial(s) of an interventional therapy to treat acute AMR [Archdeacon et al, 2011]. Studies in transplantation have shown that eGFR by the

Modification of Diet in Renal Disease (MDRD) equation more accurately reflected clinical function than measured GFR by plasma iothalamate measurements [Tortoricci et al, 2013]. Further, other methods of measuring GFR are complicated by inaccuracies associated with sample collections and feasibility concerns in clinical study scenarios. Thus, eGFR appears to be the most reliable endpoint measure of kidney allograft function.

This phase 3 pivotal trial is designed to assess the efficacy and safety of C1-INH in combination with IVIg-containing standard of care regimens in subjects that have failed standard of care therapy alone, and hence, have very limited options to prevent allograft failure. Subject response will be assessed by parameters including eGFR, allograft failure, and death. As current treatment for AMR vary by center and regions, the background IVIg regimen is standardized during the study to reduce variability.

Refractory AMR patients have already failed standard therapy, and there is a signal that human plasma-derived C1-INH has an effect in preventing allograft damage in kidney transplant patients with acute AMR allowing for improvement in renal allograft function [CCI Viglietti et al, 2016a]. The most feasible and appropriate design of any randomized placebo controlled study in subjects with refractory AMR is an open-label run-in, randomized withdrawal design. In this study design, all subjects receive active treatment because their unresponsiveness to standard therapy indicates that they would lose their allograft without additional intervention. Responders would then be randomized to either active treatment or placebo in order to test the longer term effects of C1-INH therapy. Any difference that emerges between the group receiving continued active treatment and the group randomized to placebo would then demonstrate the effect of the active treatment [International Conference on Harmonisation, 2000].

Based on a pilot study of subjects with refractory AMR [Viglietti et al, 2016a], all subjects showed some improvement of allograft function by 12 weeks. Thus, the open label run-in portion of this study was limited to 12 weeks. Four of 6 subjects in that study required retreatment to preserve their allograft function with some of those retreated several months after cessation of C1-INH therapy (personal communication). Thus, it was determined necessary to observe subjects on investigational product for at least 6 months after randomization to confirm the efficacy of continued C1-INH therapy in the blinded portion of this study.

Subjects in this study will have been determined "responders" to C1-INH therapy if their eGFR at the End-of-TP1 (mean of Week 11 and Week 12) is stable, defined as $\geq$ 90% of

baseline and ≥ 20 mL/min/1.73m$^2$ (see Section 10.3.1), since patients with refractory AMR would be expected to have declining eGFR. This may be considered a more realistic and clinically important indication of investigational product effect compared with an improvement of renal allograft function, particularly since the improvement seen in Vigletti's pilot study with a sample size of 6 [Viglietti et al, 2016a] may not be reproducible in a larger, multicenter study. Loss of this response is the primary endpoint as determined by Week 38 post-randomization, concurrent with end of investigational product therapy. Taking into account usual fluctuations of measured creatinine in transplant patients and standard deviations of accredited assays, loss-of-response has been defined using the criteria specified in Section 10.3.1.

Because this study investigates the efficacy of C1-INH therapy on stabilizing allograft function diminished by acute AMR, it will be necessary to confirm this effect on long-term allograft survival to 4 years after enrollment. As investigational product will be tested as add-on therapy to standard of care, it is necessary to allow for the use of IVIg and / or plasmapheresis for all study subjects if the investigator deems it necessary. In such instances, study subjects may receive 5 plasmapheresis runs. Also, if there is evidence of recurrent AMR on any for-cause biopsy obtained in the Responder Follow-up Period (including the Week 38 biopsy), a subject may be retreated with the same investigational product the subject received in TP2 (ie, blinded C1-INH or placebo).

### 3.3.2 Dose Rationale

C1-esterase inhibitor is consumed in the process of inhibiting complement; therefore, the initial IV dosing regimen is intended to rapidly attenuate AMR progression. The initial IV dosing regimen of C1-INH (60 IU/kg, 5 doses over 13 days) is based on the following in vitro and clinic data, and PK simulations:

- In vitro studies show that an approximate 2-fold C1-INH increase above normal physiologic levels suppressed 90% of complement activity in rat and human plasma [C1-INH (500 IU/mL) Investigator's Brochure, 2019]. Therefore, targeting C1-INH peak functional levels in AMR patients of approximately 2-fold above normal physiologic levels should inhibit approximately 90% of complement activity.
- A total of 20,000 IU C1-INH, administered in 5 doses over 13 days, was administered to kidney allograft recipients with acute AMR. C1-esterase inhibitor functional activity reached a median of 1.73-fold higher than normal physiologic levels [Montgomery et al, 2016].

- C1-esterase inhibitor PK simulations estimate peak IV C1-esterase inhibitor functional levels of 2.3-fold above normal physiologic levels.

The continued SC maintenance dosing regimen of C1-INH (60 IU/kg every 3 or 4 days) is based on the following:

- Providing sustained average C1-INH levels of 1.5-fold above normal levels (based on PK simulation estimation), thereby maintaining suppression of complement activity by approximately 75%, and replacing endogenous C1-esterase inhibitor functional protein that is consumed due to the residual AMR inflammatory processes.
- C1-esterase inhibitor PK simulations estimate mean peak SC C1-esterase inhibitor functional levels of 1.7-fold above normal physiologic levels.

The planned dosing regimen is anticipated to be safe and effective based on existing in vitro and nonclinical data, as well as previous human experience in both kidney transplant and hereditary angioedema patients [Montgomery et al, 2016; Viglietti et al, 2016a; Vo et al, 2015; C1-INH (500 IU/mL) Investigator's Brochure, 2019].

## 3.4 Planned Study Duration

The duration of the study for an individual subject is expected to be approximately 210 weeks (48 months). This estimation is based on:

- A 2-week Screening Period.
- A 13-week open-label treatment period (TP1).
- A 25-week double-blind treatment period (TP2).
- Follow-up Periods
    - A 39-month (170 weeks) Responder Follow-up Period (up to 48 months following enrollment).
    - 45-month Non-responder Follow-up Period (up to 48 months following enrollment).

The overall study duration (ie, first subject's Screening Visit to last subject's final study visit) is anticipated to be approximately 6 years.

## 3.5 Planned Number of Subjects and Sites

Approximately 120 subjects (up to 175) are planned to participate in the open-label TP1 in order to randomize 60 subjects into the double-blind TP2.

The study is planned to be conducted at approximately 35 sites globally.

## 3.6 Definition of End of the Clinical Study

The end of the clinical study (ie, completion of the study at all participating study sites) is defined as the date of the last visit of the last subject.

## 3.7 Study Oversight

### 3.7.1 Data Monitoring Committee(s)

The independent data monitoring committee (IDMC) is an independent expert advisory group consisting of medically qualified transplant nephrologists or surgeons with appropriate expertise in subjects with AMR, kidney transplant recipients, and/or evaluation of AEs and laboratory results relevant for detecting any possible safety issues, and a statistician. The IDMC is being utilized to provide an independent evaluation of the study at regular intervals with regard to the progress of the study and the safety data, namely for the incidence, frequency and nature of AEs, and in particular for TEEs. In particular, any systemic TEE, not associated with dialysis access or other vascular access devices, reported as related to the administration of investigational product by the investigator, will be reviewed ad hoc by the IDMC. The IDMC will adjudicate the causality assessment for the TEE based on the unblinded case report. In addition, the IDMC will review the primary efficacy endpoint data only at the planned interim analysis. Other data (eg, PK) may also be reviewed, as appropriate. Unblinding of data and provision of unblinded data to the IDMC will be performed by an independent statistical data analysis center that is not associated in any other way with the study. After this review, recommendations will be issued to CSL Behring (CSL) regarding the continuation of the study, eventual need for protocol modifications, or study termination.

The analysis plan for all IDMC data reviews will be outlined in the IDMC charter. The composition, activities, and responsibilities of the IDMC will also be described in the IDMC charter.

## 3.8 Study Stopping Criteria for a Thromboembolic Event

In the case of any systemic TEE, not associated with dialysis access or other vascular access devices, and reported as related to the administration of investigational product by the investigator, administration of the investigational product will be halted for that subject until the IDMC adjudicates the causality assessment for the TEE based on evaluation of the unblinded case report. However, dosing will continue for all other subjects who are already enrolled. Details of the IDMC adjudication process for TEE evaluation, as well as required timelines for the adjudication will be contained in the IDMC charter.

All subjects will receive regular physical examinations, and will have medically appropriate follow-up for any sign of a TEE.

The IDMC will meet on a regular basis and will have the opportunity to assess AEs per treatment assignment as it relates to the overall safety of the ongoing trial.

# 4 Selection and Withdrawal of Subjects

## 4.1 Eligibility Criteria

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study. Subject eligibility will be reviewed and documented by an appropriately medically-qualified member of the investigator's study team before subjects are included in the study.

### 4.1.1 Inclusion Criteria

To be enrolled into the study, subjects must meet all of the following inclusion criteria:

1. Provide written informed consent and willing and able to adhere to all protocol requirements.
2. At least 18 years of age at the time of providing written informed consent.
3. Evidence of at least one DSA (to HLA class I and/or class II)
4. Recipient of a kidney transplant from an ABO compatible or ABO incompatible donor, living or deceased.
5. At least one of the following if clinical data are available:
    a. Achieved a steady-state, post-transplant eGFR $\geq$ 40 mL/min/1.73 $m^2$ (as determined by local practice) within 60 days post-transplant, OR

b. A 50% increase in urine output with a 50% decrease in serum creatinine over the first 7 days post-transplant in subjects with slow or delayed graft function.

6. Acute AMR, defined per Banff 2015 criteria [Loupy et al, 2017], on pre-enrollment kidney biopsy (performed within 90 days of enrollment), as the following:
   a. Histologic evidence of acute tissue inflammation with presence of neutrophils and/or monocytes (g > 0, v > 0, and/or ptc > 0), AND
   b. C4d positive or, if C4d negative, then g + ptc ≥ 2.

   **NOTE:** Subjects who have mixed cellular rejection with AMR are eligible for participation.
7. Acute AMR that is unresponsive (ie, no improvement in renal function as determined by the treating physician) after standard of care treatment:

a. If standard of care treatment is ≥ 100 mg/kg IVIg and plasmapheresis (with or without rituximab): ≥ 7 days since the current AMR diagnosis at the Day 1 Visit, OR

b. If standard of care treatment is ≥ 1 gram/kg IVIg without plasmapheresis (with or without rituximab): ≤ 45 days since the current AMR diagnosis.

8. Subject must be willing and able to comply with the requirements of the study protocol.
9. Investigator believes that the subject understands the nature, scope and possible consequences of the study.

### 4.1.2 Exclusion Criteria

Subjects must not be enrolled into the study if they meet any of the following exclusion criteria:

1. Recipient of an en bloc kidney transplant.
2. Ongoing dialysis > 2 weeks at Screening.
3. Hepatobiliary disease as indicated by 1 of the following:
   a. Viral hepatitis ie, positive for HCV or HBV confirmed by nucleic acid testing (if positive, subjects must be receiving or have received antiviral therapy and have no history of cirrhosis), OR
   b. Alanine aminotransferase > 3 times upper limit of normal, OR
   c. Total bilirubin > 1.5 times upper limit of normal.
4. History of human immunodeficiency virus with acquired immunodeficiency syndrome at Screening.

5. Active bacterial or fungal infection that is clinically significant in the opinion of the investigator.
6. Not otherwise explained thrombotic microangiopathy on pre-enrollment kidney biopsy.
7. Known congenital bleeding or coagulopathy disorder.
8. Evidence of non-catheter or non-dialysis access-related deep vein thrombosis, stroke, myocardial infarction, or arterial embolus within the 3 months before the Day 1 Visit; catheter-related thrombosis or history of clotting a dialysis access is NOT exclusionary, unless a hereditary coagulopathy has been diagnosed.
9. Treatment with a complement inhibitor (eg, Soliris [eculizumab], Berinert [C1-INH], Cinryze [C1-INH]), or experimental therapies for the treatment of AMR other than IVIg or rituximab (eg, bortezomib) within 14 days before administration of C1-INH at the Day 1 Visit.
10. Current cancer or a history of cancer within 2 years before providing informed consent, with the exception of successfully treated non-metastatic basal or squamous cell carcinoma of the skin, in situ breast or other in situ lesions considered cured by therapy.
11. Any medical condition that, in the opinion of the investigator, might interfere with the subject participation in the study, poses an added risk to the subject, or confounds the assessment of the subject.
12. Female subjects who are pregnant (as evidenced by a positive serum pregnancy test for choriogonadotropin beta at Screening) or breast feeding.
13. Female subject of childbearing potential or male subject not using or not willing to use a medically reliable method of contraception from the first dose of investigational product in any treatment period until 1 month after the last dose of investigational product in the same treatment period.

**NOTE:** Childbearing potential and the acceptable methods of contraception are defined in Section 7.4.

14. Participation in another interventional clinical study for AMR at Screening; subject may have been withdrawn from an AMR study at any time before Screening.
15. Known or suspected hypersensitivity to the investigational product (ie, C1-INH or placebo), to any excipients of the investigational product, or to any other C1-esterase inhibitor preparation (eg, Berinert) or albumin preparation.

16. Involved in the planning and/or conduct of the study (applies to CSL staff, staff at the study site, and third-party vendors).

## 4.2 Discontinuation of Treatment and/or Subject Withdrawal

### 4.2.1 Reasons for Discontinuation of Treatment and/or Subject Withdrawal

Subjects may discontinue treatment with investigational product or withdraw from the study at any time at their own request, or at the discretion of the investigator or CSL for safety, behavioral or administrative reasons (eg, due to an AE, protocol deviation, loss to follow-up, subject noncompliance, study termination).

In accordance with International Council for Harmonisation (ICH) principles of Good Clinical Practice (GCP), the investigator always has the option to advise a subject to withdraw from the study if the subject's safety or well-being is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

The investigator should record in the electronic case report form (eCRF) and in the subject's medical records the reason and date of subject withdrawal or discontinuation of treatment with investigational product.

### 4.2.2 Procedures for Handling Withdrawals

If a subject declines further participation or is withdrawn from the study, attempts will be made to complete and document the assessments scheduled as described in Section 8.5.8.

If the subject is withdrawn from the study after receiving Investigational Product, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the investigator to complete other study assessments.

If a subject discontinues treatment with investigational product but remains in the study, they should complete follow-up assessments as detailed in the Schedule of Assessments.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, CSL may retain and continue to use any data collected before such withdrawal of consent. CSL may also continue to collect the subject’s allograft function and survival information from the study site, with the subject’s consent.

### 4.2.3 Replacement Policy

Subjects withdrawn from the study following randomization will not be replaced.

# 5 Study Interventions

## 5.1 Description of Investigational Product(s)

### 5.1.1 C1-esterase Inhibitor, Human (500 IU/mL)

**Table 11 Description of C1-INH**

| | |
|---|---|
| **Substance name** | C1-esterase Inhibitor, Human (500 IU/mL) |
| **Active substance** | C1-esterase inhibitor |
| **Trade name** | Not applicable |
| **Dosage form** | Lyophilized powder for reconstitution; 1500 IU C1-INH per single-use vial. |
| **Dose** | 60 IU/kg |
| **Mode of administration** | Intravenous/subcutaneous injection |

C1-esterase Inhibitor, Human (500 IU/mL) will be manufactured by CSL in accordance with ICH Good Manufacturing Practice guidelines and local regulatory requirements.

Before use, each vial of C1-INH is reconstituted with 3 mL water for injection. 60 IU/kg C1-INH is equivalent to a volume of 0.12 mL/kg.

Instructions for reconstitution are presented in the Investigational Medicinal Product Handling Instructions.

The dose of C1-INH will be based on the body weight obtained with vital signs assessment at the Screening Visit, and will not be changed throughout the study. The actual dose of C1-INH will be rounded to the lowest 500 IU, as this corresponds with a practical volume of 1 mL of C1-INH. Refer to the Investigational Medicinal Product Handling Instructions.

### 5.1.2 Placebo

**Table 12 Description of Placebo**

| | |
|---|---|
| **Substance name** | placebo |
| **Substance** | Excipients of C1-INH plus albumin |
| **Trade name** | Not applicable |
| **Dosage form** | Lyophilized powder for reconstitution |
| **Dose** | 0.12 mL/kg |
| **Mode of administration** | Subcutaneous injection |

Placebo will be manufactured by CSL in accordance with ICH Good Manufacturing Practice guidelines and local regulatory requirements.

Before use, each vial of placebo is reconstituted with 3 mL water for injection.

Instructions for reconstitution are presented in the Investigational Medicinal Product Handling Instructions.

The volume of placebo will be based on the body weight obtained with vital signs assessment at the Screening Visit, and will not be changed through the study. The actual dose of placebo will be rounded to the lowest 1 mL as if the subject receiving C1-INH.

## 5.2 Packaging, Labeling, Supply and Storage

### 5.2.1 Packaging and Labeling

The investigational products will be packaged and labeled according to current ICH Good Manufacturing Practice and GCP guidelines, and national legal requirements.

The investigational product used in TP1 (ie, C1-INH only) will be packaged in a way to make it visually distinct from the investigational product used in TP2 (ie, C1-INH or placebo).

### 5.2.2 Supply and Storage

The investigational product will be supplied to the study sites by CSL or delegate.

The investigational product must be stored under temperature-controlled and monitored conditions at the predefined temperature range in a secure storage area as specified in the site Investigational Product Handling Instructions.

### 5.2.3 Direct to Patient

Investigational product may be shipped directly to the subject's home in those countries where it is acceptable. To ensure proper patient data confidentiality a dedicated process with a special courier service will be implemented.

## 5.3 Accountability and Destruction

The investigational product must be used only as directed in the clinical study protocol.

The investigator (or delegate) will confirm receipt of all shipments of investigational product in the interactive response technology (IRT).

All supplies of investigational product must be accounted for throughout the study.

Records for the delivery of investigational product to the study site, the inventory at the study site, the use by each subject, and the destruction or return of investigational product to CSL/designee must be maintained by the investigator (or delegate) using the appropriate form or IRT.

The investigator (or delegate) must provide reasons for any discrepancies in drug accountability.

Used and partially used vials of investigational product will be collected, as applicable. Any unused, partially used, or empty vials of investigational product should not be destroyed until the drug accountability documentation or institution specific destruction procedure has been checked by the study monitor. Any destruction of investigational product must be documented and provided to CSL.

All drug accountability records must be stored in the site file and must be readily available for inspection by the study monitor and/or auditor, and open to regulatory inspection at any time.

Further details regarding accountability and destruction of investigational product are provided in the site Investigational Product Handling Instructions.

## 5.4 Other Intervention(s)

### 5.4.1 Intravenous Immunoglobulin

During the open-label TP1, IVIg will be administered every 4 weeks at a dose of 2 grams/kg. The dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days. The administration of IVIg will begin on Study Day 1 with the following exceptions:

1. For subjects who have received their last dose of IVIg < 1 gram/kg as part of standard of care within the 2 weeks before Study Day 1 OR

2. For subjects who have received their last dose of IVIg ≥ 1 gram/kg as part of standard of care within the 4 weeks before Study Day 1

For these subjects, the administration of IVIg will begin on the Week 4 Visit.

During TP2 and Retreatment Period, IVIg may be administered if DSA ≥ 2000 mean fluorescence intensity (MFI) based on the clinical judgement of the investigator.

The complete schedules for IVIg dosing during TP1, TP2, and any Retreatment Period are presented in Table 1, Table 2, and Table 5, respectively.

All blood draws scheduled for the same visit as IVIg dosing should be taken BEFORE the initiation of IVIg dosing.

If a scheduled dose of IV C1-INH is the same day as IVIg administration, it should be administered AFTER the IVIg dose. Subcutaneous C1-INH may be administered during an IVIg infusion.

### 5.4.2 Plasmapheresis

Donor-specific antibodies will be measured in both the central and local laboratories (see Section 8.1.3.5). Central laboratory results will be used for analyses. Local laboratory results will be used by the investigator in addition to other clinical findings to make treatment decisions, including the initiation of plasmapheresis.

Plasmapheresis should be performed if a subject has DSA with clinical significance based on the PI's medical judgement.

The timing and duration of plasmapheresis should occur as per the local standard of care and be documented in the eCRF. The use of any replacement fluid should also be documented.

If blood draws for laboratory testing (including PK samples) are scheduled at the same visit as plasmapheresis, blood samples should be taken BEFORE plasmapheresis.

If a scheduled dose of C1-INH is the same day as plasmapheresis, it should be administered AFTER plasmapheresis.

If plasmapheresis occurs during a scheduled IVIg administration, administration of IVIg should be postponed until the plasmapheresis session is complete.

Donor-specific antibodies should be tested in the local laboratory within between 24 and 72 hours after completing plasmapheresis.

If the strongest DSA does not decrease by ≥ 50% of pre-plasmapheresis MFI, then plasmapheresis may be repeated, at the discretion of the investigator.

## 5.5 Dose Modification

Modifications of the C1-INH dose (ie, dose increase or dose decrease) are not permitted during the study.

# 6 Allocation, Dosing, and Administration

## 6.1 Allocation to Treatment

### 6.1.1 Subject Assignment

After providing written informed consent, the subject will be issued with a study-level unique subject identification number. The subject identification number will be used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned or reused.

### 6.1.2 Randomization Procedures

All subjects will receive open-label C1-INH during TP1. Subjects who are eligible for TP2 (ie, responder subjects, as defined in Section 8.1.3.2) will be assigned to either continued C1-INH or matched placebo in accordance with a computer-generated randomization list. Investigational product assigned in TP2 will be allocated on a 1:1 ratio. The randomization (permuted block) will be stratified on the following factors:

- DSA: sensitized prior to transplantation versus de novo; de novo is defined as the development of DSA after transplantation. In the case of both sensitized and de novo, the subject will be considered sensitized for stratification purposes.
- AMR severity: severe versus non-severe (ie, all other severities); severe is defined as new onset oliguria (<400 cc/24 hours) or anuria with the current episode of AMR.

Treatment assignment will be determined centrally. The randomization list will be generated and managed by the study's IRT external service provider. A detailed user guide for the IRT will be available.

### 6.1.3 Blinding Procedures

Treatment Period 1 is open-label.

Treatment Period 2 is double-blind. The blind will be maintained during TP2 for investigational site staff, including investigators, and subjects, and CSL.

The blind will be maintained for investigational site staff, including investigators, and subjects during the Responder Follow-up Period, and any Retreatment Periods.

#### 6.1.3.1 Blinding Method

Vials of investigational product (ie, either C1-INH or placebo) will be packaged identically and individual packages may be identified only by the kit number.

Investigational product vials will be fully covered to avoid visual inspection of the contents by the subjects and study personnel. A standard procedure will be followed to completely reconstitute the lyophilized product to make up the solution. The solution will then be withdrawn through a filter and will be inspected in the syringe prior to administration. C1-INH or placebo will be administered in a blinded manner.

A dose of 60 IU/kg C1-INH is equivalent to a volume of 0.12 mL/kg. In order to maintain the blind in TP2, the same volume of investigational product (ie, 0.12 mL/kg, rounded to the lowest mL) will be administered to all subjects regardless of treatment assignment.

#### 6.1.3.2 Breaking the Blind for an Emergency

In emergency situations involving the safety of the subject, the Investigator may break the blind using the IRT system. The reason for unblinding the randomization code must be fully

documented. Emergency unblinding will be performed using the IRT. Steps for navigating the IRT for emergency unblinding are defined in the IRT Manual.

## 6.2 Dosing and Administration

A description of the dose and dosing regimen of the investigational product can be found in Section 3.2.

A description of the investigational product can be found in Section 5.1.

## 6.3 Treatment Compliance

Treatment compliance will be assessed using data captured in the eCRF including the date and time of the injection of investigational product (C1-INH or placebo) and the volume of investigational product that is administered.

# 7 Contraindications, Permitted Therapies, and Prohibited Therapies

## 7.1 Contraindications and Precautions to Further Dosing

The investigational product is contraindicated in individuals who have manifested severe immediate hypersensitivity reactions, including anaphylaxis to C1-INH, albumin, or to any of the excipients of the investigational product (ie, C1-INH or placebo).

## 7.2 Permitted Therapies

The following therapies are PERMITTED during the study (note, this list is not intended to be all inclusive):

- Maintenance immune suppression, steroid therapy, and anti-lymphocyte therapy licensed for clinical use, unless specifically prohibited in Section 7.3.
- Prophylactic antibacterial, antifungal, and antiviral agents.
- Prescribed medication(s) required for the management of chronic medical conditions.
- Over the counter medications and dietary supplements.
- Plasmapheresis, as described in Section 5.4.2.

## 7.3 Prohibited Therapies

The following therapies are NOT PERMITTED during TP1, TP2, and the Retreatment Period:

- Other C1-esterase inhibitor products (eg, Berinert, Cinryze).
- Other complement inhibitors, including eculizumab.
- Proteasome inhibitors, including but not limited to bortezomib, carfilzomib, and ixazomib.
- Any immune suppression agent used to treat AMR that is not licensed for clinical use.
- Administration of any other investigational agent during the study.

Subjects are not to be enrolled into the study if they receive any prohibited therapy or any therapy in a prohibited dosage that cannot be discontinued or reduced to a permitted dose before enrollment.

If administration of any prohibited therapy becomes necessary during the study for medical reasons, the subject may be withdrawn from further study participation.

Subjects are not permitted to receive any prohibited therapies between the time of signing informed consent and the time of completing participation in the study.

## 7.4 Lifestyle Restrictions

Female subjects of childbearing potential and all male subjects must use medically reliable methods of contraception from the first dose of investigational product in any treatment period until 1 month after the last dose of investigational product in the same treatment period.

Childbearing potential is assumed in all female subjects except:

- Female subjects aged > 60 years.
- Female subjects aged 45 to 60 years (inclusive) with amenorrhea for ≥ 1 year.
- Female subjects who are surgically sterile for at least 3 months before providing informed consent.

Acceptable methods of contraception are:

- Abstinence, where abstinence is the preferred and usual lifestyle of the subject, including refraining from heterosexual intercourse during the entire period of risk associated with the investigational product. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable definitions of abstinence.

- Hormonal methods; acceptable hormonal methods include: oral contraceptives, contraceptive medication patch, contraceptive medication injection, estrogen/progestin vaginal ring, or contraceptive medication implant.
- 2 barrier methods; acceptable barrier methods include: female or male condoms, with spermicidal foam or spermicidal jelly, or diaphragm, with spermicidal foam or spermicidal jelly. The female condom and male condom should not be used together.
- Use of intrauterine device (placed more than 3 months before providing informed consent).
- Surgical sterilization (more than 3 months before providing informed consent) of subject or subject's partner.

## 7.5 Overdose

Overdose is defined as the accidental or intentional infusion or ingestion of any dose of the investigation product that is higher than the dose established in this protocol. In a previous study of subjects with HAE, doses up to 6000 IU (up to approximately 120 IU/kg) were administered twice weekly for 4 weeks without any safety issues [C1-INH (500 IU/mL) Investigator's Brochure, 2019].

The effects of any potential overdose with C1-INH have not been otherwise studied. The development of thrombosis has been reported after IV administration of C1-INH doses up to 500 IU/kg body weight when used off label in newborns and young children with congenital heart anomalies during or after cardiac surgery under extracorporeal circulation [Arzteblatt, 2000].

In case of overdose, the subject should be closely monitored, and supportive treatment should be administered, as needed. See Section 9.6.4 for overdose reporting requirements.

# 8 Study Procedures and Visit Schedule

## 8.1 Clinical Procedures

The timing and frequency of the clinical procedures described in the following sections are detailed in the following Schedules of Assessments:

- Schedule of Assessments: Screening and Open-label Treatment Period 1
- Schedule of Assessments: Blinded Treatment Period 2
- Schedule of Assessments: Responder Follow-up

- Schedule of Assessments: Non-responder Follow-up Period
- Schedule of Assessments: Blinded Retreatment Period
- Schedule of Assessments: Sequential Pharmacokinetic / CCI Sampling Conducted in a Subset of Subjects

More frequent evaluations may be performed, if clinically indicated, at the discretion of the investigator at unscheduled study visits. The specific procedures performed at any unscheduled study visit are at the discretion of the investigator and are to be captured in the eCRF, including representative allograft biopsies.

### 8.1.1 Demographics and Safety Assessments

The clinical procedures to be conducted during this study related to the evaluation of population demographics and safety are provided in Table 13. Clinical laboratory assessments are to be performed at time points as detailed in the schedule of assessments. The time windows for each type of assessment are detailed in Section 8.5.1.

**Table 13 Study Procedures: Demographics and Safety Assessments**

| Assessment | Description |
|---|---|
| Demographics | • Date of birth<br>• Sex<br>• Race<br>• Ethnicity |
| Medical history | • Relevant medical history within 6 months before informed consent<br>• Documentation of date of biopsy<br>• Allograft donor information<br>• Diagnosis and disease status:<br>  ○ Transplant history<br>  ○ Previous episodes of rejection<br>  ○ Documentation of thrombotic microangiopathy and Banff category scores from the biopsy used to qualify for enrollment<br>  ○ Serum creatinine drawn at the time of inclusion biopsy (± 2 weeks)<br>• Prior therapies within 3 months before informed consent<br>• Current/concomitant therapies |
| Pregnancy test | • Urine or blood test for choriogonadotropin beta, as indicated for women of childbearing potential. |
| Physical examination | • As per the investigator's standard procedure, and including assessment of unilateral pain and/or swelling of the lower extremities |
| Adverse events | • Refer to Section 9 |

| Assessment | Description |
|---|---|
| Vital signs | • Blood pressure (systolic and diastolic)<br>• Pulse rate (per minute)<br>• Body temperature<br>• Body weight<br>• Body height (Screening only) |
| Hematology | • Hemoglobin<br>• Hematocrit<br>• Red blood cell indices: mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume (if any available)<br>• Blood cell counts: basophils, eosinophils, erythrocytes, leukocytes, lymphocytes, monocytes, neutrophils, neutrophil band forms (if available), platelets, reticulocytes (if available) |
| Serum biochemistry panel | • Albumin<br>• Alkaline phosphatase<br>• Alanine aminotransferase<br>• Aspartate aminotransferase<br>• Bilirubin (total)<br>• Blood urea nitrogen (or Urea)<br>• Calcium<br>• Carbon dioxide<br>• Chloride<br>• Creatinine<br>• Glucose<br>• Potassium<br>• Sodium<br>• Protein (total)<br>Note: Creatinine will be measured by the central laboratory and as a part of the serum biochemistry panel by the local laboratory. |
| CCI [redacted] | • CCI [redacted] |
| Virus testing | • Hepatitis panel<br>o Hepatitis B core antibody (IgM)<br>o Hepatitis B surface antigen with nucleic acid testing confirmation<br>o Hepatitis C antibody with nucleic acid testing confirmation<br>• Retention samples may be tested for transmissible infectious agents |

### 8.1.2 Pharmacokinetic and CCI [redacted] Assessments

Pharmacokinetic and CCI evaluations will be conducted during the study. Table 14 presents a description of the analytes that will be measured. Table 1, Table 2, and Table 3 present the timing of measurement for each analyte.

**Table 14 Pharmacokinetic and CCI Analytes**

| Assessment | Description |
|---|---|
| C1-esterase inhibitor activity/antigen | • C1-esterase inhibitor antigen concentration.<br>• C1-esterase inhibitor functional activity. |
| Immunoglobulin concentration | • Immunoglobulin concentration. |
| CCI | • CCI .<br>• CCI .<br>• CCI .<br>• CCI .<br>• CCI . |

CCI

### 8.1.3 Efficacy Assessments

Efficacy assessments conducted during the study will include:

- eGFR.
- Responder status (ie, response/loss-of-response).
- Biopsy histopathology.
- Splenectomy.
- DSA.
- CCI
- Allograft failure.
- Subject survival.
- CCI
- Development of recurrent/persistent AMR.

#### 8.1.3.1 Estimated Glomerular Filtration Rate (eGFR)

Creatinine will be assessed as a part of the serum biochemistry panel or as an independent assessment. Creatinine measurements, in addition to what is pre-specified per protocol, may be performed as a part of standard of care.

For the purposes of determining eGFR for the primary endpoint, creatinine will be measured in a central laboratory. Creatinine will be measured using a standardized creatinine assay calibrated to be traceable to an isotope dilution mass spectrometry reference measurement procedure.

For purposes of determining eGFR at the time of inclusion biopsy and in non-responders during the Non-responder Follow-up Period prior to Amendment 3, creatinine measurements that are performed as part of clinical standard of care may be abstracted from the medical record.

In addition, creatinine will also be measured in the local laboratory as part of the serum biochemistry panel or additionally at the discretion of the physician. If it is measured in the local laboratory, then the results should be documented in the eCRF.

In all cases, eGFR will be calculated using the following MDRD formula [Levey et al, 2008]:

$$eGFR = [(175) \times (\text{standardized } S_{cr}^{-1.154}) \times (age^{-0.203}) \times (1.212, \text{ if black}) \times (0.742, \text{ if female})],$$
where $S_{cr}$ is expressed as mg/dL

Additional details regarding the assessment of eGFR will be presented in the laboratory manual.

### 8.1.3.2 Responder Status and Loss-of-Response

Responder status in TP1 is determined at the Week 13 Visit to randomize subjects into the double-blind TP2. Only responders in TP1 are randomized.

Responder status and loss-of-response at the End-of-TP2 are defined in Section 10.3.1.

Central laboratory measurements of creatinine will be used for calculation of eGFR, except for creatinine values collected from the medical record (Section 8.1.3.1). Response and loss-of-response will be determined by CSL.

### 8.1.3.3 Renal Allograft Biopsy

***Inclusion Biopsy***

The renal allograft biopsy used to determine inclusion into the study will have been performed as standard of care within 90 days before the Day 1 Visit. The diagnosis of AMR can be made > 90 days before Day 1 as long as the inclusion biopsy establishes that AMR is ongoing within 90 days of Day 1. Slides stained with hematoxylin and eosin stain, periodic acid-Schiff, trichrome stain, and silver stain or will be provided to the central histopathologist for evaluation as the baseline for comparison with the Week 38 biopsy.

***Week 38 Biopsy***

A biopsy will be performed at Week 38 (ie, the End-of-TP2), and will be compared to the inclusion biopsy to assess changes in histopathology. Where possible, a biopsy should also be performed for subjects who discontinue treatment before the Week 38 Visit. The central histopathologist will be blinded to treatment assignment beginning with TP2.

***Biopsy during the Responder Follow-up Period***

Subjects may have additional biopsies as part of their local standard of care treatment at any point during the study, including during the Responder Follow-up Period. A biopsy at the Week 38 Visit or during the Responder Follow-up Period that shows evidence of infiltrating neutrophils and/or monocytes with or without the presence of C4d ($g > 0$, $v > 0$, and/or $ptc > 0$; if C4d is negative, $g + ptc \geq 2$) will qualify as an episode of acute AMR (see Appendix 3). A subject with a biopsy-proven persistent or recurrent episode of AMR may receive additional treatment according to their previous randomization (C1-INH or placebo) in addition to monthly IVIg (2 grams/kg) (Table 5). Slides of any biopsy taken during the Responder Follow-up Period documenting a persistent or recurrent episode of AMR will be provided to the central histopathologist.

***Histopathology***

Representative histopathology sections from each renal allograft biopsy will be processed with hematoxylin and eosin stain, periodic acid-Schiff, trichrome stain, and silver stain. In addition, frozen or formalin fixed biopsy sections will be processed for the presence of C4d by any immunoassay.

In addition, any electron micrograph images (if available) from representative allograft biopsies should be sent to the central repository for the study pathologist.

Biopsy histopathology will be assessed by a central study pathologist for CCI [redacted] and Banff category scoring (see Appendix 3). Biopsy histopathology will be recorded in the eCRF.

Additional details regarding the processing of biopsy sections and assessment of histopathology will be presented in the laboratory manual.

#### 8.1.3.4 Splenectomy

If a splenectomy (or total splenic irradiation) is performed for any reason, then the date and reason will be recorded in the eCRF.

#### 8.1.3.5 Donor-specific Antibody (DSA)

Donor-specific antibody identification and specificity will be performed using a tiered approach. DSA to HLA Class I and Class II antigens will be identified by the Luminex solid-phase single-bead antigen immunoassay. If any DSA is ≥ 5000 MFI on a neat serum sample, then dilution testing of 1:16 should be performed to determine if the DSA drops to below 2000 MFI or remains strong (≥ 5000 MFI). Additional titers may be tested at the discretion of the investigator. Local DSA results will not be recorded in the eCRFs.

Decisions regarding the conduct of plasmapheresis will be based on local laboratory analysis of DSA, as outlined in Section 5.4.2. Samples will also be sent for central laboratory testing. Central laboratory results will be used for analyses.

Additional details regarding the assessment of DSA will be presented in the laboratory manual.

#### 8.1.3.6 CCI [redacted]

CCI [redacted]

#### 8.1.3.7 Allograft Failure

Allograft failure is defined as 1 of the following, whichever occurs first:

- Allograft nephrectomy.
- Institution of permanent dialysis; permanent dialysis is defined as dialysis ongoing for ≥ 30 days.
- Return to the transplant waitlist for renal transplant.

The date and cause of the first failure event will be recorded in the eCRF (if known).

#### 8.1.3.8 Subject Survival

Subject survival (yes/no) will be determined by site visits or phone call. The date of each assessment will be recorded in the eCRF. In the case of subject death, the date and cause of death, and allograft status at time of death will be recorded in the eCRF (if known).

#### 8.1.3.9 CCI

CCI

### 8.1.4 Health-related Quality of Life Assessments

The EQ-5D-3L provides a simple descriptive profile of the subject's health state and a single visual analogue scale index value for overall health that can be used in the clinical and economic evaluation of health care as well as in population health surveys [Dolan, 1997; Cleemput et al, 2004]. It will be performed in countries where validated language versions of the questionnaires are available.

The EQ-5D-3L descriptive profile of health state consists of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The subject rates

## 8.2 Blood Samples

During the study, blood will be taken from each subject for laboratory safety assessments and PK/CCI evaluations.

The Investigator must review the laboratory report and evaluate any results (other than renal function tests) that are outside the normal range and determine clinical significance.

All abnormal laboratory values will be entered on the eCRF with a comment. The following codes should be used to add a comment on the respective eCRF:

- Error (ER; e.g., laboratory error, improper sample preparation, hemolysis, delayed transit to laboratory, etc.).
- Abnormal, not clinically significant (ANCS).
- Abnormal, clinically significant (ACS).

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

Refer to the Laboratory Manual for details about the collection (including volume of blood sample), storage, handling and processing of blood samples.

## 8.3 Retention of Samples

Blood samples for retention will be obtained at the Day 1 Visit (prior to the first dose of C1-INH in TP1) and Week 12 during TP1 and at the Week 38 Visit during TP2. Subjects who withdraw before completing TP1 and TP2 will be asked to complete scheduled blood draw for retention samples.

For subjects who participate in a Retreatment Period, blood samples for retention will be obtained at the Day 1 Retreatment Visit (prior to the first dose of C1-INH in a Retreatment Period) and at the Week 26 Retreatment Visit.

Retention samples will be shipped to CSL and stored at -70°C for potential testing of viral markers, and will be destroyed within 5 years after completion of the study. Refer to the Laboratory Manual for further details about the storage and destruction of retention samples.

## 8.4 Prior and Concomitant Therapies

All therapies (eg, medications and/or procedures) that have been administered to a subject within 3 months of signing informed consent are regarded as prior therapies and must be documented as such in the eCRF.

All therapies (eg, medications and/or procedures) being administered to a subject at the time of signing informed consent, and which continue to be taken in addition to investigational product during the study, are regarded as concomitant therapies and must be documented as such in the eCRF.

## 8.5 Visit Schedule

### 8.5.1 Assessment Time Windows

The time windows associated with all visits and assessments are provided in the following Schedules of Assessments:

- Schedule of Assessments: Screening and Open-label Treatment Period 1
- Schedule of Assessments: Blinded Treatment Period 2
- Schedule of Assessments: Responder Follow-up
- Schedule of Assessments: Non-responder Follow-up Period
- Schedule of Assessments: Blinded Retreatment Period
- Schedule of Assessments: Sequential Pharmacokinetic / CCI Sampling Conducted in a Subset of Subjects

### 8.5.2 Screening

All subjects must provide written informed consent before any study-specific assessments or procedures are performed. Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for diagnosis or treatment); results from such assessments may be used in the determination of study eligibility.

Screening should be completed within 14 days before the intended date of the first administration of C1-INH at the Day 1 Visit. The procedures scheduled for Screening may be conducted over more than a single day, when necessary.

For all subjects who had the Screening Visit prior to Amendment 3, creatinine measurement at the time of the inclusion biopsy (± 2 weeks) will be collected retrospectively by way of medical history records.

The following procedures will be conducted and documented at Screening:

- Written informed consent.
- Registration of the subject via IRT.
- Demographics.
- Medical history, including creatinine measurement at the time of the inclusion biopsy.
- Physical examination.
- Vital signs.
- CCI [redacted]
- Blood draws:
  - Serum pregnancy test (for female subjects of childbearing potential).
  - HBV and HCV test.
  - Retention sample for viral serology.
  - Creatinine.
  - Serum biochemistry panel.
  - Hematology.
- Adverse events.
- Prior and concomitant therapies.
- Inclusion and exclusion criteria.

**Screen Failure:** If the subject is not eligible for the study, the primary reason for screen failure must be entered in the eCRF.

**Re-screening after screen failure:** If a potential subject was not enrolled into the study within 14 days after providing informed consent, then potential subjects may re-consent and may be screened again; however, only pregnancy testing, creatinine, and any assessments for which the subject failed on the first screening need to be conducted. In the event that a potential subject has screening assessments ≥ 60 days prior to entering the study, all screening assessments must be repeated.

### 8.5.3 Treatment Period 1

#### 8.5.3.1 Day 1 Visit

The following procedures will be conducted at the Day 1 Visit:

- Physical examination.
- Vital signs.
- Serum pregnancy test (for female subjects of childbearing potential) if the screening pregnancy test was > 24 hours before the Day 1 Visit.
- EQ-5D-3L questionnaire.
- Blood draws:
  - Creatinine.
  - Serum biochemistry panel.
  - Hematology.
  - CCI [redacted]
  - DSA.
  - C1-esterase inhibitor activity/antigen.
  - Immunoglobulin concentration.
  - CCI [redacted]
  - CCI [redacted]

  **NOTE:** All blood draws should be completed before administration of C1-INH and IVIg.
- Intravenous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- IVIg begins (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).

  **NOTE:** See Section 5.4.1 for details.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

### 8.5.3.2 Day 4 Visit

The following procedures will be conducted at the Day 4 Visit:

- Intravenous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- Adverse events.
- Concomitant therapies.
- C1-esterase inhibitor activity/antigen.
- Schedule next visit.

### 8.5.3.3 Day 7 Visit

The following procedures will be conducted at the Day 7 Visit:

- Physical examination.
- Vital signs.
- Blood draws:
  - Creatinine.
  - Serum biochemistry panel.
  - Hematology.
  - C1-esterase inhibitor activity/antigen.

  **NOTE:** All blood draws should be completed before administration of C1-INH.
- Intravenous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

### 8.5.3.4 Day 10 Visit

The following procedures will be conducted at the Day 10 Visit:

- Blood draws:
  - C1-esterase inhibitor activity/antigen.
  - CCI [redacted]

  **NOTE:** The blood draw should be completed before administration of C1-INH.
- Intravenous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).

- Adverse events.
- Concomitant therapies.
- Schedule next visit.

Subjects who are a part of the CCI [redacted] will undergo procedures as presented above, but will also have additional blood draws, as presented in Table 6.

#### 8.5.3.5 Day 13 Visit

The following procedures will be conducted at the Day 13 Visit:

- Intravenous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).

  **NOTE:** This is the final IV dose of C1-INH.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.3.6 Day 14 Visit

The following procedures will be conducted at the Day 14 Visit:

- Physical examination.
- Vital Signs.
- Blood draws:
  - Creatinine.
  - Serum biochemistry panel.
  - Hematology.
  - C1-esterase inhibitor activity/antigen.
  - CCI [redacted]

  **NOTE:** All blood draws should be completed before administration of C1-INH.
- Subcutaneous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).

  **NOTES:**
  - This is the first SC dose of C1-INH.
  - This administration of C1-INH should be timed to occur 24 to 48 hours after the final IV dose of C1-INH.

- Subsequent administrations of the investigational product should occur every 3 or 4 days (ie, twice weekly).

- Investigational product dispense, if applicable.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.3.7 Week 3 Visit

The following procedures will be conducted at the Week 3 Visit:

- Blood draws:
  - Creatinine.
  - Serum biochemistry panel.

  **NOTE:** All blood draws should be completed before administration of C1-INH.
- Subcutaneous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.3.8 Week 4 Visit

The following procedures will be conducted at the Week 4 Visit:

- Physical examination.
- Vital signs.
- Urine or serum pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.
  - Serum biochemistry panel.
  - CCI
  - DSA.

- C1-esterase inhibitor activity/antigen.
- Immunoglobulin concentration.
- CCI

**NOTE:** All blood draws should be completed before administration of C1-INH and IVIg.

- Adverse events.
- Concomitant therapies.
- Subcutaneous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- IVIg begins (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).

  **NOTE:** See Section 5.4.1 for details.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.3.9 Week 5, Week 6, and Week 7 Visits

The following procedures will be conducted at the Week 5, 6, and 7 Visits:

- Blood draws:
  - Creatinine.
  - Serum biochemistry panel.

  **NOTE:** All blood draws should be completed before administration of C1-INH.
- Subcutaneous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

### 8.5.3.10 Week 8 Visit

The following procedures will be conducted at the Week 8 Visit:

- Physical examination.
- Vital Signs.
- Urine or serum pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.
  - Serum biochemistry panel.
  - CCI [redacted]
  - DSA.
  - C1-esterase inhibitor activity/antigen.
  - Immunoglobulin concentration.
  - CCI [redacted]

  **NOTE:** All blood draws should be completed before administration of C1-INH and IVIg.
- Subcutaneous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- IVIg begins (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

### 8.5.3.11 Week 9 and Week 10 Visits

The following procedures will be conducted at the Week 9 and 10 Visits:

- Blood draws:
  - Creatinine.
  - Serum biochemistry panel.
  - C1-esterase inhibitor activity/antigen (Week 10 only).

  **NOTE:** All blood draws should be completed before administration of C1-INH.

- Subcutaneous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.3.12 Week 11 Visit

The following procedures will be conducted at the Week 11 Visit:

- Blood draws:
  - Creatinine.
  - Serum biochemistry panel.

  **NOTE:** All blood draws should be completed before administration of C1-INH.
- Subcutaneous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

Subjects who are a part of the CCI [redacted] will undergo procedures as presented above, but will also have additional blood draws, as presented in Table 6.

CCI [redacted]

#### 8.5.3.13 Week 12 Visit

The following procedures will be conducted at the Week 12 Visit:

- EQ-5D-3L questionnaire.
- Blood draws:
  - Creatinine.

- Serum pregnancy test (for female subjects of childbearing potential).
- Serum biochemistry panel.
- Hematology.
- CCI [redacted]
- DSA.
- C1-esterase inhibitor activity/antigen.
- Immunoglobulin concentration.
- CCI [redacted]
- CCI [redacted].
- Retention sample for viral serology.

**NOTE:** All blood draws should be completed before administration of C1-INH and IVIg.

- Subcutaneous administration of C1-INH (60 IU/kg, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- IVIg begins (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.3.14 Week 13 Visit/End of Treatment Period 1 for Non-responders/Start of Treatment Period 2 for Responders

The following procedures will be conducted at the Week 13 Visit, or if a subject withdraws/discontinues from the study during TP1:

- Physical examination.
- Vital Signs.
- Adverse events.
- Concomitant therapies.
- Responder status, as determined by CSL.

- Randomization of responders to treatment with blinded investigational product (either C1-INH or placebo) in TP2.
- Investigational product dispense, if applicable.
- Subcutaneous administration of C1-INH/placebo (60 IU/kg, dose rounded to the lowest 1 mL) for responders.
- Investigational product vial return, if applicable.
- Schedule next visit.

**Early Withdrawal During Treatment Period 1**

In addition, for subjects who withdraw/discontinue from the study during TP1, the following blood draws should also be collected:

- Creatinine.
- Serum biochemistry panel.
- Hematology.
- CCI [redacted]
- DSA.
- C1-esterase inhibitor activity/antigen.
- Immunoglobulin concentration.
- CCI [redacted]
- CCI [redacted]
- Retention sample for viral serology.
- Serum pregnancy test (for female subjects of childbearing potential).

### 8.5.4 Treatment Period 2

Beginning at the final visit in Treatment Period 1 (ie, the Week 13 Visit), and throughout TP2:

- Beginning during TP2, a blood sample for creatinine measurement will be drawn once every 14 days (± 7 days) at the study site, at home by a medical professional. The frequency of blood draw for creatinine measurement may occur more frequently at the investigator's discretion.
- Subcutaneous investigational product (ie, C1-INH or placebo) will be administered every 3 or 4 days (ie, twice weekly), as per the randomization schedule.

#### 8.5.4.1 Week 16 Visit

The following procedures will be conducted at the Week 16 Visit:

- Blood draws:
  - Creatinine.
  - Serum pregnancy test (for female subjects of childbearing potential).
  - CCI [redacted]
  - DSA.
  - C1-esterase inhibitor activity/antigen.
  - CCI [redacted]

  **NOTE:** All blood draws should be completed before administration of investigational product and IVIg.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- IVIg may begin if DSA is ≥ 2000 MFI (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.4.2 Week 20 Visit

The following procedures will be conducted at the Week 20 Visit:

- Urine or serum pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.
  - Serum Biochemistry panel.
  - Hematology.
  - CCI [redacted]

- DSA.

**NOTE:** All blood draws should be completed before administration of investigational product and IVIg.

- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- IVIg may begin if DSA is ≥ 2000 MFI (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.4.3 Week 24 Visit

The following procedures will be conducted at the Week 24 Visit:

- Physical Examination.
- Vital Signs.
- Urine or serum pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.
  - CCI [redacted]
  - DSA.

  **NOTE:** The blood draw should be completed before administration of investigational product and IVIg.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.

- IVIg may begin if DSA is ≥ 2000 MFI (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.4.4 Week 28 Visit

The following procedures will be conducted at the Week 28 Visit:

- Urine or serum pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.
  - Serum Biochemistry panel.
  - Hematology.
  - CCI [redacted]
  - DSA.

  **NOTE:** All blood draws should be completed before administration of investigational product and IVIg.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- IVIg may begin if DSA is ≥ 2000 MFI (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.4.5 Week 32 Visit

The following procedures will be conducted at the Week 32 Visit:

- Urine or serum pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.
  - CCI [redacted]
  - DSA.
  - C1-esterase inhibitor activity/antigen.
  - Immunoglobulin concentration.

  **NOTE:** All blood draws should be completed before administration of investigational product and IVIg.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- IVIg may begin if DSA is ≥ 2000 MFI (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.4.6 Week 38 Visit/End of Treatment Period 2 Visit

The following procedures will be conducted at the Week 38 Visit:

- EQ-5D-3L questionnaire.
- Physical examination.
- Vital Signs.
- Pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.
  - Serum pregnancy test (for female subjects of childbearing potential).
  - Serum biochemistry panel.
  - Hematology.

- CCI [redacted]
- DSA.
- C1-esterase inhibitor activity/antigen.
- CCI [redacted]
- Retention sample for viral serology.
- CCI [redacted].

**NOTE:** All blood draws should be completed before administration of investigational product.

- CCI [redacted]
- Biopsy of kidney allograft.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- **NOTE:** This is the final dose of blinded investigational product administered as a part of TP2.
- Investigational product vial return, if applicable.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

### 8.5.5 Responder Follow-up Period

Throughout the Responder Follow-up Period:

- Assessment of DSA and/or allograft biopsy will be conducted as per local standard of care. If the investigator becomes aware of an AE that has started after the observation period has finished, and there is at least a possible causal relationship to the investigational product, the event must be reported to CSL (see Section 9.4).

#### 8.5.5.1 Month 12 Visit

The following procedures will be conducted at the Month 12 Visit:

- EQ-5D-3L questionnaire.
- Blood draws:

  - Creatinine.
  - CCI .
  - C1-esterase inhibitor activity/antigen.
  - CCI
- Allograft failure (yes/no).
- Subject survival (yes/no).
- Development of biopsy-confirmed AMR since the last visit (yes/no).
- Schedule next visit.

#### 8.5.5.2 Month 18, Month 24, Month 30, Month 36, and Month 42 Visits

The following procedures will be conducted at the Month 18, 24, 30, 36, and 42 Visits:

- EQ-5D-3L questionnaire (Month 24 and 36 Visits only).
- Blood draws:
  - Creatinine.
- Allograft failure (yes/no).
- Subject survival (yes/no).
- Development of biopsy-confirmed AMR since the last visit (yes/no).
- Schedule next visit.

#### 8.5.5.3 Month 48 Visit/End of Study Visit

The following procedures will be conducted at the Month 48 Visit, or if a subject withdraws from the study during the Responder Follow-up Period:

- EQ-5D-3L questionnaire
- Blood draws:
  - Creatinine.
  - CCI .
- Allograft failure (yes/no).
- Subject survival (yes/no).
- Development of biopsy-confirmed AMR since the last visit (yes/no).
- Serious Adverse Events.

## 8.5.6 Retreatment Period(s)

- Subjects may undergo retreatment during the Responder Follow-up Period with the blinded investigational product to which they were randomized in TP2. Retreatment may occur following a diagnosis of persistent or recurrent AMR by biopsy, evidenced by infiltrating neutrophils and/or monocytes with or without the presence of C4d (g > 0, v > 0, and/or ptc > 0; if C4d is negative, g + ptc ≥ 2).
- Retreatment may start at any time during the Responder Follow-up Period, and will last for 25 weeks or until the Month 48 Visit, whichever occurs first. The Retreatment Period may also be shorter than 25 weeks at the investigator's discretion.
- If retreatment is stopped prior to completing the entire Retreatment Period, the procedures at the Retreatment Week 26 visit should replace the procedures at the scheduled monthly visit.
- Subcutaneous investigational product (ie, C1-INH or placebo) will be administered every 3 or 4 days (ie, twice weekly) during a Retreatment Period.
- Assessment of DSA will be conducted as per local standard of care.

### 8.5.6.1 Retreatment Day 1 Visit

The following procedures will be conducted at the Retreatment Day 1 Visit:

- Confirmation of recurrent, acute AMR, as shown by biopsy.
- Physical examination.
- Vital signs.
- Blood draws:
  - Creatinine.
  - Serum pregnancy test (for female subjects of childbearing potential).
  - Retention sample for viral serology.

  **NOTE:** All blood draws should be completed before administration of C1-INH and IVIg.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- IVIg may begin if DSA is ≥ 2000 MFI (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).

- Adverse events.
- Concomitant therapies.
- Schedule next visit.

### 8.5.6.2 Retreatment Day 7 Visit

The following procedures will be conducted at the Retreatment Day 7 Visit:

- Blood draws:
  - Creatinine.

  **NOTE:** The blood draw should be completed before administration of C1-INH.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

### 8.5.6.3 Retreatment Week 4 and Week 8 Visits

The following procedures will be conducted at the Retreatment Week 4 and Week 8 Visits:

- Urine or serum pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.

  **NOTE:** The blood draw should be completed before administration of C1-INH and IVIg.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- IVIg may begin if DSA is ≥ 2000 MFI (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.

- Concomitant therapies.
- Schedule next visit.

### 8.5.6.4 Retreatment Week 12 Visit

The following procedures will be conducted at the Retreatment Week 12 Visit:

- Physical examination.
- Vital signs.
- Urine or serum pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.

  **NOTE:** The blood draw should be completed before administration of C1-INH and IVIg.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.
- Investigational product vial return, if applicable.
- IVIg may begin if DSA is ≥ 2000 MFI (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

### 8.5.6.5 Retreatment Week 16 and Week 22 Visits

The following procedures will be conducted at the Retreatment Week 16 and Week 22 Visits:

- Urine or serum pregnancy test (for female subjects of childbearing potential).
- Blood draws:
  - Creatinine.

  **NOTE:** The blood draw should be completed before administration of C1-INH and IVIg.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product dispense, if applicable.

- Investigational product vial return, if applicable.
- IVIg may begin if DSA is ≥ 2000 MFI (2 grams/kg total dose; the dose must be administered over a minimum period of at least 2 days, and may be administered over a period of up to 5 days).
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

#### 8.5.6.6 Retreatment Week 26 Visit

The following procedures will be conducted at the Retreatment Week 26 Visit:

- Physical examination.
- Vital signs.
- Blood draws:
  - Creatinine.
  - Retention sample for viral serology.
  - Serum pregnancy test (for female subjects of childbearing potential).

  **NOTE:** All blood draws should be completed before administration of C1-INH.
- Subcutaneous administration of blinded investigational product (C1-INH [60 IU/kg] or placebo, dose rounded to the lowest 1 mL).
- Investigational product vial return, if applicable.
- Adverse events.
- Concomitant therapies.
- Schedule next visit.

### 8.5.7 Non-responder Follow-up Period

The following will be collected during the Non-responder Follow-up Period at 3 months (± 2 days) following the Week 13 Visit, then every 6 months (± 28 days) until the end of the Non-responder Follow-up Period:

- Graft failure (yes/no, date of failure if available)
- Subject survival (yes/no)

- Development of biopsy-confirmed AMR (yes/no)
- Creatinine measurement

  Creatinine will be measured by the central laboratory for prospectively collected samples from subjects who enter the Non-responder Follow-up Period after Amendment 3. Creatinine values may be obtained retrospectively from medical records if samples cannot be drawn prospectively.
- EQ-5D-3L (Months 12, 24, 36, and 48)

### 8.5.8 Subject Withdrawal/Discontinuation

#### 8.5.8.1 Withdrawal/Discontinuation during Treatment Period 1

If a subject is withdrawn/discontinued from the study for any reason during TP1, then the investigator should make every effort to perform the assessments scheduled for the Week 13 Visit. In addition, investigators should contact these subjects by telephone approximately 30 days after the Week 13 Visit (ie, End-of-TP1 Visit) to collect follow-up safety information.

#### 8.5.8.2 Withdrawal/Discontinuation during Treatment Period 2

If a subject is withdrawn from the study for any reason during TP2, the investigator should make every effort to perform the assessments scheduled for the Week 38 Visit. In addition, investigators should contact these subjects by telephone approximately 30 days after the Week 38 Visit (ie, End-of-TP2 Visit) to collect follow-up safety information.

#### 8.5.8.3 Withdrawal/Discontinuation during any Retreatment Period

If a subject is withdrawn from the study for any reason during a Retreatment Period, the investigator should make every effort to perform the assessments scheduled for the Retreatment Week 26 Visit. In addition, investigators should contact these subjects by telephone approximately 30 days after the Retreatment Week 26 Visit (ie, the End of Retreatment Period Visit) to collect follow-up safety information.

#### 8.5.8.4 Withdrawal/Discontinuation during the Follow-up Period

If a subject is withdrawn from the study for any reason during the Follow-up Period, the investigator should make every effort to perform the assessments scheduled for the Month 48 Visit.

# 9 Adverse Events

## 9.1 Definitions

### 9.1.1 Adverse Event

As per the ICH guidelines, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal product (eg, the investigational product), whether or not considered related to the medicinal product (eg, the investigational product).

The period of observation for AEs extends from the time the subject gives informed consent until 30 days after the last administration of any investigational product (see Section 9.4 for further details).

Adverse events may include:

- A clinical event occurring after written informed consent but before administration of the investigational product.
- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- Intercurrent illnesses with an onset after administration of investigational product.

Adverse events do not include:

- Events identified at Screening that meet exclusion criteria.
- Medical or surgical procedures (the condition that leads to the procedure is the AE).
- Situations where an untoward medical occurrence has not taken place, including:
  - Planned hospitalizations due to pre-existing conditions, which have not worsened.
  - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).
  - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy).

  - Overdose of investigational product or any concomitant therapy that does not result in any adverse signs or symptoms.
- Selected endpoints and transplant-related disease events, including:
  - Elevated creatinine.
  - Worsening of renal function and related laboratory changes.
  - Hospitalization for per protocol IVIg administration or other immune suppressive therapy.
  - Hospitalization for per protocol plasmapheresis.
  - Allograft failure.

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the investigator as clinically significant must recorded in the eCRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at Screening, unless a further increase/decrease can be considered an exacerbation of a pre-existing condition.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life or outside the measuring range).
- An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (ie, the previous result could be marked as not valid and should not necessarily be reported as an AE).

### 9.1.2 Adverse Event of Special Interest

There are several AEs that will be monitored as AEs of special interest to enable an adequate risk-benefit evaluation of the C1-INH.

The following events will be considered AEs of special interest:

- Thromboembolic events (TEEs).
  - Any systemic TEE is considered an SAE and should be reported as such. Additionally, any non-systemic TEE (eg, a TEE associated with dialysis access or other vascular access) that meets the serious criteria must be reported as an SAE.
  - Any non-serious access-related thrombosis should be entered as an AE on the eCRF and will be part of the regular review of AEs of special interest by the IDMC.
- Anaphylaxis.
  - All events of anaphylaxis are considered SAEs and should be reported as such.

### 9.1.3 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.
- **Is life-threatening** – The term "life-threatening" 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 that hypothetically might have caused death if it had been more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization** – CSL considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
- **Results in persistent or significant disability or incapacity**.
- **Is a congenital anomaly or birth defect**.
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion. Transmission of an infectious agent may be considered medically significant.

Additionally, AEs of special interest may be considered SAEs (see Section 9.1.2).

Adverse events that do not fall into the above categories are defined as non-serious AEs.

## 9.2 Severity of Adverse Events

The severity of each AE (ie, non-serious and serious AEs) is to be assessed by the investigator as described in Table 15.

**Table 15 Severity of Adverse Events**

| Severity | Definition |
|---|---|
| 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 additional 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 subject. |
| Severe | A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. |

Source: CDISC SDTM Severity Intensity Scale for Adverse Event Terminology.

## 9.3 Causality of Adverse Events

The causal relationship of an AE to the investigational product **must always be assessed** by the investigator. All AEs will be classified as either **related** or **not related** to the investigational product. If a causality assessment is not provided for an AE (including an SAE), then that AE will be considered related to the investigational product.

The degree of certainty with which an AE is attributed to the investigational product (ie, C1-INH or placebo) or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of the investigational product.
- Clinically and/or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor).
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with the investigational product, drug withdrawal or reproduced on rechallenge).

## 9.4 Observation Period for Adverse Events

For TP1 and TP2, the observation period for AEs and SAEs reporting for an individual subject will start at the time of giving written informed consent for participation in the current study and finish 30 days after the last administration of any investigational product as a part of TP1 and TP2.

Throughout the Responder Follow-up Period, if the investigator becomes aware of an AE that has started after the observation period has finished, and there is at least a possible causal relationship to the investigational product, the event must be reported to CSL (see Section 9.6).

If a subject participates in a Retreatment Period, the observation period for AEs and SAEs reporting for an individual subject will start at the Retreatment Day 1 Visit and finish 30 days after the last administration of any investigational product as a part of Retreatment Period.

## 9.5 Follow-up of Adverse Events

Every effort should be made to follow AEs until resolution or stabilization. Ongoing, non-serious AEs that have not resolved or stabilized will be followed until the subject completes the study. Serious adverse events will be followed until the AE resolves, stabilizes, or the subject is lost to follow-up.

## 9.6 Adverse Event Reporting

### 9.6.1 Adverse Events

At each clinical evaluation, the investigator (or delegate) will determine whether any AEs have occurred. AEs will be recorded in the AE/SAE eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms. The investigator must follow up on the course of an AE until resolution or stabilization. If an AE is ongoing after the end of study visit, the AE will continue to be followed up until resolution, stabilization, or the subject is lost to follow-up.

If, during the study period, a subject presents with a preexisting condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History eCRF.

### 9.6.2 Serious Adverse Event Reporting

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the eCRF.

An electronic document containing the AE page and other applicable pages of the eCRF must be sent (via facsimile or email) to CSL together with a Notification of Serious Adverse Event at Investigator Site cover page, which has been signed and dated by the Investigator. If an electronic document is not able to be generated (eg, internet access problem), a handwritten paper SAE report must be completed, which must be signed and dated by the investigator.

**All SAEs that occur during the course of the study, whether or not causally related to the investigational product, must be entered into the eCRF and CSL notified immediately (within 24 hours of the investigator becoming aware of the event).**

Adverse events occurring in the period between the time the subject gave written informed consent and the first exposure to the investigational product that meet 1 or more of the seriousness criteria be entered into the eCRF in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs after the Week 38 Visit or during the Responder Follow-up Period that is considered to be causally related to the investigational product must be reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSL.

The minimum reporting requirements for reporting of SAEs include:

- Subject identification number.
- Suspected medicinal product and/or procedure.
- Event term.
- Reporting source identification.

If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event.

In addition, the investigator must:

- Report all SAEs to the relevant Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within the timeframe specified by the IRB/IEC.
- Enter follow-up information in the eCRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
- Ensure that the causality assessment for all SAEs is entered in the eCRF.

In cases of death, the investigator should supply CSL and the IEC/IRB (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports).

### 9.6.3 Other Significant Event Reporting

Adverse events of special interest (see Section 9.1.2) that are considered SAEs should be reported accordingly (see Section 9.6.2)

### 9.6.4 Overdose

Any overdose that occurs in association with an adverse sign or symptom must be entered into the eCRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 9.6.2).

Details of overdose of the investigational product (defined in Section 7.5) must be recorded in the study treatment administration eCRF. Details of overdose of any concomitant therapy must be recorded in the Concomitant Medication eCRF.

### 9.6.5 Pregnancy and Breastfeeding

A female subject or female partner of a male subject who becomes pregnant while participating in the study, or up to and including 30 days after the last dose of the investigational product, must notify the investigator immediately.

If a female subject becomes pregnant, she must discontinue treatment with the investigational product immediately, but may continue other study procedures at the discretion of the investigator. If the female subject is in the active treatment period of the study, her participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in Section 4.2).

CSL must be notified within 5 days of the investigator becoming aware of the pregnancy (by entry of appropriate data into the eCRF).

Whenever possible, a pregnancy in a subject or in a female partner of a male subject exposed to the investigational product should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator to CSL using a Pregnancy Reporting/Outcome Form.

## 9.7 IRB/IEC Reporting Requirements

The time frame within which an IRB/IEC must be notified of deaths and investigational product-related unexpected SAEs is stipulated by each IRB/IEC. It is the investigator's responsibility to comply with the requirements for IRB/IEC notification. CSL will provide investigators with all details of all SAEs reported to regulatory authorities.

# 10 Statistics

## 10.1 Sample Size Estimation

### 10.1.1 Sample Size Based on the Primary Efficacy Endpoint

The sample size is based on the primary efficacy endpoint of loss-of-response status (binary endpoint of loss-of-response or not), at the End-of-TP2 (ie, within 25 weeks after randomization). The null hypothesis is that there is no difference between C1-INH and placebo with respect to the proportion of subjects with loss-of-response at the End-of-TP2. Let $p_0$ and $p_1$ be the expected proportion of subjects with loss-of-response in TP2 in the placebo and C1-INH treatment groups, respectively. The alternative is that there is a difference between the treatment groups. That is, $H_0$: $p_0 = p_1$ versus $H_1$: $p_0 \neq p_1$.

The power procedure in SAS STAT software (Cary, NC SAS Institute Inc.) was used to estimate the sample size, based on the likelihood ratio chi-square test. Determination of the sample size was based on the following assumptions:

- The proportions of subjects experiencing loss-of-response at the End-of-TP2 will be 0.75 with placebo and 0.30 with C1-INH.
- There will be at least 90% power to detect a statistically significant effect with two-sided test with alpha = 0.05.
- Logistic regression model with treatment effect will be used for the primary efficacy analysis. Wald test statistic for treatment effect from Logistic regression has approximately same distribution as chi-square [Fleiss et al, 2003]. Therefore, the sample

size calculation based on chi-square test is used to ensure similar power for hypothesis testing.

- Treatment allocation will be 1:1.
- The planned interim analysis for futility will not impact the type 1 error for the final analysis.

Under these assumptions, a total of 60 subjects (30 randomized to C1-INH and 30 randomized to placebo) will provide approximately 95% power. The study will enroll a sufficient number of subjects to ensure that 60 subjects are randomized.

The assumptions above are based on a prospective single-arm pilot study to investigate the C1-INH added to high-dose IVIG for the treatment of acute AMR non-responsive to conventional therapy [Viglietti et al, 2016a]. A total of 6 subjects received C1-INH and IVIg for 6 months. The primary endpoint was change in eGFR. These were compared to a historical control of 21 subjects who received IVIg. In the prospectively treated C1-INH group, 0/6 subjects experienced decline in eGFR at 6 months (0; 95% confidence interval [CI], 0 to 46%); and 4/6 subjects had a greater than 20% increase in eGFR (67%; 95% CI, 22% to 96%). In the historical control group, 15/21 subjects (71%; 95% CI, 48% to 89%) experienced decline in eGFR during a comparable 6 month period.

### 10.1.2 Power for Allograft Survival

Allograft survival status (or all-cause allograft failure) at the end of 48 months after enrollment represents clinical confirmation of the effect on the allograft of improving eGFR.

The primary comparison of the proportion of subjects with allograft survival will be between the subjects randomized to placebo or C1-INH. It is anticipated that very few subjects will be lost to follow-up as standard of care mandates close follow up by the transplanting center. This endpoint will be analyzed after all subjects have been followed for 4 years after enrollment.

The power for hypothesis testing of this endpoint was estimated using the power procedure in SAS STAT under the following assumptions:

- The proportions of subjects with allografts surviving at 4 years after enrollment will be 0.25 with the placebo cohort and 0.75 in the C1-INH cohort.
- Alpha = 0.05 (two-sided test).

- Logistic regression model with treatment effect will be used for the primary efficacy analysis. Wald test statistic for treatment effect from Logistic regression has approximately same distribution as chi-square [Fleiss et al, 2003]. Therefore, the sample size calculation based on chi-square test is used to ensure similar power for hypothesis testing.
- Approximately 30 subjects in each randomized treatment groups.

There is greater than 90% power to detect the specified target difference between C1-INH and placebo groups based on sample size of 60 (approximately 30 in the C1-INH cohort and approximately 30 in the placebo cohort).

The 4-year graft survival for placebo of 25% is based on data presented at the American Transplant Congress in Boston [Viglietti et al, 2016b]. This study involved follow-up of kidney transplant recipients with biopsy-proven active AMR diagnosed between 2007 and 2013. Among the subjects who have not responded to standard of care, the 4-year graft survival ranged from approximately 10% to 40% for subjects with high and intermediate risk scores, respectively. The 4-year graft survival for C1-INH of 75% represents what would be expected for subjects who are successfully treated.

### 10.1.3 Sample Size Re-estimation

Data on which to estimate the effect size for the primary endpoint is limited. Because of the relatively high degree of uncertainty surrounding the true treatment effect, an unblinded sample size re-estimation is planned.

The interim analysis and sample size re-estimation will be performed by the independent Statistical Data Analysis Center supporting the IDMC. In order to maintain study integrity, the results of the interim analysis will not be revealed to CSL or otherwise made public. The sample size will not be reduced based on sample size re-estimation. The details of sample size re-estimation will be provided in an independent charter for IDMC. The recommendations from IDMC to CSL will be non-binding as a guideline to aid decision-making rather than a definitive rule.

## 10.2 Description of Study Analysis Sets

### 10.2.1 Screened Analysis Set

The Screened analysis set comprises all subjects who provided written informed consent and who undergo study screening procedures.

### 10.2.2 Enrolled Analysis Set

The Enrolled analysis set comprises all subjects in the Screened analysis set who do not fail screening.

### 10.2.3 Intent-to-Treat Analysis Set

The Intent-to-treat (ITT) analysis set comprises all subjects who were randomized. Subjects will be analyzed according to the investigational product to which they were assigned (ie, continued C1-INH or placebo) regardless of what was actually received. Any subject who receives a randomization identification number will be considered to have been randomized.

### 10.2.4 Modified Intent-to-Treat Analysis Set

All subjects randomized under the original protocol and under all protocol amendments will be included in this population except the subjects randomized prior to amendment 3 who do not satisfy the criteria in amendment 3. This modified ITT set will be the primary analysis set for the analysis of efficacy data.

### 10.2.5 Safety Analysis Sets

#### 10.2.5.1 Run-in Safety Analysis Set

The Run-in Safety (RiS) analysis set will include all subjects who received at least one dose of C1-INH during TP1.

#### 10.2.5.2 Randomized Withdrawal Safety Analysis Set

The Randomized Withdrawal Safety (RWS) analysis set will include all subjects in the ITT analysis set who received at least one dose of the investigational product after randomization during TP2. The RWS analysis set will be based on the investigational product actually received (ie, continued C1-INH or placebo) during TP2.

### 10.2.6 Pharmacokinetic Analysis Set

The PK analysis set will comprise all subjects who receive ≥ 1 dose of C1-INH and who have ≥ 1 measurable level of C1-esterase inhibitor functional activity or C1-esterase inhibitor antigen concentration.

### 10.2.7 CCI

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## 10.3 Statistical Analyses and Methods

A complete description of the statistical analyses and methods will be available in a statistical analysis plan, which will be finalized before the database is locked.

Unless otherwise stated, efficacy analyses will be based on the modified ITT analysis set for analyses of endpoints defined in TP2. Sensitivity analyses will be based on the ITT set.

Enrolled analysis set will be used for the analysis of endpoints defined over the entire study. Sensitivity analyses of these endpoints will be done with ITT and modified ITT sets.

Safety will be summarized over the entire study, and according to treatment period. Safety will be analyzed for either the RiS analysis set or the RWS analysis set, as appropriate.

All data will be summarized in tables or figures and all ICH-required data in the database will be listed. Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations, mean, standard deviation, median, minimum and maximum. Other descriptive statistics (eg, 25th and 75th percentile, coefficient of variation) will be reported when appropriate. Categorical variables will be summarized by presenting the number of subjects and percentage for each category.

Unless otherwise stated, the statistical model on which inference is based will contain terms for the randomization strata as well as treatment. It is anticipated that subject accrual will be spread thinly across the centers. There will be no pooling of centers for purposes of analysis. Therefore, investigation of center-by-treatment interaction will not be possible.

Unless otherwise specified, all confidence intervals and *P*-values will be two-sided. From a formal inferential perspective, the type I error will be fully allocated to the analysis of the primary efficacy variable, and the selected secondary efficacy variable (ie, all-cause allograft failure after randomization into TP2 and through the Responder Follow-up Period). A serial gatekeeper hierarchical testing strategy will be used to protect the overall type I error rate of 0.050 (two-sided). Statistical significance will be claimed only when the results of the two-sided test favor C1-INH.

Supportive and secondary analyses will be inspected for consistency and directionality. P-values for supportive and/or secondary analyses will be used to provide guidance on the weight of evidence for any observed effects. P-values for supportive and/or secondary analyses will not be adjusted for multiplicity.

### 10.3.1 Definitions

**Baseline**

Baseline eGFR measurements are the nadir of the eGFR of the measurements on the Screening and Day 1 Visits for those subjects who entered prior to Amendment 1 and the mean of these values for subjects who entered post Amendment 1.

Day 1 is the baseline for vital signs, laboratory values, and other measures unless otherwise specified.

**Responder Status**

Responders are defined as subjects whose End-of-TP1 (the mean of Week 11 and Week 12) eGFR $\geq$ 90% of baseline and $\geq$ 20 mL/min/1.73 $m^2$. The baseline eGFR is defined as the mean of the eGFR values obtained during Screening and the Day 1 Visit.

Loss-of-response at the End-of-TP2 is defined as any 1 of the following 3 conditions:

- End-of-TP2 eGFR (mean of Week 36 and Week 38 eGFR) that is not stable, defined as:

- End-of-TP2 eGFR that is < 90% of the End-of-TP1 eGFR for subjects whose End-of-TP1 eGFR (mean of Week 11 and Week 12 eGFR) is ≥ 100% of baseline;
- End-of-TP2 eGFR that is < 90% of baseline for subjects whose End-of-TP1 eGFR is ≥ 90% of baseline and < 100% of baseline.

- Allograft failure (defined by allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first)
- Subject death by any cause.

## 10.3.2 Subject Disposition and Characteristics

### 10.3.2.1 Subject Disposition

The following summaries will be provided:

- The number of subjects in each of the analysis sets defined for this study.
- Subject status, including subjects ongoing, subjects completed, and subjects withdrawn from the study, and primary reason for withdrawal.
- Investigation product status, including premature discontinuation of the investigational product and primary reason for premature discontinuation.

### 10.3.2.2 Subject Characteristics

The following will be summarized using descriptive statistics or frequency counts, as appropriate:

- Demographic characteristics.
- Relevant medical history.
- Allograft/allograft donor characteristics.
- Diagnosis and disease characteristics.
- Prior and concomitant therapies.

## 10.3.3 Efficacy Analyses

All efficacy endpoints will be analyzed based on Modified-ITT analysis set. Sensitivity analyses for efficacy endpoints will be based on ITT set.

### 10.3.3.1 Primary Efficacy Analysis

The primary analysis of the primary efficacy endpoint of loss-of-response at the End-of-TP2, will be based on a logistic regression model. The randomized treatment groups, C1-INH and placebo, will be compared based on the logistic model.

Subjects will be considered to have lost response if they drop-out or are lost to follow-up before the response status at the End-of-TP2 could be determined.

If $\pi$ is the probability that an individual in a given treatment group will have a loss-of-response at the End-of-TP2, the logistic model assumes that in each treatment group, binary outcome of response status can be described by a model which assumes independence between subjects. Also, the model assumes that all subjects with the same covariate values have the same probability, such that the logit of $\pi$ is a linear function of the regression coefficients particular to that individual:

$$\text{Logit}(\pi) = \log ( \pi/1\text{-}\pi) = \alpha + \beta_T X_T,$$

where $X_T$ is the indicator variable for treatment (C1-INH=1, placebo = 0).

Please note the stratification factors for randomization are not included in this model as difference in efficacy is not expected based on these strata. However, subjects have been randomized based on these strata of DSA sensitized versus DSA de novo and AMR severity (severe versus all other severities) to ensure balance among these strata.

The odds ratio for C1-INH versus placebo is $\exp(\beta_T)$ based on this model for primary efficacy analysis. The primary hypothesis to be tested is $H_0$: $\beta_T = 0$ vs $H_1$:$\beta_T \neq 0$. This will be tested using the Wald statistic derived from maximum likelihood estimation of the logistic model. If this hypothesis is rejected at the 0.05 level of significance and the point estimate of $\beta_T$ is positive, efficacy will be declared. The logistic model will be used to provide point estimates of the odds ratio and risk difference, with 95% confidence intervals by treatment groups. Summary statistics of proportion of subjects with loss-of-response will also be presented by treatment. If maximum likelihood estimation of the logistic model fails to converge then exact methods for logistic regression will be used for hypothesis and estimation.

Components of loss-of-response at the End-of-TP2 will be summarized by treatment groups in terms of the proportion of subjects with:

- End-of-TP2 eGFR (mean of Week 36 and Week 38 eGFR values) that is not stable, defined as:
  - End-of-TP2 eGFR that is < 90% of the End-of-TP1 eGFR for subjects whose End-of-TP1 eGFR is ≥ 100% of baseline,
  - End-of-TP2 eGFR that is < 90% of baseline for subjects whose End-of-TP1 eGFR is ≥ 90% of baseline and < 100% of baseline
- All-cause allograft failure (ie, allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant).
- Death by any cause.

***Sensitivity analysis of loss-of-response at the End-of-TP2***

A sensitivity analysis will be performed to access the possible effect of other factors on the analysis by performing the logistic regression including the stratification variables DSA (sensitized versus de novo) and AMR severity (severe versus all other severities), and possibly other key variables, as covariates in the model. If maximum likelihood estimation of the logistic model fails to converge subgroup analyses determined by the above factors will be performed using exact methods for logistic regression. Summary statistics by covariate levels will also be presented.

Further details of the sensitivity analyses will be specified in the SAP.

### 10.3.3.2 Secondary Analyses

***Analysis of key secondary endpoint of proportion of all-cause allograft failure at the end of 48 months after enrollment***

The primary comparison for the proportion of subjects with all-cause allograft failure at the end of 48 months after enrollment will be based on a logistic regression model. The randomized treatment groups, C1-INH and placebo, will be compared based on the logistic model.

The same logistic model as described for the primary endpoint will also be used for this analysis.

Analysis of components of all-cause allograft failure after enrollment into TP1 through the Responder Follow-up Period (ie, within 48 months after enrollment) will be summarized for the randomized treatment groups and also the non-responder subjects who were not randomized in TP2. The summary will be based on the proportion of subjects with:

- Any event (ie, all-cause allograft failure or death by any cause).
- All-cause allograft failure (defined by allograft nephrectomy, or institution of permanent dialysis, or return to the transplant waitlist for renal transplant);
- Surviving allografts
- Death by any cause

Proportion of subjects with all cause allograft failure will be also summarized by treatment groups at 1 year, 2 years, and 3years since enrollment.

***Analysis of key secondary endpoint of time to all-cause allograft failure through 48 months after enrollment***

Treatment group differences will be analyzed with a Cox proportional hazards regression model with randomization strata as covariates. This model will be used to estimate the C1-INH /placebo hazard ratio and two-sided 95% confidence interval. Kaplan-Meier plots of time to failure through the Responder Follow-up Period will be produced.

***Subgroup analysis of loss-of-response at the End-of-TP2***

Details of subgroup analyses will be provided in the SAP.

The following subgroups, and possibly others to be described in the SAP, will be summarized by treatment group with respect to the proportion of loss-of-response:

- Geographic region: USA, non-USA.
- DSA by randomization strata: sensitized, de novo.
- DSA by classification: HLA class I, HLA class II, both HLA class I and II.
- AMR severity: severe, non-severe (all other severities).
- Type of donor: deceased, living.
- Recipient race: Black, non-Black.
- Recipient sex: male, female.
- Recipient age: $< 65$ years, $\geq 65$ years.

***Subgroup analysis of all-cause allograft failure at the end of 48 months after enrollment***

Subject Proportions by treatment group for components of all-cause allograft failure will be presented for similar subgroups as described above

***Analysis of responders at the End-of-TP1***

The proportion of responders at the End-of-TP1 will be presented together with an exact 95% confidence interval. To calculate this proportion, the denominator will include all subjects in the Enrolled analysis set, and the numerator will include all subjects meeting the definition of response (Section 8.1.3.2).

The eGFRs during TP1 (ie, with open-label C1-INH) will be summarized by scheduled visit using descriptive statistics, as will the absolute and percent changes from baseline. The descriptive statistics will use available data from the Enrolled analysis set (ie, missing data will be not imputed).

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***New or worsening chronic active AMR***

The proportion of subjects with new or worsening chronic active AMR during TP2, as defined by the Banff 2015 Criteria [Loupy et al, 2017], will be analyzed using the logistic model as described for the primary efficacy endpoint and also with this model stratified by the randomization strata, for the ITT analysis set.

***Splenectomy***

The proportion of subjects with splenectomy during TP1 will be summarized. Descriptive statistics of time from first dose of C1-INH will be presented. Splenectomy during TP1 will be summarized for the Enrolled analysis set.

The proportions of subjects with splenectomy during TP2 will be summarized by treatment group. Descriptive statistics for time from first dose of C1-INH, and time from last dose of C1-INH will be presented. Splenectomy during TP2 will be summarized for the ITT analysis set.

***C1-esterase inhibitor functional activity***

C1-esterase inhibitor functional activity at the designated time points will be summarized using descriptive statistics.

#### 10.3.3.3 CCI

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### 10.3.4 Safety Analyses

The extent of exposure to open-label C1-INH; and to double-blind C1-INH or placebo will be summarized using descriptive statistics.

#### 10.3.4.1 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) dictionary. The number and percentage of subjects with AEs will be reported. Frequency counts and percentages will also be presented for subjects with SAEs, AEs leading to withdrawal, AEs by severity, and AEs by relationship to investigational product. Adverse events will be presented for TP1 and TP2.

#### 10.3.4.2 Other safety evaluations

Clinical laboratory parameters for this study will be summarized by scheduled visit using descriptive statistics or frequency counts and percentages, as appropriate. Vital signs will be summarized similarly.

### 10.3.5 Pharmacokinetics Analyses

Blood samples will be collected for the assessment of C1-esterase inhibitor antigen concentrations and C1-esterase inhibitor functional activity at designated timepoints. C1-esterase inhibitor functional activity will be determined by a validated assay.

The observed C1-esterase inhibitor antigen concentrations and functional activity will be summarized by time, route of administration, and treatment subgroup (placebo vs C1-INH).

The parameters $AUC_{0\text{-}t}$ and $C_{max}$ will be estimated, if feasible, using non-compartmental PK analyses in the subset of ~20 subjects who have more frequent, sequential PK sampling at the Day 10 Visit and the Week 11 Visit.

In addition, population PK analyses may also be conducted and reported separately.

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### 10.3.7 CCI

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### 10.3.8 Other Analyses

Health-related quality of life will be assessed using the EQ-5D-3L with country specific value sets to assess the disutility associated with AMR refractory to treatment [Dolan, 1997; Cleemput et al, 2004].

### 10.3.9 Interim Analysis

Two unblinded analyses of the primary endpoint are planned: one interim analysis and a final analysis. The interim analysis will occur when 50% of randomized subjects (ie, 30 subjects) have been followed for 25 weeks. The final primary efficacy endpoint analysis will take place after all randomized subjects have been followed for 25 weeks after randomization. The final analysis for the study (ie, the analysis associated with the study completion date) will take place after all randomized subjects have been followed for 48 months after enrollment.

The interim analysis of the primary endpoint will be performed for purposes of sample size re-estimation and for futility monitoring. Sample size re-estimation is addressed in Section 10.1.3.

To protect the integrity of the study, results of interim efficacy of the primary endpoint will only be known to the IDMC. These results will not be made public. Full details of the futility analysis and who will have access to what data/information and when they will have access will be specified in the IDMC Charter. Although statistical stopping guidelines will be providing in the charter, a number of factors must be considered thoroughly as part of the

decision to modify or terminate the trial [Pocock, 1993]. A recommendation to modify or terminate the trial will not be based solely on statistical grounds.

# 11 Quality Assurance

The study may be subject to an audit by CSL, an authorized representative(s) of CSL and/or inspections by an authorized regulatory authority (eg, US Food and Drug Administration [FDA]). Regulatory authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. CSL will notify the investigator of any upcoming audit/inspection.

In the event of an audit, all pertinent study-related documentation must be made available to the auditor(s). If an audit or inspection occurs, the investigator at each study site will permit the auditor/inspector direct access to all relevant documents and allocate their time as well as the time of relevant staff to discuss the findings and any relevant issues.

# 12 Regulatory and Ethics Considerations

## 12.1 Regulatory Considerations

CSL or its agents will submit the appropriate documents to the local regulatory agencies and will await approval before study start.

This study will be conducted under an FDA Investigational New Drug Application and documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this study protocol are designed to ensure that CSL and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

## 12.2 Institutional Review Board/Independent Ethics Committee

The investigator must submit the protocol and informed consent forms (ICFs) for review by an authorized and properly constituted (according to local guidelines) IRB/IEC. Written approval must be received from the IRB/IEC before commencement of the study.

## 12.3 Subject Information and Informed Consent

Informed consent of study subjects according to the standards of GCP must be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form and should be deemed appropriate by the IRB/IEC. Subjects, their relatives (or if necessary, legally acceptable representatives) must be given ample opportunity to inquire about details of the study.

The subject (or if necessary, legally acceptable representatives) must be provided with a copy of the signed informed consent form.

Should there be any amendments to the protocol that would directly affect the subject's participation in the study (eg, a change in any procedure), the ICF must be amended to incorporate this modification. Subjects must be informed of the change and they must sign the amended ICF indicating that they re-consent to participate in the study.

## 12.4 Subject Confidentiality

All subject names and contact details will be kept confidential. Subjects will be identified throughout documentation and evaluation by the number allotted to them during the study. Each subject will be told that all study findings will be handled in the strictest confidence.

The investigator at the study site will be responsible for retaining sufficient information about each subject (eg, name, address, phone number and identity in the study) so that regulatory agencies or CSL may access this information should the need arise. These records should be retained in a confidential manner as long as legally mandated according to local requirements.

Subject medical records pertaining to the study may be inspected/audited at any time by CSL employees or their duly authorized representatives, a regulatory authority or the IRB/IEC. All records accessed will be strictly confidential. Consent to participate in the study includes consent to these inspections/audits.

## 12.5 Indemnity and Compensation

CSL has taken out insurance to cover its obligations under both the Indemnity and the Compensation guidelines for injury to subjects involved in the study.

Other details regarding compensation and the obligations of the investigator/CSL are provided in the Clinical Trial Agreement for the study (see Section 13.1).

# 13 Administrative Considerations

## 13.1 Clinical Trial Research Agreement

This study will be conducted under a Clinical Trial Agreement between CSL ("Sponsor") and the institution(s) representing the investigational study site(s) ("Authority"). Financial support to the investigational site(s) will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of investigator and CSL, and will form the contractual basis under which the clinical study will be conducted.

## 13.2 Clinical Study Registration and Results Disclosure

CSL will provide the relevant study protocol information in public database(s) before or at commencement of the study. CSL may also provide study information for inclusion in national registries according to local regulatory requirements.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record.

## 13.3 Implementation of the Protocol/Protocol Amendment(s)

With the exception of medical emergencies, no changes or deviations in the conduct of the signed protocol will be permitted without documented approval of the CSL Medical Monitor or designee and the IRB/IEC. In the event of a medical emergency, the investigator at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the CSL Medical Monitor and the IRB/IEC.

Modifications to the protocol that may affect subject safety or the way the study is to be conducted will be documented in a protocol amendment, which must be approved by the IRB/IEC.

Administrative changes to the protocol, defined as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, will not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information.

## 13.4 Protocol Deviations

All instances where the requirements of the study protocol were not complied with will be tracked. Corresponding subjects may be withdrawn from the study at the discretion of the investigator and/or CSL. Study protocol deviations arise when either subjects who have been entered in the study and/or the study sites deviate from the IEC/IRB-approved study protocol.

If a major protocol deviation (ie, a deviation that could have a significant effect on the subject's safety, rights, or welfare and/or on the integrity of the study data) occurs, the investigator must notify CSL and the appropriate IRB/IEC as soon as possible or as per local requirements.

## 13.5 Documentation and Record Keeping

### 13.5.1 Data Collection

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, records of vital signs, medical history, or physical examinations, administration of investigational product or concomitant therapy, any AEs experienced, and other notes as appropriate. These records (electronic or paper) constitute source data.

Electronic CRF entries will be considered source data if the eCRF is the site of the original recordings (ie, there is no other written or electronic record of the data).

An eCRF will be provided by CSL (or delegate) for each subject enrolled into the study. The investigator is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the eCRF must be backed up by source data unless the eCRF is considered source data. All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

### 13.5.2 Data Quality Assurance

Data generated throughout the study will be monitored and the eCRFs checked against the subject records for completeness and accuracy. The investigator must provide direct access to source data documents. CSL's study monitor will perform this function.

Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically for consistency and plausibility. Queries will be generated for questionable data and clarification sought from the investigator. These data queries must be resolved in a timely manner by the investigator (or delegate).

### 13.5.3 Record Retention

The investigator must follow the principles for record retention outlined in the Clinical Trial Research Agreement. An investigator study file prepared by CSL (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. All study documentation and materials maintained in the investigator study file must be kept in conformance with applicable national laws and regulations.

All study documentation and materials maintained in the investigator study file at the study site must be available for inspection by CSL's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited or inspected by qualified delegates from CSL or a competent regulatory authority.

Following completion of the study, the investigator is responsible for archiving the investigator's study file, the subject's records and the source data according to applicable regulatory requirements.

## 13.6 Study and Site Closure

CSL reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, the CSL Study Monitor (or delegate) will discuss this with the investigator at each study site at that time and notify the investigators in writing. If the study is suspended or terminated for safety reasons, then all investigators and the relevant regulatory agencies will be immediately notified of the action, as well as the reason for the suspension/termination. The investigator at each study site will advise their IRB/IEC overseeing the study of the suspension/termination.

## 13.7 Clinical Study Report

A clinical study report will be written after the completion of the study. CSL or its agent will write the report in consultation with the investigator or, if applicable, a nominated

coordinating investigator (or delegate). It is required by CSL that the coordinating investigator will sign the clinical study report.

Progress reports may be provided to the relevant regulatory bodies in accordance with their requirements.

## 13.8 Use of Data and Publications

The rights and obligations of investigators and CSL concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study.

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# 15 Appendices

**Appendix 1** **Signature on Behalf of Sponsor**

**Study Title:** A Double-blind, Randomized-withdrawal, Placebo-controlled Study to Evaluate the Efficacy and Safety of Human Plasma-derived C1-esterase Inhibitor as Add-on to Standard of Care for the Treatment of Refractory Antibody Mediated Rejection in Adult Renal Transplant Recipients

**Protocol Number:** CSL842_3001

I have read the Clinical Study Protocol titled "A Double-blind, Randomized-withdrawal, Placebo-controlled Study to Evaluate the Efficacy and Safety of Human Plasma-derived C1-esterase Inhibitor as Add-on to Standard of Care for the Treatment of Refractory Antibody Mediated Rejection in Adult Renal Transplant Recipients" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

**(Signature)**

PPD

**Date (DD MMM YYYY)**

PPD, MD

**(Printed name)**

PPD

**(Title)**

## Appendix 2 Signature of Principal Investigator

**Study Title:** A Double-blind, Randomized-withdrawal, Placebo-controlled Study to Evaluate the Efficacy and Safety of Human Plasma-derived C1-esterase Inhibitor as Add-on to Standard of Care for the Treatment of Refractory Antibody Mediated Rejection in Adult Renal Transplant Recipients

**Protocol Number:** CSL842_3001 **Site Number:**

I have read the Clinical Study Protocol titled "A Double-blind, Randomized-withdrawal, Placebo-controlled Study to Evaluate the Efficacy and Safety of Human Plasma-derived C1-esterase Inhibitor as Add-on to Standard of Care for the Treatment of Refractory Antibody Mediated Rejection in Adult Renal Transplant Recipients".

By signing this Clinical Study Protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the Clinical Study Protocol, the standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and applicable regulatory requirements.

Changes to the Clinical Study Protocol will only be implemented after written approval is received from CSL Behring LLC (CSL) and the Institutional Review Board or Independent Ethics Committee (as appropriate) with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the Clinical Study Protocol.

**(Signature)** **Date (DD MMM YYYY)**

**(Printed name)**

**(Title)**

## Appendix 3 Banff 2015 Scoring System for Antibody-mediated Rejection [Loupy et al, 2017]

| Score | Description |
|---|---|
| **i: inflammation** | |
| 0 | No inflammation or in < 10% of unscarred cortical parenchyma |
| 1 | Inflammation in 10 to25% of unscarred cortical parenchyma |
| 2 | Inflammation in 26 to 50% of unscarred cortical parenchyma |
| 3 | Inflammation in > 50% of unscarred cortical parenchyma |
| **t: tubulitis** | |
| 0 | No mononuclear leukocytes in tubules |
| 1 | Foci with 1 to 4 leukocytes per tubular cross-section (or 10 tubular cells) |
| 2 | Foci with 5 to 10 leukocytes per tubular cross-section (or 10 tubular cells) |
| 3 | Foci with >10 leukocytes per tubular cross-section or the presence of two or more areas of tubular basement membrane destruction accompanied by i2/i3 inflammation and t2 elsewhere |
| **v: intimal arteritis** | |
| 0 | No arteritis |
| 1 | Mild to moderate intimal arteritis in at least one arterial cross-section |
| 2 | Severe intimal arteritis with at least 25% luminal area lost in at least one arterial cross-section |
| 3 | Transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel |
| **g: glomerulitis** | |
| 0 | No glomerulitis |
| 1 | Glomerulitis in < 25% of glomeruli |
| 2 | Segmental or global glomerulitis in 25 to 75% of glomeruli |
| 3 | Glomerulitis in > 75% of glomeruli |

| Score | Description |
|---|---|
| **ptc: peritubular capillaritis** | |
| 0 | ≥ 1 leukocyte in < 10% of cortical PTCs and/or maximum number of leukocytes < 3 |
| 1 | ≥ 1 leukocyte cell in ≥ 10% of cortical PTCs with 3 or 4 leukocytes in most severely involved PTC |
| 2 | ≥ 1 leukocyte in ≥ 10% of cortical PTCs with 5 to 10 leukocytes in most severely involved PTC |
| 3 | ≥ 1 leukocyte in ≥ 10% of cortical PTCs with > 10 leukocytes in most severely involved PTC |
| **ti: total inflammation** | |
| 0 | No or trivial interstitial inflammation (<10% of total cortical parenchyma) |
| 1 | 10–25% of total cortical parenchyma inflamed |
| 2 | 26–50% of total cortical parenchyma inflamed |
| 3 | >50% of total cortical parenchyma inflamed |
| **i-IFTA: inflammation in area of interstitial fibrosis and tubular atrophy** | |
| 0 | No inflammation or <10% of scarred cortical parenchyma |
| 1 | Inflammation in 10–25% of scarred cortical parenchyma |
| 2 | Inflammation in 26–50% of scarred cortical parenchyma |
| 3 | Inflammation in >50% of scarred cortical parenchyma |
| **C4d** | |
| 0 | No staining of peritubular capillaries (0%) |
| 1 | Minimal C4d staining; > 0 to < 10% of peritubular capillaries |
| 2 | Focal C4d staining; 10 to 50% of peritubular capillaries |
| 3 | Diffuse C4d staining; > 50% of peritubular capillaries |
| **cg: glomerular double contours** | |
| 0 | No GBM double contours by light microscopy or EM |

| Score | Description |
|---|---|
| 1a | No GBM double contours by light microscopy but GBM double contours (incomplete or circumferential) in at least three glomerular capillaries by EM |
| 1b | Double contours of the GBM in 1 to 25% of capillary loops in the most affected nonsclerotic glomerulus by light microscopy |
| 2 | Double contours affecting 26 to 50% of peripheral capillary loops in the most affected glomerulus |
| 3 | Double contours affecting > 50% of peripheral capillary loops in the most affected glomerulus |
| **mm: mesangial matrix expansion** | |
| 0 | No more than mild mesangial matrix increase in any glomerulus |
| 1 | At least moderate mesangial matrix increase in up to 25% of nonsclerotic glomeruli |
| 2 | At least moderate mesangial matrix increase in 26–50% of nonsclerotic glomeruli |
| 3 | At least moderate mesangial matrix increase in >50% of nonsclerotic glomeruli |
| **ah: arteriolar hyalinosis** | |
| 0 | No PAS-positive hyaline arteriolar thickening |
| 1 | Mild to moderate PAS-positive hyaline thickening in at least one arteriole |
| 2 | Moderate to severe PAS-positive hyaline thickening in more than one arteriole |
| 3 | Severe PAS-positive hyaline thickening in many arterioles |
| **aah: hyaline arteriolar thickening** | |
| 0 | No typical lesions of calcineurin inhibitor–related arteriolopathy |
| 1 | Replacement of degenerated smooth muscle cells by hyaline deposits in only one arteriole, without circumferential involvement |
| 2 | Replacement of degenerated smooth muscle cells by hyaline deposits in more than one arteriole, without circumferential involvement |
| 3 | Replacement of degenerated smooth muscle cells by hyaline deposits with circumferential involvement, independent of the number of arterioles involved |

| Score | Description |
|---|---|
| **cv: vascular fibrous intimal thickening** | |
| 0 | No chronic vascular changes |
| 1 | Vascular narrowing of up to 25% luminal area by fibrointimal thickening |
| 2 | Vascular narrowing of 26–50% luminal area by fibrointimal thickening |
| 3 | Vascular narrowing of >50% luminal area by fibrointimal thickening |
| **ci: interstitial fibrosis** | |
| 0 | Interstitial fibrosis in ≤ 5% of cortical area |
| 1 | Interstitial fibrosis in 6 to 25% of cortical area |
| 2 | Interstitial fibrosis in 26 to 50% of cortical area |
| 3 | Interstitial fibrosis in > 50% of cortical area |
| **ct: tubular atrophy** | |
| 0 | No tubular atrophy |
| 1 | Tubular atrophy involving up to 25% of the area of cortical tubules (mild tubular atrophy) |
| 2 | Tubular atrophy involving 26 to 50% of the area of cortical tubules (moderate tubular atrophy) |
| 3 | Tubular atrophy involving in > 50% of the area of cortical tubules (severe tubular atrophy) |

ah = arteriorlar hyalinosis; cg = glomerular double contours; ci = interstitial fibrosis; ct = tubular atrophy; cv = arterial fibrointimal thickening; EM = electron microscopy; g = glomerulitis; GBM = glomerular basement membrane; i = inflammation; PAS = periodic acid–Schiff; ptc = peritubular capillaritis; PTC = peritubular capillary; t = tubulitis; v = intimal arteritis.

# Signature Page

## CSL842_3001 - Protocol Amendment - 3 - 31Jan2020

| Signed By | Date (GMT) |
|---|---|
| PPD | 07-Feb-2020 19:25:41 |
| Approved-PPD Approval | |
| PPD | 10-Feb-2020 00:10:19 |
| Approved-PPD Approval | |
| PPD | 10-Feb-2020 08:20:25 |
| Approved-Clinical Safety Physician Approval | |



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