CLINICAL STUDY PROTOCOL

A Pivotal Phase 3 Trial to Evaluate the Safety and Efficacy of Clazakizumab for the Treatment of Chronic Active Antibody-Mediated Rejection in Kidney Transplant Recipients

Study Number:	CSL300_3001 (Formerly VKTX01)
Study Product:	Clazakizumab (CSL300)
Development Phase:	3
Short Title:	A Trial to Evaluate the Safety and Efficacy of Clazakizumab for the Treatment of Chronic Active Antibody-Mediated Rejection in Kidney Transplant Recipients
Sponsor:	CSL Behring, LLC 1020 First Avenue King of Prussia, PA 19406
Protocol Version:	Amendment 9
EudraCT Number:	2018-003682-34
IND Number:	134376
Protocol Date:	10 July 2023
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) 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 Behring (or delegate) and provided to the study sites as needed.

REVISION HISTORY

Date	Version	Summary of Changes
22 October 2018	Original	Not applicable
7 December 2018	Amendment 1	1. Investigational product dose was changed from 25 mg/mL to 12.5 mg/mL 2. Belatacept added to allowed medications (only if already taking at screening) 3. Clarification that CNI levels should reach target levels during Screening, if possible, and then maintained 4. Requirement for prophylactic treatment of pneumocystis jiroveci pneumonia (PJP) for the first year of the study (ie, from Screening up to and including Week 52), and thereafter at the discretion of the investigator. 5. Treatments for ABMR (including CABMR) or T cell-mediated rejection (TCMR), are not allowed within 3 months of the start of Screening 6. Prior exposure to all IL-6 / IL-6R blockers, including, tocilizumab or other IL-6 / IL-6R blockers, in addition to excluded clazakizumab, added as exclusions 7. Spot urine albumin creatinine ratio (UACR) ≥ 2200 mg/g (≥ 220 mg/mmol) replaces urine protein creatinine ratio (UPCR) ≥ 3000 mg/g (≥ 300 mg/mmol) as an exclusion criterion 8. ABO-incompatible transplant recipient, severe hypogammaglobulinemia (defined as immunoglobulin G (IgG) < 400 mg/dL) and prior exposure to proteasome inhibitors (eg, bortezomib) added as exclusion criteria 9. Extent of monitoring for liver function test (LFT) abnormalities, neutropenia and thrombocytopenia was clarified 10. Monitoring for hypogammaglobulinemia was added and timing of monitoring provided and in the case of severe hypogammaglobulinemia (IgG < 400 mg/dL), reduction of background

		immunosuppression and treatment with IVIG is be permitted 11. Subjects who prematurely discontinue investigational treatment with clazakizumab / placebo, and who have not reached an endpoint of allograft loss will be required to continue in the study, attend regular clinic visits and undergo all assessments per the Schedule of Events (SOE) (up to and including Visit 68, if possible) and must comply with all aspects of the protocol (including prohibited medications). 12. Stratification by baseline proteinuria parameters changed from (UACR < 1000 mg/g (< 100 mg/mmol) or UACR ≥ 1000 mg/g (≥ 100 mg/mmol)) changed to (UACR < 300 mg/g (< 30 mg/mmol) or UACR ≥ 300 mg/g (≥ 30 mg/mmol)
6 February 2019	Amendment 2	1. Reduction of investigational drug dose 2. Updates to exclusion criteria 3. Updates to risks/precautions 4. Treatment of hypogammaglobulinemia and routine monitoring of IgG levels 5. Updates to concomitant medications 6. Prophylactic treatment for PJP 7. Editorial changes
29 October 2019	Amendment 3	1. Inclusion Criterion 3 has been amended to clarify that a window of +3 weeks is allowed with respect to screening biopsy/donor-specific antibodies (DSA) results 2. Exclusion Criterion 2 was clarified to specify that recipients of multiple previous kidney transplants are eligible for the study. 3. Exclusion Criterion 11 was broadened to exclude subjects with a known hypersensitivity to clazakizumab or any constituent of the drug product. 4. Exclusion Criterion 18 was clarified to specify that the “mismatch” refers to the status at the time of transplantation.

		5. Exclusion Criterion 19 was amended to allow subjects with fully excised diverticular disease to enter the study as this risk factor will have been surgically removed. 6. Exclusion Criterion 23 was amended to clarify that active infection is defined as any polymerase chain reaction (PCR) value above the lower limit of quantification (LLOQ). 7. Exclusion Criterion 33 was changed to only exclude subjects exposed to proteasome inhibitors within 2 years of the start of Screening. 8. The requirement for subjects to use "highly effective methods of contraception" was amended as requested by multiple European health authorities to also allow "acceptable methods" as defined in the European "Heads of Medicines Agencies" 2014 Clinical Trial Facilitation Group (CTFG) document "Recommendations related to contraception and pregnancy testing in clinical trials." 9. Throughout the protocol, the terminology with respect to discontinuation of investigational drug was clarified so that the term "discontinuation" now refers to permanent discontinuation and the term "withholding" refers to temporary discontinuation. Accordingly, Section 5.6 was amended to clarify permanent discontinuation versus withholding of investigational drug. In addition, the instructions to stop treatment with investigational drug due to severe LFT abnormalities, severe neutropenia, and/or severe thrombocytopenia were amended to state that treatment with investigational drug should be "withheld or permanently discontinued." 10. The dose modification guidelines were clarified and expanded throughout the protocol. Recommendations to consider "stopping" investigational drug were

		amended to specify withholding and/or discontinuing investigational drug (as appropriate). The instructions to "stop investigational drug" in the event of severe LFT abnormalities, severe neutropenia, and/or severe thrombocytopenia were amended to "withhold or discontinue investigational drug and contact the Medical Monitor." 11. Recommendations regarding concomitant background immunosuppression were clarified to explicitly state that subjects are expected to be on background immunosuppression per standard of care. 12. The first planned formal safety review by the Data and Safety Monitoring Board (DSMB) was changed to occur after 50 subjects (instead of 100 subjects) have been randomized and received at least 1 dose of investigational drug. 13. The guidelines for subjects with severe hypogammaglobulinemia were amended to add a 4-week waiting period after reduction of background immunosuppression followed by a re-check of IgG levels before implementing treatment with intravenous immunoglobulin. 14. Home health visits were added as a potential option for certain visits in order to reduce the burden on study subjects. The required in-clinic visits were specified along with a recommended in-clinic visit schedule. 15. Changes were made to clarify the process for reporting preexisting medical conditions that meet the definition of a serious adverse event (SAE).

11 December 2019	Amendment 4	1. Inclusion Criterion 3 has been amended to clarify that a window of +3 weeks is allowed with respect to Screening biopsy/ DSA results. 2. Exclusion Criterion 2 was clarified to specify that recipients of multiple previous kidney transplants are eligible for the study. 3. Exclusion Criterion 11 was broadened to exclude subjects with a known hypersensitivity to clazakizumab or any constituent of the drug product. 4. Exclusion Criterion 18 was clarified to specify that the "mismatch" refers to the status at the time of transplantation. 5. Exclusion Criterion 19 was amended to allow subjects with fully excised diverticular disease to enter the study as this risk factor will have been surgically removed. 6. Exclusion Criterion 23 was amended to clarify that active infection is defined as any PCR value above the lower limit of quantification (LLOQ). 7. Due to the potential confounding long-term effects of proteasome inhibitors on the immune system, subjects with any prior exposure to proteasome inhibitors are currently excluded from the study. 8. The requirement for subjects to use "highly effective methods of contraception" was amended as requested by multiple European health authorities to also allow "acceptable methods" as defined in the European "Heads of Medicines Agencies" 2014 Clinical Trial Facilitation Group (CTFG) document "Recommendations related to contraception and pregnancy testing in clinical trials." 9. Throughout the protocol, the terminology with respect to discontinuation of investigational drug was clarified so that the term "discontinuation" now refers to permanent discontinuation and the term

		"withholding" refers to temporary discontinuation. 10. The dose modification guidelines were clarified and expanded throughout the protocol. Recommendations to consider "stopping" investigational drug were amended to specify withholding and/or discontinuing investigational drug (as appropriate). 11. Recommendations regarding concomitant background immunosuppression were clarified to explicitly state that subjects are expected to be on background immunosuppression per standard of care. 12. To further ensure subject safety and to be consistent with the DSMB charter, the first planned formal safety review by the DSMB was changed to occur after 50 subjects (instead of 100 subjects) have been randomized and received at least 1 dose of investigational drug. 13. For consistency with standard clinical practice of some investigators, the guidelines for subjects with severe hypogammaglobulinemia were amended to add a 4-week waiting period after reduction of background immunosuppression followed by a re-check of Immunoglobulin G (IgG) levels before implementing treatment with intravenous immunoglobulin. 14. Home health visits were added as a potential option for certain visits in order to reduce the burden on study subjects. The required in-clinic visits were specified along with a recommended in-clinic visit schedule. 15. Changes were made to clarify the process for reporting preexisting medical conditions that meet the definition of a SAE. 16. The appearance of Clazakizumab Drug Product in 12.5 mg/mL vials was corrected to state "clear, colorless solution." Text related to drug preparation and blinding was amended to remove reference to "masked" syringes which are not required given that

		within syringes, clazakizumab 12.5 mg/mL is indistinguishable from placebo. 17. The telephone numbers for the 24-hour SAE reporting lines were updated. 18. With the exception of pulse steroid treatment for acute TCMR (see Protocol Section 7.6.2), treatments for ABMR (including CABMR) and TCMR are not allowed during the study. As a point of clarification, T cell depleting agents were added to the list of prohibited therapies and medications as these agents may confound the effects of clazakizumab. 19. Minor editorial changes were implemented for clarification and/or correction of typographical errors.
1 June 2020	Amendment 5	1. Exclusion Criterion 19 was amended to allow for subjects with fully excised ulcerative colitis to enter the study as this risk factor will have been surgically removed. 2. In order to minimize the risk to subjects and study personnel participating in the study the protocol was revised to include coronavirus disease 2019 (COVID-19) PCR testing at screening and an additional exclusion criterion was added to exclude subjects with an active COVID-19 infection. 3. The processing of blood samples for pharmacokinetic (PK) and anti-drug antibody (ADA) analysis requires a refrigerated centrifuge, which is not available to the home health providers. In order to address this, and ensure all tests are completed per the SOE, the schedule of mandatory in-clinic visits was amended. 4. The rescreening procedures were amended so that a subject being rescreened does not require a repeat chest X-ray for tuberculosis (TB) screening if the first screening chest X-ray was normal and conducted within 6 months from the start date of rescreening.

		5. The prohibited medications section was amended to recommend that the administration of live vaccines (eg, measles, mumps, and rubella; varicella zoster) should be avoided during the course of the study. 6. Minor editorial changes were implemented for clarification and/or correction of typographical errors.
04 February 2021	Amendment 6	1. Inclusion Criterion 3 updated to diagnosis of CABMR based on kidney biopsy and the presence of human leukocyte antigen (HLA) DSA using single-antigen bead-based assays. Diagnosis of CABMR with histopathologic and serologic diagnostic criteria consistent with Banff 2015 criteria. 2. Exclusion Criterion 2 updated to no longer exclude simultaneous kidney-pancreas or previous multiple kidney transplants. 3. Exclusion Criterion 6 updated to "biopsy indicating predominant cause of renal dysfunction caused by pathology other than CABMR". 4. Exclusion Criterion 9 updated to no longer allow collection of a 24-hour urine to confirm nephrotic range if urine albumin creatinine ratio (UACR) is above defined limits. 5. In Exclusion Criterion 19, diverticular disease is now defined as clinically significant diverticulosis (except if disease has been fully excised) 6. In Exclusion Criterion 34, screening of subjects with prior COVID-19 has been clarified. 7. The definition, End of Treatment (EOT) has been added to the SOE and throughout the protocol, and the definition of End of Study (EOS) has been likewise updated. 8. A pharmacokinetic / pharmacodynamic substudy has been added to better capture clazakizumab exposures and relate these to IL-6 and hsCRP levels.

		9. Patient-reported outcome assessments have been added. 10. Sponsor changed to CSL Behring, LLC. 11. Editorial, style and formatting changes made through the document.
30 April 2021	Amendment 7	1. Clarified the required timing of the biopsy required to determine study eligibility after the end of any prior treatment for ABMR (including CABMR) or TCMR, in order to show continuing CABMR and presence of HLA DSA. 2. Corrected Table 4 to reflect administration of subcutaneous clazakizumab. 3. Corrected an inconsistency in the timing of interim analyses. 4. Removed an exploratory healthcare utilization endpoint. 5. Outlined that patient-reported outcome assessments would not be performed for subjects randomized prior to the deployment of an electronic clinical outcome assessment solution.
12 July 2022	Amendment 8	1. The overall study design and treatment duration was changed from up to 260 weeks (or until allograft loss or death) to until the subject permanently discontinues IP, withdraws from the study, experiences allograft loss, dies, or reaches the common treatment end date. 2. The duration of an individual subjects was defined as 5.5 years on average. 3. The frequency of procedures in Years 2 to End of Study was decreased in order to maintain appropriate safety monitoring yet ease the burden on subject's participation. 4. The study procedures were updated based upon the changes to the Schedule of Events in Years 2 to End of Study. 5. A new secondary objective (To evaluate the effects of clazakizumab on loss of allograft function [defined as a 40% decline in eGFR from Baseline that is sustained for at least 60 days]) was added to the study.

		6. A corresponding new secondary endpoint (Incidence and time to loss of allograft function as defined by a 40% decline in eGFR from Baseline) was added to the study. 7. A description of the common treatment end date criteria was added throughout the protocol. 8. Text that is currently described in the Investigator Brochure was removed from the protocol. 9. Access to study product after the end of the study will now be available at the discretion of the treating physician and offered to subjects as agreed upon in their respective country. 10. Subjects who receive IVIG will undergo PK assessments. 11. The inclusion and exclusion criteria were modified to increase the number of subjects who may be eligible to participate in the study, ie. age range for inclusion into the study was increased from 70 to 75 years old, the screening window for kidney biopsy was increased from 6 to 12 months (±3 weeks). 12. Clarifications to exclusion criteria were added ie, Nephrotic range proteinuria defined as spot UACR ≥ 2200 mg/g (≥ 248.4 mg/mmol) and Neutropenia (< 1500/mm^3) or thrombocytopenia (< 75,000/mm^3). 13. Text from the Clinical Trials Facilitation and Coordination Group was added to the adequate contraception language. 14. Subjects who permanently discontinue IP will remain in the study until the common treatment end date. 15. Text regarding unblinding procedures was amended to provide clear directions in the case of a SUSAR. 16. Text describing dose, administration, storage, accountability, and destruction of IP was deleted from the protocol as this

		information is provided in the IMP and / or pharmacy manual. 17. Text regarding allowed concomitant medications / interventions was updated to allow treatment with Lymphocyte immune globulin / anti-thymocyte globulin therapy for TCMR Banff ≥ IIa, V1 lesion. 18. Text regarding prohibited concomitant medications / interventions was expanded to prohibit the use of IVIG and PLEX for any reason for 3 months prior to the start of Screening and can only be administered during the study for hypogammaglobulinemia or if the subject meets the 40% decline in eGFR endpoint. 19. Recommendations for immunizations within 6 weeks prior to the start of Screening was added to the protocol. 20. A detailed description of End of Study procedures was provided for subjects who complete the study, subjects who permanently discontinue IP, subjects who withdraw from the study, and subjects who are on treatment when the primary endpoint of the study is reached.
10 July 2023	Amendment 9	1. The primary objective was revised to include “or irreversible loss of allograft function”. 2. The primary composite efficacy endpoint and associated footnote were revised to include “a sustained (≥ 60 days) 40% decline in eGFR from Baseline”. 3. The “End of Study” (EOS) visit terminology was revised to the “Safety Follow-up Visit” (SFV) or the “Common Treatment End Visit (CTEV)”, where applicable. 4. Testing methodology for COVID-19 was expanded to include rapid antigen testing. 5. Minor corrections and clarifications, including word modifications and administrative changes. 6. Protocol text under the synopsis subsection entitled “Guidelines for Dose Modification,

		Withholding or Discontinuation of Investigational Product, and / or Modification of Background Immunosuppression" was deleted. 7. Protocol text under the synopsis subsection entitled "Post-treatment Follow-up (5 months after the last dose of IP)" was deleted. 8. "Secondary Safety Endpoints" was revised to "Safety Endpoints". 9. The text describing the confirmatory measurement requirements for subjects who met the primary efficacy endpoint by the one component of eGFR of < 15 mL/min/1.73 m^2 was revised. 10. Protocol text was revised to outline the sequence of assessments (kidney biopsy and DSA analysis) required if treatment (other than steroids) for ABMR or TCMR was administered prior to the start of Screening. Details regarding the acceptable dosing regimen of steroids was also provided. 11. Protocol text was revised regarding how to manage study subjects who remain in the study after permanently discontinuing IP. 12. An exploratory objective and corresponding exploratory endpoints were added to the protocol. 13. Text describing calcineurin inhibitor (CNI) monitoring was revised. 14. "Acceptable" methods of contraception were removed from the protocol. 15. The secondary objectives were revised to include the previous primary efficacy objective as the first secondary objective. The remaining secondary objectives were adjusted in position after the new first secondary objective. 16. The order of the secondary objectives was revised to list the "evaluation of the effects of clazakizumab on the histology of kidney biopsies" before the "evaluation of the

		effects of clazakizumab on the incidence of acute rejection episodes (TCMR and ABMR)". 17. A statement regarding how to manage study subjects who reach the endpoint of "a sustained (≥ 60 days) 40% decline in eGFR from Baseline" was added to the text of the protocol. 18. Protocol text regarding how to manage study subjects who withdraw from the study was clarified. 19. The number of participating study sites was increased from 135 to 155. 20. Exclusion criterion 11 was revised to "a history of anaphylaxis or known hypersensitivity related to IP". 21. Exclusion criterion for COVID-19 was clarified. 22. Exclusion criterion 35 was revised to confirm the dose of anti-hypertensive agents has been stable for at least 2 months prior to the start of Screening. 23. The timing for initiating pneumocystis jiroveci pneumonia (PJP) prophylactic therapy has been revised to a Sponsor recommendation. 24. Protocol text regarding the administration of live vaccines was revised to prohibited during the study. Administration of live vaccines is allowed during the 5-month safety Follow-up period following the last dose of IP after careful consideration of risk / benefit profile evaluated by a health care provider. 25. The dose range of mycophenolate mofetil (MMF) and mycophenolic acid (MPA) (allowed concomitant medications) was revised. 26. Based upon the revised primary composite efficacy endpoint and a relative risk reduction of 31%, the graft survival rate was

		increased from 24.7% to 38.3% over 4 years. 27. The original primary efficacy endpoint is now listed as the first secondary efficacy endpoint. The remaining secondary endpoints were adjusted in position after the new first secondary endpoint. 28. The original first secondary efficacy endpoint is now the second secondary efficacy endpoint and now includes "irreversible loss" of allograft function. 29. The original second secondary efficacy endpoint is now the third secondary efficacy endpoint and includes the new endpoint component of "a sustained (≥ 60 days) 40% decline in eGFR from Baseline". 30. The order of the secondary endpoints was revised to align with the revised secondary objectives. "The change in Banff lesion grading score of pre-treatment to post-treatment kidney biopsies" is now listed before the "incidence of acute rejection episodes (TCMR and ABMR) from Baseline to EOT". 31. Two footnotes (D and E) were added to the Study Schema regarding the Safety Follow-up Visit, the common treatment end date visit, and study subjects who permanently discontinue IP. 32. A "Q6 month (Q6M) after DC of IP" visit and a "common treatment end date visit" and their respective assessment schedules were added to the Schedule of Events (Table 1 and Table 2). 33. The definition of Baseline eGFR was added where needed. 34. The procedure entitled "MPA levels" was revised to "as clinically indicated per investigator discretion" in the Schedule of Events (Table 1 and Table 2). 35. The order of presented information was revised to align with the title of this section.

		36. Protocol text regarding subjects who discontinue IP due to pregnancy was revised. 37. Protocol text describing withholding or discontinuing IP due to AE, abnormal LFTs, neutropenia and / or thrombocytopenia, and BKV, CMV, or EBV viral infection was revised. 38. Protocol text describing emergency unblinding of IP was revised. 39. Drug product description was updated to "Clear to slightly opalescent, colorless to yellow colored solution". 40. Protocol text describing studies in Crohn's disease and rheumatoid arthritis was deleted from the protocol. A statement was added to the protocol text to refer the reader to the CSL300 Investigator's Brochure. 41. The subsection under potential risks entitled "autoimmunity" was deleted from the protocol. 42. The sample collection timepoints for several of the test types in Table 8 now includes the SFV, the Q6M (or Q12M) visit, and / or the CTEV, where applicable. 43. The protocol text for the following procedures was updated with the appropriate visit(s) schedule: viral monitoring, monitoring for hypogammaglobulinemia, eGFR, DSA titers and MFI scores, Plasma hsCRP, Plasma IL-6, serum clazakizumab, immunogenicity, MPA levels, standard 12-lead electrocardiogram, and the health-related qualify of life. 44. The timing of the DSA analysis and renal biopsy was revised. 45. Protocol text was revised to allow a study subject to rescreen if they screen failed for either clinical or administrative reasons. 46. The following visits were added to Table 10 (Schedule of Mandatory In-Clinic Visits):

		SFV, Q6 months after DC of IP visit, and CTEV. 47. Visit 16 (Week 52) was deleted from Table 11 (Schedule of "Mandatory In-clinic" Visits that may be Completed as Remote Visits During Extraordinary Circumstances). 48. The list of site visits that are not permitted to be completed remotely was revised. 49. Section title clarified to apply to study subjects who met any of the other non-fatal composite all-cause allograft loss endpoints. Additional assessments that are now required at the SFV were added to this subsection of the protocol text. 50. Additional text was added to the protocol regarding how to manage study subjects once the common treatment end date for the study has been reached. 51. The telephone number for the serious adverse event hotline was removed from the protocol. The email address was moved before the fax number. 52. The summary table of all scheduled study visits (Appendix 2) was revised to include the SFV, the Q6M visit (for study subjects who permanently DC IP), and the CTEV.

PROTOCOL SYNOPSIS

Title	A Pivotal Phase 3 Trial to Evaluate the Safety and Efficacy of Clazakizumab for the Treatment of Chronic Active Antibody-Mediated Rejection in Kidney Transplant Recipients
Sponsor	CSL Behring
Study Code	CSL300_3001 (Formerly VKTX01)
Study Name	IMAGINE (**I**nterleukin 6 Blockade **M**odifying **A**ntibody-Mediated **G**raft **IN**jury and **e**GFR Decline)
Development Phase	3
Number of Sites	Approximately 155 study sites planned in North America, Europe, Asia, and Australia
Rationale	Active antibody-mediated rejection (ABMR), especially chronic active antibody-mediated rejection (CABMR), is now recognized as the most common cause of allograft failure after a successful kidney transplant. Current standard of care antirejection treatments target cellular-mediated (ie, T cell-mediated rejection [TCMR]) processes and do not affect this antibody-mediated process. Currently, there are no approved or effective treatments for active ABMR, including CABMR. Interleukin 6 (IL-6) appears to be a critical cytokine involved in ABMR. It promotes the development and maturation of B cells to plasma cells that produce donor-specific antibodies (DSA) targeting the allograft. These DSA damage the allograft via complement and non-complement mediated pathways and induce graft endothelial cells to produce inflammatory (eg, p-selectin, vascular cell adhesion molecule 1 [VCAM-1]) and pro-thrombotic (eg, von Willebrand factor) molecules. Furthermore, IL-6 shapes the T cell immune response resulting in promotion of long-lived pro-inflammatory T helper (Th) cells (eg, follicular Th cells Th17, Th1, Th2 cells) and inhibition of immune regulatory T (Treg) cells that promote allograft tolerance. This trial investigates whether clazakizumab (an anti-IL-6 monoclonal antibody [mAb]) may be beneficial for the treatment of CABMR in recipients of a kidney transplant by inhibiting the production of DSA and re-shaping T cell alloimmune responses.
Indication	Treatment of CABMR in kidney transplant recipients.
Study Design	Randomized, double-blind, parallel-group, placebo-controlled, phase 3 multicenter study. Subjects will receive treatment with either 12.5 mg clazakizumab (n = 175) or placebo (n = 175) by SC injection Q4W until permanent discontinuation of Investigational Product (IP), withdrawal from the study, allograft loss, death, or the common treatment end date (CTED) is reached, whichever occurs first). The CTED is the date when the primary efficacy endpoint is achieved, ie, the date the target number of primary composite all-cause allograft loss or irreversible loss of allograft function events (221) has been reached.
Primary Objectives	1. To evaluate the efficacy of clazakizumab in preventing all-cause allograft loss (including death) or irreversible loss of allograft function, due to CABMR.

	2. To evaluate the efficacy of clazakizumab in slowing / preventing the progressive loss of kidney function (as measured by eGFR using the Modification of Diet in Renal Disease 4 [MDRD4] equation [Interim Analysis #2 {IA #2}]). 3. To evaluate the safety of clazakizumab.
Secondary Objectives	1. To evaluate the efficacy of clazakizumab in preventing all-cause allograft loss (including death) due to CABMR. 2. To evaluate the effects of clazakizumab on loss of allograft function (defined as a 40% decline in eGFR from Baseline that is sustained for at least 60 days). 3. To evaluate the effects of clazakizumab on death-censored allograft loss. 4. To evaluate the effects of clazakizumab on albuminuria. 5. To evaluate the effects of clazakizumab on DSA titers and mean fluorescence intensity (MFI) scores. 6. To evaluate the effects of clazakizumab on the histology of kidney biopsies according to the Banff 2015 lesion grading scores. 7. To evaluate the effects of clazakizumab on incidence of acute rejection episodes (TCMR and ABMR). 8. To evaluate the effects of clazakizumab on overall subject survival. 9. To evaluate the PK of clazakizumab following subcutaneous (SC) injection in kidney transplant recipients with CABMR (for those subjects in the Pharmacokinetic [PK] / Pharmacodynamic [PD] Substudy only). 10. To evaluate the immunogenicity of clazakizumab in kidney transplant recipients with CABMR.
Exploratory Objectives	1. To evaluate the PD of clazakizumab (serum IL-6 [total and free] and / or high-sensitivity C-reactive protein [hsCRP]) following SC injection in kidney transplant recipients with CABMR (for those in the PK / PD Substudy only). 2. To explore the relationship between clazakizumab PK and PD parameters (serum IL-6 [total and free] and / or hsCRP [for those in the PK / PD Substudy only]). 3. To evaluate the effects of clazakizumab on health-related quality of life (HRQoL) associated with the treatment of antibody-mediated rejection to Week 52 as well as to the Safety Follow-up Visit (SFV). 4. To evaluate the efficacy of clazakizumab in slowing / preventing the progressive loss of kidney function up to the EOT (as measured by eGFR using the MDRD4 equation).
Number of Subjects / Events	It is estimated that approximately 350 subjects randomized to clazakizumab 12.5 mg SC injection once every 4 weeks (Q4W) (175 subjects) or placebo SC injection Q4W (175 subjects) will be required to accrue at least 221 composite all-cause allograft loss or irreversible loss of allograft function events over approximately 5 to 8 years. A subset of 44 subjects (out of the 350 enrolled in the main study) will have the option to participate in a PK / PD Substudy. Subjects enrolled in the PK / PD Substudy will provide consent for additional blood samples for the purpose of PK / PD analyses.

Investigational Treatment	IP: clazakizumab single-dose vials (12.5 mg/mL) for SC injection. Clazakizumab (12.5 mg) will be administered Q4W by SC injection for approximately 260 weeks (5 years) on average. Each 12.5 mg dose will be administered as a 1 mL injection of clazakizumab (12.5 mg/mL). In the case of dose reductions directed by protocol-defined safety parameters, each 6.25 mg dose will be administered as a 0.5 mL injection of clazakizumab (12.5 mg/mL). Placebo Control: normal saline for injection. Placebo will be administered Q4W by SC injection, for approximately 260 weeks (5 years) on average. Each dose of placebo (for subjects on target dose) will be administered as a 1 mL injection of normal saline. Each dose of placebo for subjects on a reduced dose as described above will be administered as a 0.5 mL injection of normal saline.
Concomitant Medications / Interventions	**Allowed**: antidiabetic agents (eg SGLT2 inhibitors), anti-hypertensive agents (eg, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin II receptor blockers [ARBs]), azathioprine (AZA), calcineurin inhibitors (CNIs), low dose corticosteroids (prednisone / prednisolone ≤ 10 mg/day), belatacept (only if already taking at Screening) and mycophenolate mofetil (MMF) / mycophenolic acid (MPA) or equivalent after approval by the Medical Monitor. If the subject is on an ACEI or ARB or starting these drugs, the dose should be stable for at least 2 months prior to the start of Screening Visit and not planned to be increased. Subjects are expected to be on background immunosuppression per standard of care. Recommended AZA / MMF / MPA dose and CNI target trough blood levels: • AZA dose: 1.0 to 2.0 mg/kg/day. • MMF dose: 1.0 to 2.0 g/day. • MPA dose: 720 to 1440 mg/day. • Target tacrolimus plasma trough levels: 5 to 8 ng/mL. • Target cyclosporine plasma trough levels: 50 to 150 ng/mL. Note: Given the potential for drug-drug interactions between clazakizumab and CNIs, CNI trough levels will be monitored at Year 1: Visits 2 (Baseline) through 6, 8, 10, 12, 14, and 16; Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit (for subjects taking a concomitant CNI). CNIs will also be monitored Q2W following a change in CNI dose, withholding, discontinuation, or restarting of IP until target CNI trough levels are achieved. After Year 1, CNI levels may be checked per local practice through local laboratories, including being a part of evaluating any significant changes in creatinine. Locally drawn CNI levels may qualify for monitoring if drawn within the specified interval of ± 2 weeks. Routine monitoring of CNI levels is summarized in the Schedule of Events (SOE). With prior alignment and permission from CSLB, CNI monitoring may be conducted locally during Year 1. If monitored locally during Year 1,CNI monitoring should be conducted at the same laboratory throughout the study, ie beginning from and including the Baseline CNI level. Also, if CNI monitoring is conducted locally in Year 1, a sample

should be drawn and submitted to the central laboratory each time CNI levels are assessed as per the schedule described in the SOE (see Table 1 and Table 2).

- Investigators should attempt to achieve recommended CNI target trough levels within the Screening Period and maintain these levels throughout the study.

Lymphocyte immune globulin / anti-thymocyte globulin therapy is allowed for TCMR Banff ≥ IIa, V1 lesion. The next administration of IP and any DSA testing as per the SOE should occur ≥ 2 weeks after lymphocyte immune globulin / anti-thymocyte globulin therapy.

Pneumocystis jiroveci pneumonia (PJP) prophylaxis:

- All subjects will be required to take prophylactic treatment for PJP. For the first year of the study (ie, from Screening up to and including Week 52), subjects should take trimethoprim / sulfamethoxazole as single-strength pill (80 mg as trimethoprim) daily or double-strength pill (160 mg as trimethoprim) 3 times per week. It is recommended that treatment with trimethoprim / sulfamethoxazole should be started approximately 1 week before the Day 1 Baseline Visit (Visit 2) or 1 week before Screening if already taking it. If a subject is already receiving a suitable Investigator-approved alternative PJP prophylactic therapy, the subject should remain on that therapy and not start trimethoprim / sulfamethoxazole. Subjects who are intolerant to trimethoprim / sulfamethoxazole and not already receiving an Investigator-approved alternative should be started on atovaquone (mepron), inhaled pentamidine, or oral dapsone approximately 1 week before the Day 1 Baseline Visit (Visit 2) based on consultation with the Medical Monitor. In the event of acute kidney injury (AKI [eg, interstitial nephritis]) considered related to trimethoprim / sulfamethoxazole, prophylactic treatment with this drug should be discontinued, and the subject should be started on another Investigator-approved antibiotic therapy (see Section 7.1.3.2). In the event of other serious adverse reactions, the Medical Monitor should be consulted with respect to discontinuing prophylactic treatment or switching to another prophylactic treatment.
- For the remainder of the study (ie, after Week 52), PJP prophylaxis should be continued at the discretion of the Investigator.

Treatment for acute TCMR allowed:

- Pulse steroid (eg, IV methylprednisolone 1000 mg, or oral prednisone 200 mg/day [or equivalent] and taper to Baseline level over 2 weeks).
- Lymphocyte immune globulin / anti-thymocyte globulin therapy is allowed for TCMR Banff ≥ IIa, V1 lesion.

Treatment with oral valganciclovir or intravenous (IV) ganciclovir is permitted for cytomegalovirus (CMV) infection (see “Monitoring for polyoma BK virus [BKV], CMV, and Epstein-Barr virus [EBV] infection”).

In general, the use of herbal and homeopathic medicines (eg, St. John's Wort, echinacea, goldenseal, Schisandra sphenanthera extracts) is strongly discouraged.

Prohibited:
Treatments for ABMR (including CABMR) and TCMR are not allowed within 3 months prior to the start of Screening with the exception of steroids. Subjects who received these treatments at any time prior must have both a renal biopsy and DSA testing performed after halting / completing treatment in order to confirm eligibility per the inclusion criteria (see Section 5.2).

mTOR inhibitors (everolimus, sirolimus) are not allowed within 4 weeks prior to the start of Screening or during the study. Subjects may discontinue mTOR inhibitors and switch to another suitable immunosuppressant and be treated for at least 4 weeks prior to Screening for eligibility.

Administration of live vaccines (eg, measles, mumps, and rubella; varicella zoster) is prohibited within 6 weeks prior to the start of Screening and during the study. During the 5-month safety follow-up period following the last dose of IP, live vaccines, and any additional immunosuppressive therapies should be administered only after careful consideration of the risk / benefit profile by the health care provider.

In addition, the following are prohibited during the study:

- Anti-IL-6 / IL-6R mAbs (approved or investigational).
- Belatacept, unless subject is already taking belatacept at the start of Screening.
- Eculizumab.
- Intravenous Immunoglobulin (IVIG) and plasma exchange (PLEX):
  - **Screening**: IVIG and PLEX are prohibited for any reason for the 3-month period prior to Screening.
  - **During the study**[1]**:** IVIG and PLEX may be administered only to subjects who 1) have hypogammaglobulinemia at any point during the study, 2) meet the 40% decline in eGFR (from Baseline) endpoint and who have received > 12 months of IP (see Section 7.5.3).
    - Double-blind medication and IVIG should be administered 2 weeks apart due to potential binding of IVIG to clazakizumab. For treatment with IVIG, subjects may be called in for unscheduled visits between regularly scheduled dosing with IP according to the SOE.
    - DSA testing, per the SOE, should occur ≥ 2 weeks after administration of IVIG.
    - Pharmacokinetic samples for the assessment of clazakizumab will be collected for subjects that receive IVIG as defined in Table 9.
- Proteasome inhibitors (eg, bortezomib).
- Rituximab.
- T cell depleting agents (eg, alemtuzumab, anti-thymocyte globulin [except for acute TCMR]).
- Other IPs / treatments.

	[1] In a specific clinical setting only (ie, worsening DSA and / or worsening proteinuria, AND pathology showing stable to worsening cg score or other measure[s] of chronic pathology on recent / updated biopsy, accompanied by a worsening measure[s] of activity [eg, peritubular capillaritis score {ptc}, glomerulitis score {g}, complement component 4d Banff score {C4d}]), consideration for use of this medication must be discussed with the Medical Monitor prior to its use.
Selection Criteria	Unless specified otherwise, all eligibility criteria time intervals are assessed with respect to the Screening Visit. **Inclusion Criteria:** 1.A8 Age 18 to 75 years. 2. Living donor / deceased donor kidney transplant recipients ≥ 6 months from time of transplant. 3.A9 Diagnosis of CABMR determined by kidney biopsy and the presence of human leukocyte antigen (HLA) DSA using single-antigen bead-based assays. For eligibility, kidney biopsy must not be older than 12 months and DSA analysis must be performed no longer than 6 months prior to the start of Screening. NOTE: • Within 3 months prior to the start of Screening, treatments for ABMR or TCMR, with the exception of steroids*, are not allowed (see Exclusion Criterion 3). • If treatment for ABMR (including CABMR) or TCMR (other than steroids*) was given between 3 to 12 months of Screening, a repeat kidney biopsy and DSA analysis are required at least 6 weeks after the end of treatment to confirm continuing CABMR and presence of HLA DSA and to determine eligibility. * A maximum dose of 2g of methylprednisolone intravenously (or dose equivalent of other steroids), followed by a taper to the original maintenance steroid dose is allowed. The following histopathologic and serologic diagnostic criteria (based on Banff 2015 criteria [Loupy et al, 2017]) must be met for inclusion: a. Morphologic evidence of chronic tissue injury, as demonstrated by transplant glomerulopathy (TG) (cg>0). Biopsies without evidence of chronic tissue injury on light microscopy, but with glomerular basement membrane double contours on electron microscopy (cg1a) are eligible. b. Evidence of current / recent antibody interaction with vascular endothelium, including 1 or more of the following:

i. Linear complement component 4d (C4d) staining in peritubular capillaries or medullary vasa recta (Banff scores C4d2 or C4d3 by immunofluorescence on frozen sections, or C4d > 0 by immunohistochemistry on paraffin sections).

ii. At least moderate microvascular inflammation (glomerulitis score, [g] + peritubular capillaritis score [ptc] ≥ 2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥ 1.

NOTE: The local pathologist's diagnosis must be reviewed by a central pathologist to confirm eligibility for entry into the study. Biopsies with other histopathologic changes (eg, BKV nephropathy or recurrent glomerulonephritis) may be eligible if concurrent CABMR changes (as detailed above) are present and determined to be the predominant cause of renal dysfunction.

c. Serologic evidence of circulating HLA DSA.

NOTE: The local laboratory DSA results must be reviewed and confirmed by the central HLA reviewer during the Screening Period.

4. Written informed consent obtained from the subject (or legally acceptable representative) before any trial-related procedures.

Exclusion Criteria:

1.A8 Subject is unable or unwilling to comply with study procedures in the opinion of the Investigator.

2.A6 Multi-organ transplant recipient (except for simultaneous kidney-pancreas or previous multiple kidney transplants) or cell transplant (islet, bone marrow, stem cell) recipient.

3. Treatment for ABMR (including CABMR) or TCMR within 3 months prior to the start of Screening with the exception of steroids.

4. Received T cell depleting agents (eg, alemtuzumab, anti-thymocyte globulin) within 3 months prior to the start of Screening.

5. Treatment with mTOR inhibitors within 4 weeks prior to the start of Screening (see Section 7.6.1).

6.A9 Biopsy indicating predominant cause of renal dysfunction caused by pathology other than CABMR, within 12 months prior to the start of Screening.

7.A8 Impaired renal function due to disorders in the transplanted allograft (eg, renal artery stenosis, significant vascular disease of the donor, hydronephrosis).

8. eGFR < 25 mL/min/1.73 m^2 or > 65 mL/min/1.73 m^2 (MDRD4).

9.A8 Nephrotic range proteinuria defined as spot urine albumin-to-creatinine ratio (UACR) ≥ 2200 mg/g (≥ 248.4 mg/mmol). If spot UACR is above the defined limits, a single repeat test can be performed on a separate day to confirm ineligibility.

10.A9 Pregnant, breastfeeding, or unwillingness to practice adequate contraception (eg, a highly effective method of contraception) during the study and for 5 months after the last dose of IP.

11.A9 History of anaphylaxis or known hypersensitivity related to clazakizumab or to any constituent of the drug product.

12.A8 Abnormal liver function tests (LFTs [alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or bilirubin > 1.5 x upper limit of normal]) or other significant liver disease. Subjects with an established diagnosis of Gilbert's syndrome are allowed.

13.A8 Active tuberculosis (TB) or history of active TB.

14.A8 History of latent TB (eg, positive QuantiFERON-TB test) without history of active TB unless the subject has completed a documented course of prophylactic treatment.

15. History of human immunodeficiency virus (HIV) infection or positive for HIV.

16. Seropositive for hepatitis B surface antigen (HBsAg).

17. Hepatitis C virus (HCV) RNA positive.

18.A8 Known EBV mismatch (at time of transplant): donor seropositive, recipient seronegative. Seroconversion to EBV IgG-positive post-transplant is allowed, if documented.

19.A8 History of gastrointestinal (GI) perforation; diverticular disease defined as clinically significant diverticulosis (except if disease has been fully excised and the subject has recovered from surgery) or diverticulitis (except if disease has been fully excised and the subject has recovered from surgery); or inflammatory bowel disease (except fully excised ulcerative colitis and the subject has recovered from surgery).

20.A8 Neutropenia (< 1500/mm^3) or thrombocytopenia (< 75,000/mm^3).

21. Active infections requiring systemic antimicrobial agents and unresolved prior to Screening.

22.A8 History of or current invasive fungal infection or other opportunistic infection, including (but not limited to) the following: a nontuberculous mycobacterial infection, aspergillosis, pneumocystosis, and toxoplasmosis, etc.

23.A8 Active viral infections such as BKV, CMV, or EBV based on plasma polymerase chain reaction (PCR) testing. Active infection is defined as a test result ≥ lower limit of quantification (LLOQ) (see definition in Table 6).

24. Current or recent (within 3 months) participation in an interventional trial.

25. Administration of a live vaccine within 6 weeks prior to the start of Screening, including but not limited to the following:

a. Adenovirus.
b. Measles, mumps, and rubella.
c. Oral polio.
d. Oral typhoid.

	e. Rotavirus. f. Varicella zoster. g. Yellow fever. 26.A8 History of alcohol or illicit substance (including marijuana) abuse < 5 years before Screening. 27.A8 Present or previous (within 3 years) malignancy except for basal cell carcinoma, fully excised squamous cell carcinoma of the skin; other malignancies or those that required significant therapy may require longer duration documented cancer-free (5 years) such as nonrecurrent cervical carcinoma in-situ or malignancy treated with resection and chemotherapy. These cases should be discussed with the Medical Monitor and Sponsor on a case-by-case basis. 28. The presence of a condition or abnormality (ie, clinically significant endocrine, autoimmune, metabolic, neurological, psychiatric / psychological, renal, GI, hepatic, and hematological or any other system abnormalities that are uncontrolled with standard treatment) that in the opinion of the Investigator would compromise the safety or life expectancy of the subject or the quality of the data. 29.A9 History of intolerance to trimethoprim and / or sulfamethoxazole. This criterion does not apply if the subject is already taking another suitable Investigator-approved alternative therapy for PJP prophylaxis, or if the subject is willing to begin taking a suitable Investigator-approved alternative prophylactic therapy approximately 1 week prior to the Day 1 Baseline Visit (Visit 2). 30. Prior exposure to clazakizumab, TCZ, or other IL-6 / IL-6R blockers. 31. ABO-incompatible transplant recipient. 32. Severe hypogammaglobulinemia (defined as immunoglobulin G [IgG] < 400 mg/dL). 33. Prior (within 2 years prior to the start of Screening) exposure to proteasome inhibitors (eg, bortezomib). 34.A9 Active infection with coronavirus disease 2019 (COVID-19): Subjects must have a negative rapid antigen test or PCR test result during the Screening Period as near to the Day 1 Baseline Visit (Visit 2) as possible. If the subject is unwell with symptoms suggestive of COVID-19 but rapid antigen test or PCR test result is negative, other causes for symptoms must be ruled out to determine subject eligibility. Subjects must be without symptoms attributable to COVID-19 for at least 1 month prior to the start of Screening. 35.A9 For subjects receiving anti-hypertensive agents (eg, ACEIs or ARBs), the dose of the agent has been stable for at least 2 months prior to the start of Screening.
Duration of Subject Participation	The average study duration for an individual subject will be approximately 5.5 years. This includes a Screening Period of up to 42 days, a Treatment Period from Day 1 until the subject permanently discontinues treatment with IP, withdraws from the study, experiences allograft loss, dies, or reaches the CTED, whichever occurs first (approximately 260 weeks on average), and a Follow-up period of 5 months after the last dose of IP (completion or early termination). The CTED will be communicated to study sites when the target number of primary composite all-cause allograft loss or irreversible

	loss of allograft function events (221) has been reached to enable study sites to plan their subjects' final visit (common treatment end date visit).
Pharmacokinetic assessments	Blood samples will be collected for assessment of clazakizumab PK in serum in a subset study and in those subjects who receive IVIG.
Pharmacodynamic assessments	Blood samples will be collected for assessment of PD biomarkers, including but not limited to: IL-6 levels (total and free) and / or hsCRP.
Interim Efficacy Endpoint	A sample size reestimation, Interim Analysis #1 (IA #1), will be conducted when approximately 100 subjects have been randomized and completed at least 52 weeks of study participation and may result in an increase in the number of subjects included in IA #2. Interim Efficacy Analysis 2 (IA #2) Surrogate Endpoint: • Change in mean eGFR (in mL/min/1.73 m^2) from Baseline to Week 52. An interim efficacy analysis will be performed to support expedited marketing approval based on a surrogate endpoint of change in mean eGFR from Baseline to Week 52. Baseline eGFR is defined as an average of 2 pre-treatment measurements up to 8 weeks apart. This analysis is planned for when approximately 200 subjects have been randomized and completed at least 52 weeks of study participation.
Primary Efficacy Endpoint: Final Analysis	• Time to composite all-cause allograft loss or irreversible loss of allograft function, defined as time to first occurrence of any of the following components: o eGFR < 15 mL/min/1.73 m^2* o return to dialysis* o allograft nephrectomy o retransplantation o death from any cause, or o a sustained (≥ 60 days) 40% decline in eGFR from Baseline. *total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days. If the eGFR < 15 mL/min/1.73 m^2 is the only component reached, the value must be sustained over at least 60 days and must be confirmed by a repeat measurement after ≥ 60 days from the first measurement. Subjects who reach the endpoint of sustained 40% decline in eGFR from Baseline (but did not reach any of the non-fatal endpoint components of allograft failure) will continue to receive double-blind medication until they reach any of the other primary endpoints of allograft loss. The subject will remain in the study attending all regular clinic visits and undergoing all assessments per the SOE. IVIG and PLEX may be administered at the discretion of the Investigator to these subjects if they have completed the Week 52 visit. Double-blind medication and IVIG should be administered 2 weeks apart due to potential binding of IVIG to clazakizumab. For treatment with IVIG, subjects may be called in for unscheduled visits between regularly scheduled dosing with IP according to the SOE.

	The primary efficacy endpoint will be analyzed as part of the final analysis when at least 221 composite all-cause allograft loss or irreversible loss of allograft function events have occurred.
Safety Endpoints	• Treatment-emergent adverse events (TEAEs), serious TEAEs, and adverse events of special interest (AESIs). • Viral infection monitoring for BK virus (BKV), cytomegalovirus (CMV), and EBV by plasma PCR. • Laboratory tests including LFTs, complete blood count (CBC), plasma lipids, hsCRP. • Vital signs, electrocardiograms (ECGs), and physical examination. • Incidence of antibodies to clazakizumab.
Secondary Efficacy Endpoints	• Time to composite all-cause allograft loss, defined as, time to first occurrence of any of the following components: o eGFR < 15 mL/min/1.73 m^2* o return to dialysis* o allograft nephrectomy o retransplantation, or o death from any cause. • Incidence and time to irreversible loss of allograft function as defined by a 40% decline in eGFR from Baseline. • Incidence of composite all-cause allograft loss or irreversible loss of allograft function, defined by occurrence of any of the following components: o eGFR < 15 mL/min/1.73 m^2* o return to dialysis* o allograft nephrectomy o retransplantation o death from any cause, or o a sustained (≥ 60 days) 40% decline in eGFR from Baseline. • Incidence and time to death-censored allograft loss, defined as occurrence of any of the following components: o eGFR < 15 mL/min/1.73 m^2* o return to dialysis* o allograft nephrectomy, or o retransplantation. • Change in mean eGFR from Baseline to End of Treatment (EOT). • Change in spot UACR from Baseline to EOT. • Change in DSA titers and MFI scores from Baseline to EOT. • Change in Banff lesion grading score (2015 criteria) of pre-treatment to post-treatment (Week 52) kidney biopsies. • Incidence of acute rejection episodes (TCMR and ABMR) from Baseline to EOT. • Overall subject survival. *total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days.

	If the eGFR < 15 mL/min/1.73 m^2 is the only component reached, the value must be sustained over at least 60 days and must be confirmed by repeat measurement after ≥60 days from the date of the first measurement.
Secondary Pharmacokinetic Endpoints	The pharmacokinetic endpoints for a subset of subjects who consent to participate in the PK / PD Substudy will include the following: • maximum concentration (C_{max}, steady state C_{max} [$C_{max\ ss}$]). • trough concentrations (C_{trough}, steady state C_{trough} [$C_{trough\ ss}$]). • area under the concentration-time curve at steady state ($AUC_{0\text{-}tau\ ss}$). • time of maximum concentration (T_{max}, steady state T_{max} [$T_{max\ ss}$]).
Exploratory Endpoints	**PK / PD Endpoints:** • The pharmacodynamic endpoints for subjects who consent to participate in the PK / PD Substudy will include the following: evaluation of IL-6 (total), IL-6 (free), and hsCRP. o Baseline and change from Baseline of free interleukin 6 (IL-6) in plasma. o Baseline and change from Baseline of total interleukin 6 (IL-6) in plasma. o Baseline and change from Baseline of hsCRP levels in serum. • Correlation of hsCRP and IL-6 (total and free) to plasma clazakizumab plasma concentration. **Other Exploratory Endpoints:** • HRQoL associated with the treatment of CABMR to Week 52 as well as to EOT. • Change from Baseline in eGFR at 2 years. • 40% decline in eGFR accompanied by the Investigator's decision to supplement the therapy by additional treatment.
DSMB and Planned Interim Analyses	An independent Data and Safety Monitoring Board (DSMB) will review cumulative study data to evaluate safety, study conduct, scientific validity, and data integrity. The first formal safety review will occur after approximately 50 subjects per group have been randomized and received at least 1 dose of IP. A second safety review will occur after approximately 100 subjects per group have been randomized and received at least 1 dose of IP. Further safety reviews may be conducted at the discretion of the DSMB as outlined in the DSMB charter. Two formal interim analyses will be conducted: IA #1 for sample size reestimation: After approximately 100 subjects (50 per group) have been randomized and completed at least 52 weeks of study participation, a formal interim analysis will be conducted by an independent statistician (external to the blinded study team) to assess the adequacy of the sample size for the interim efficacy analysis of the 52-week eGFR endpoint (see IA #2 below). Observed data from subjects not completing / not reaching Week 52 will also be included in the analysis. The DSMB will review and approve the recommendation of the independent statistician. IA #1 may result in an increase in the number of subjects included in the interim efficacy analysis (see IA #2 below). IA #2: An interim efficacy analysis of the 52-week eGFR endpoint is planned when approximately 200 subjects (100 per group) have been randomized and completed at least

	52 weeks of study participation. The number of subjects included in this interim efficacy analysis may be increased by the outcome of IA #1. If IA #2 shows a statistically significant ($p \leq 0.05$) and clinically meaningful treatment effect on eGFR between the clazakizumab and placebo treatment groups, the results will be submitted to regulatory authorities for expedited marketing approval. If this analysis does not reach statistical or clinical significance, the study will continue until 221 composite all-cause allograft loss or irreversible loss of allograft function events have been observed. Any decision to stop the study in the event of a non-significant effect on eGFR or to increase the sample size for the primary efficacy endpoint (time to composite all-cause allograft loss or irreversible loss of allograft function) would be made based on the recommendation of the DSMB after review of the totality of the data, ie, observed effect on eGFR, updated predicted survival based on the model using data observed in the study, and safety data. The DSMB can recommend stopping the study for safety reasons at any time. A DSMB charter will be created and finalized after the first DSMB operational meeting and before any data review meetings.
Procedures	See the SOE for full details of protocol-required procedures and applicable visits and timings. **Screening (Up to 42 days)** Subjects who provide signed and dated informed consent will be enrolled in the study and screened for eligibility (Visit 1). **Randomization and Study Visits During the Treatment Period** Subjects who satisfy the inclusion and exclusion criteria will be randomized to treatment with either 12.5 mg clazakizumab or placebo administered at clinical sites by SC injection Q4W. Subjects will return to the clinic for post-randomization visits as detailed in the SOE. Throughout the Treatment Period, clazakizumab (or placebo) will be administered Q4W as SC injections. Prior to dosing at each applicable visit, review of the most recent LFT and CBC analyses and viral monitoring results from a prior visit (scheduled or otherwise) will be reviewed for safety considerations. Subjects will receive treatment until the subject permanently discontinues treatment with IP, withdraws from the study, experiences allograft loss, dies, or reaches the CTED, whichever occurs first. Baseline assessments will be performed before the first dose of IP at Day 1 (Visit 2). Safety monitoring, including eGFR, pregnancy testing (for women of childbearing potential), AE, and concomitant medication monitoring will be conducted at dosing visits. Additional assessments will occur at Week 1, Q4W between Week 4 and Week 12, every 8 to 12 weeks up to Week 52, and then every 8 to 24 weeks until the SFV as detailed in the SOE. **Guidelines for Dose Modification, Withholding or Discontinuation of Investigational Product, and / or Modification of Background Immunosuppression** <u>Abnormal LFTs, Neutropenia, and Thrombocytopenia</u> During the study, LFT abnormalities will be monitored and neutropenia and thrombocytopenia will be evaluated at Screening and every 4 to 8 weeks in Year 1, and every 8 weeks after Year 1 as detailed in the SOE. Depending on Common Toxicity

Criteria for Adverse Events (CTCAE) Version 5.0 severity grading, IP dose reduction (to 6.25 mg SC Q4W), withholding, or discontinuation will be permitted in the event of abnormal LFTs (ie, AST / ALT), neutrophil, or platelet counts as per the table of Guidelines for Dose Modification, Withholding, or Discontinuation of IP and / or Modification of Background Immunosuppression. Investigational Product should be temporarily withheld or discontinued for any LFT abnormalities, neutrophil or platelet counts that meet CTCAE Grade ≥ 3. Once the adverse event (AE) resolves, IP may be restarted (at reduced dose or target dose) if clinically appropriate. The table below provides further guidelines for dose adjustment of IP and / or background immunosuppression according to CTCAE severity grade. Decisions regarding dose modification, withholding, discontinuation, or restarting of IP should be made in consultation with the Medical Monitor.

Parameter	**Guidelines for Dose Modification, Withholding or Discontinuation of Investigational Product, and / or Modification of Background Immunosuppression**
LFTs (AST / ALT)	
> ULN to 3.0 x ULN (CTCAE Grade 1)	• No change to IP dose.
> 3.0 to 5.0 x ULN (CTCAE Grade 2)	• In addition, if total bilirubin is ≥ 2.0 x ULN (or INR > 1.5), withhold or discontinue IP and contact Medical Monitor. • If total bilirubin is < 2.0 x ULN, reduce dose of IP to 6.25 mg SC Q4W. Repeat LFT analysis every 2 to 4 weeks and consult Medical Monitor. • Increase dose of IP back up to 12.5 mg SC Q4W if circumstances allow or continue at 6.25 mg SC Q4W. • Perform investigations to exclude other causes of abnormal LFTs (eg, other hepatotoxic drugs, alcohol, viral infections, autoimmune hepatitis, hemochromatosis, etc.).
> 5.0 x ULN (CTCAE Grade ≥ 3)	• Withhold or discontinue IP treatment and contact Medical Monitor.
LFTs (Total bilirubin)	
> 3.0 x ULN	• Withhold or discontinue IP and contact Medical Monitor.
Neutrophil Count (cells per mm^3)	
< 2500 to 1500 (CTCAE Grade 1)	• Reduce dose of MMF / MPA / AZA by 50%. • No change to IP dose.
< 1500 to 1000 (CTCAE Grade 2)	• Reduce dose of MMF / MPA / AZA by 50%. • Reduce dose of IP to 6.25 mg SC Q4W. Repeat CBC every 2 to 4 weeks and consult Medical Monitor. • Increase dose of IP back up to 12.5 mg SC Q4W if circumstances allow or continue at 6.25 mg SC Q4W.
< 1000 (CTCAE Grade ≥ 3)	• Withhold or discontinue IP and contact Medical Monitor.
Platelets (cells per mm^3)	
< LLN to 75,000 (CTCAE Grade 1)	• Reduce dose of MMF / MPA / AZA by 50%. • No change to IP dose.
< 75,000 to 50,000	• Reduce dose of MMF / MPA / AZA by 50%.

(CTCAE Grade 2)	• Reduce dose of IP to 6.25 mg SC Q4W. Repeat CBC every 2 to 4 weeks and consult Medical Monitor. • Increase dose of IP back up to 12.5 mg SC Q4W if circumstances allow or continue at 6.25 mg SC Q4W.
< 50,000 (CTCAE Grade ≥ 3)	• Withhold or discontinue IP and contact Medical Monitor.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AZA = azathioprine; CBC = complete blood count; CTCAE = Common Toxicity Criteria for Adverse Events; INR = International Normalized Ratio; IP = investigational product; LFT = liver function test; LLN = lower limit of normal; MMF = mycophenolate mofetil; MPA = mycophenolic acid; Q4W = once every 4 weeks; SC = subcutaneous; ULN = upper limit of normal.

In general, in cases where IP is reduced to 6.25 mg SC Q4W, it should be continued at the reduced dose for 1 or 2 doses and laboratory test monitoring performed before considering increasing IP dose back to 12.5 mg SC Q4W. In the case of neutropenia or thrombocytopenia, increasing the IP back to 12.5 mg SC Q4W should be considered first before increasing MMF / MPA / AZA. If this is not possible, the subject should continue in the study at the reduced dose of IP.

In consultation with the Medical Monitor, the above approach to IP dose modification, withholding, discontinuation, or restarting should be followed at the discretion of the Investigator for any laboratory abnormality depending on the CTCAE severity (Grade 1 [mild], Grade 2 [moderate], Grade 3 [severe or medically significant]), and corrective actions taken.

Monitoring for BKV, CMV, and EBV Infection

During the study, monitoring for BKV, CMV, and EBV infection will be performed by plasma PCR testing at Screening and every 8 to 24 weeks after Baseline thereafter as detailed in the SOE. If the DNA Viral PC test result is positive (ie, exceeds the LLOQ) or viral load increases, IP dose reduction (to 6.25 mg SC Q4W), withholding or discontinuation will be permitted as summarized in the table below. IP should be permanently discontinued for serious BKV, CMV, or EBV infections according to the criteria defined. The following table provides further guidelines for dose adjustment / withdrawal of IP and / or background immunosuppression according to the viral load as detected by the plasma PCR test result. Decisions regarding dose modification, withholding, discontinuation, or restarting of IP should be made in consultation with the Medical Monitor.

Parameter			**Guidelines for Dose Modification, Withholding or Discontinuation of Investigational Product, and / or Modification of Background Immunosuppression**
BKV[(a)]			
> LLOQ to < 320 IU/mL	> LLOQ to < 2.51 log IU/mL	> LLOQ to < 1000 copies/mL	• Reduce dose of MMF / MPA / AZA by 50% or reduce CNI target trough levels (ie, cyclosporine: 25 to 75 ng/mL; tacrolimus: 4 to 6 ng/mL). • No change to IP dose. • Repeat PCR test every 2 weeks and contact Medical Monitor.

	≥ 320 to < 3200 IU/mL	≥ 2.51 to < 3.51 log IU/mL	≥ 1000 to < 10,000 copies/mL	• Reduce dose of MMF / MPA / AZA by 50% and / or reduce CNI target trough levels (ie, cyclosporine: 25 to 75 ng/mL; tacrolimus: 4 to 6 ng/mL). • Reduce IP to 6.25 mg SC Q4W or consider withholding or discontinuing IP depending on severity of infection. • Repeat PCR test every 2 weeks and contact Medical Monitor. • Increase IP dose back up to 12.5 mg SC Q4W if circumstances allow or continue at 6.25 mg SC Q4W. Or, if IP was temporarily withheld, restart at 6.25 mg SC Q4W if circumstances allow. Repeat PCR at discretion of Investigator.
	Biopsy-proven BKV nephropathy or:			• Discontinue IP and contact Medical Monitor. (Adjustment of MMF / MPA / AZA dose and CNI levels at Investigator's discretion.)
	≥ 3200 IU/mL	≥ 3.51 log IU/mL	≥ 10,000 copies/mL	
	CMV[(b)]			
	> LLOQ to < 1000 IU/mL	> LLOQ to < 3.0 log IU/mL	> LLOQ to < 640 copies/mL	• No change to IP dose. • Repeat PCR test weekly and contact Medical Monitor.
	≥ 1000 to < 5000 IU/mL	≥ 3.0 to < 3.70 log IU/mL	≥ 640 to < 3200 copies/mL	• Treat with oral valganciclovir or IV ganciclovir. • Repeat PCR test weekly and contact Medical Monitor.

Parameter			Guidelines for Dose Modification, Withholding or Discontinuation of Investigational Product, and / or Modification of Background Immunosuppression
CMV[(b)] (Cont'd)			
≥ 5000 IU/mL	≥ 3.70 log IU/mL	≥ 3200 copies/mL	• Reduce dose of MMF / MPA / AZA by 50% and / or reduce CNI target trough levels (ie, cyclosporine: 25 to 75 ng/mL; tacrolimus: 4 to 6 ng/mL). • Treat with oral valganciclovir or IV ganciclovir. • Repeat PCR test weekly and contact Medical Monitor. • Reduce IP to 6.25 mg SC Q4W or consider withholding or discontinuing IP depending on severity of infection. • Increase IP dose back up to 12.5 mg SC Q4W if circumstances allow or continue at 6.25 mg SC Q4W. Or, if IP was temporarily withheld, restart at 6.25 mg SC Q4W if circumstances allow. Repeat PCR at discretion of Investigator.
CMV end-organ disease (eg, hepatitis, colitis, pneumonitis, retinitis)			• Discontinue IP and contact Medical Monitor. (Adjustment of MMF / MPA / AZA dose and CNI levels at Investigator's discretion.)
EBV[(c)]			
> LLOQ to < 10,200 IU/mL	> LLOQ to < 4.01 log IU/mL	>LLOQ to < 5000 copies/mL	• No change to IP dose. • Repeat PCR test every 2 weeks and contact Medical Monitor.
≥ 10,200 to < 20,400 IU/mL	≥ 4.01 to < 4.31 log IU/mL	≥ 5000 to < 10,000 copies/mL	• Reduce dose of MMF / MPA / AZA by 50% and / or reduce CNI target trough levels (ie, cyclosporine: 25 to 75 ng/mL; tacrolimus: 4 to 6 ng/mL). • Repeat PCR test every 2 weeks and contact Medical Monitor.
Post-transplant lymphoproliferative disorder or primary EBV infection in seronegative recipient or:			• Discontinue IP and contact Medical Monitor. (Adjustment of MMF / MPA / AZA dose and CNI levels at Investigator's discretion.)
≥ 20,400 IU/mL	≥ 4.31 log IU/mL	≥ 10,000 copies/mL	

AZA = azathioprine; BKV = polyoma BK virus; CMV = cytomegalovirus; CNI = calcineurin inhibitor; EBV = Epstein-Barr virus; IP = investigational product; IU = International Units; IV = intravenous; LLOQ = lower limit of quantification; MMF = mycophenolate mofetil; MPA = mycophenolic acid; PCR = polymerase chain reaction; Q4W = once every 4 weeks; SC = subcutaneous.

Notes:

[a].LLOQ for BKV: 50.12 IU/mL (1.70 log IU/mL; 156 copies/mL).
[b] LLOQ for CMV: 371.54 IU/mL (2.57 log IU/mL; 238 copies/mL).
[c] LLOQ for EBV: 50.12 IU/mL (1.70 log IU/mL; 24.6 copies/mL).

In general, in cases where IP is reduced to 6.25 mg SC Q4W, it should be continued at the reduced dose for 1 or 2 doses and plasma PCR test monitoring performed before considering increasing IP dose back to 12.5 mg SC Q4W. Restoring the IP dose back to 12.5 mg SC Q4W should be considered first before restarting / increasing MMF / MPA / AZA or increasing CNI levels. If this is not possible, the subject should continue in the study at the reduced dose. Decisions regarding dose modification, discontinuation, withholding and / or restarting of IP should be made in consultation with the Medical Monitor.

For any other clinically significant infections, IP should be withheld, discontinued or dose reduced to 6.25 mg SC Q4W (the Investigator's decision in consultation with Medical Monitor), and subject should be managed as per clinical practice with respect to background immunosuppressants. Once the infection has been treated and resolved, IP can be restarted at reduced dose or dose increased back to 12.5 mg SC Q4W at the discretion of the Investigator.

Monitoring for Hypogammaglobulinemia

During the study, IgG levels will be monitored at Screening and every 12 weeks after Baseline in Year 1 and every 16 weeks in Year 2 through SFV as detailed in the SOE. In the case of severe hypogammaglobulinemia (IgG < 400 mg/dL), reduction of background immunosuppression and treatment with IVIG will be permitted as detailed in the table below. Decisions regarding dose modification of IP and treatment with IVIG should be made in consultation with the Medical Monitor.

Parameter	Guidelines for Modification of Dose of Background Immunosuppression and Treatment with IVIG for Severe Hypogammaglobulinemia
IgG (mg/dL)	
≥ 400	• No change to background immunosuppression. • No change in dose of IP.

< 400	• Reduce dose of MMF / MPA by 50%.
	• No change in dose of IP.
	• After 4 weeks, if IgG < 400 mg/dL, continue with reduced dose of MMF / MPA and treat with IVIG, 0.5 g/kg monthly for 6 months, administered in between doses of IP (ie, 2 weeks postdose of IP is recommended).
	• After 6 months of IVIG treatment:
	  o If IgG ≥ 400 mg/dL, continue with reduced MMF / MPA dose. If IgG levels remain ≥ 400 mg/dL after another 6 months post-IVIG treatment, MMF / MPA dose may be increased back to original dose.
	  o If IgG < 400 mg/dL, consider stopping MMF / MPA and consult the Medical Monitor.

IgG = immunoglobulin G; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; MPA = mycophenolic acid.
Notes:
Clazakizumab should not be administered within 2 weeks of IVIG due to potential binding of clazakizumab by IVIG. Subjects are not allowed to receive IVIG for any reason during the 3-month pre-Screening Period. For treatment with IVIG, subjects may be called in for unscheduled visits between regularly scheduled dosing with IP according to the SOE.

Discontinuation of Investigational Product

If IP is withheld for ≥ 3 consecutive doses because of an AE, the Medical Monitor should be consulted to consider discontinuing IP permanently.

Subjects who permanently discontinued treatment with IP for any reason and who have not reached an endpoint of composite all-cause allograft loss or irreversible loss of allograft function event, defined as either:

- eGFR < 15 mL/min/1.73 m^2*
- return to dialysis*
- allograft nephrectomy
- retransplantation
- death from any cause, or
- a sustained (≥ 60 days) 40% decline in eGFR from Baseline,

will remain in the study and be followed for the occurrence of such events, or until subject withdraws from the study, or until the CTED is reached, whichever occurs first.

Subjects who subsequently reach the endpoint of sustained (≥ 60 days) 40% decline in eGFR from Baseline will continue to remain in the study and will be followed for all-cause allograft loss events, or until subject withdraws from the study, or until the CTED is reached, whichever occurs first.

(*total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days.)

If possible, the subject will return for an in-clinic EOT / Early withdrawal visit within 4-weeks of receiving the last dose of IP. Following the EOT/ Early withdrawal visit, all subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. In addition, all subjects will be contacted by telephone call (TC) 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data. If a subject is unable to return for 6-monthly follow-up visits, he / she will be asked to agree to be contacted at CTED to collect allograft and survival status.

Subjects who permanently discontinued treatment with IP ≥ 5 months before their EOT Visit (and attended regular visits as per SOE) will not require any follow-up telephone calls. An in-clinic SFV will be performed after the 5-month Follow-up-period.

Post-treatment Follow-up (5 Months After the Last Dose of Investigational Product)

After the EOT / Early Withdrawal Visit, the subjects enter the 5-month safety follow-up period. All subjects who complete the study (ie, reached any of the composite non-fatal all-cause allograft loss endpoints) will be contacted monthly by telephone call for monitoring for new AEs, serious AEs, or pregnancies with the final in-clinic SFV 5 months after the last dose of IP. In addition, live vaccines and any additional immunosuppressive therapies should be administered only after careful consideration of the risk / benefit profile by the health care provider. An in-clinic SFV will be performed after the 5-month Follow-up period.

Study Withdrawal

Only if a subject is **unable** / **unwilling** to continue in the study will he / she be withdrawn from the study. Every effort should be made, before the subject withdraws from the study, either voluntarily or at the investigator's discretion, to undergo the EOT assessments and safety follow-up as it is in the best interest of the subject. If possible, the subject will return for an in-clinic EOT /Early Withdrawal visit within 4-weeks of the subject's last dose of IP. If the subject agrees to the safety follow-up following the EOT / Early withdrawal visit, the subject will be asked to return for 2 additional in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. Subjects may be called in for additional clinic visits during the 5-month Follow-up period at the discretion of the investigator.

Subjects may withdraw consent from further participation in the study at any time. No further assessments will be performed after the subject has withdrawn consent from study participation.

Statistical Methods: Primary Analysis Plan	The analysis of the primary and secondary efficacy endpoints will be an intention-to-treat and per-protocol analysis. All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05.

Analysis Sets

The intention-to-treat set will consist of all subjects who received at least 1 dose of IP and who completed a Baseline assessment and at least 1 assessment after Baseline. These subjects will be analyzed according to their randomization group.

The Per-Protocol Analysis Set will consist of all subjects who satisfy the intention-to-treat criteria and have no major protocol deviations that impact the primary efficacy endpoint for the final or interim analysis.

The PK Analysis Set consists of all subjects in the Safety Analysis Set with at least 1 quantifiable PK concentration of IP after administration.

The PK / PD Substudy Analysis Set consists of all subjects in the Safety Analysis Set who consent to be a part of the PK / PD Substudy, and have at least 1 quantifiable PK concentration of IP after administration.

The Safety Analysis Set will consist of all randomized subjects who have received at least 1 dose of IP. Subjects in the Safety Analysis Set will be analyzed according to the actual treatment received.

Randomization

Approximately 350 subjects will be randomized 1:1 into the 2 treatment arms using a stratified block randomization scheme: 175 subjects in the clazakizumab group and 175 subjects in the placebo group.

Stratification factors will include Baseline eGFR (25 to 45 mL/min/1.73 m^2) or > 45 mL/min/1.73 m^2; (Baseline eGFR is defined as an average of 2 pre-treatment measurements up to 8 weeks apart); Baseline proteinuria (UACR < 300 mg/g [< 30 mg/mmol] or UACR ≥ 300 mg/g [≥ 30 mg/mmol]); treatment for early (within 6 months of transplant) ABMR rejection episodes (yes / no); and treatment for late (greater than 6 months post-transplant) ABMR rejection episodes (yes / no).

Interim Analysis #1 (IA #1)

IA#1 will be conducted to confirm the sample size required for the IA#2.

Interim Efficacy Analysis #2 (IA #2)

The interim efficacy endpoint is the difference between the clazakizumab and placebo groups in the change in mean eGFR (in mL/min/1.73 m^2) from Baseline to Week 52.

The interim efficacy endpoint will be analyzed using a mixed model repeated measures approach. The model will include terms for treatment, stratification factors, Baseline eGFR and other pre-defined covariates.

Sensitivity analyses will include the following:

- Missing values imputed using the mean of the observed values at that time point within the same treatment group.
- The delta adjustment method will be used to estimate the tipping point beyond which the active treatment would have an unfavorable effect.
- Nonparametric rank-based method where subjects will first be ranked on the time point that they last provided data, and then by the value of eGFR at that visit. A Wilcoxon rank sum test will then be applied to compare treatment groups using the ranks.

Primary Efficacy Analyses

The primary efficacy endpoint is the time to composite all-cause allograft loss or irreversible loss of allograft function, defined as time to first occurrence of any of the following components:

- eGFR < 15 mL/min/1.73 m^2*
- return to dialysis*
- allograft nephrectomy
- retransplantation
- death from any cause, or
- a sustained (≥ 60 days) 40% decline in eGFR from Baseline.

(*total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days.)

A stratified log rank test will be used to compare the median time-to-event between each treatment arm. Incidence rates and hazard ratios will also be presented.

To assess the robustness of the primary efficacy analysis, the primary efficacy variable will be repeated in sensitivity analyses using the Per-Protocol Analysis Set. An additional sensitivity analysis will address the nature of composite all-cause allograft loss or irreversible loss of allograft function as a recurrent event.

Secondary Efficacy Analyses

Secondary efficacy endpoints will be analyzed in a manner analogous to the primary efficacy endpoint. For time-to-event analysis, a stratified log rank test will be used to estimate the median time-to-event for each treatment arm. Incidence rates will be analyzed using nonparametric approaches.

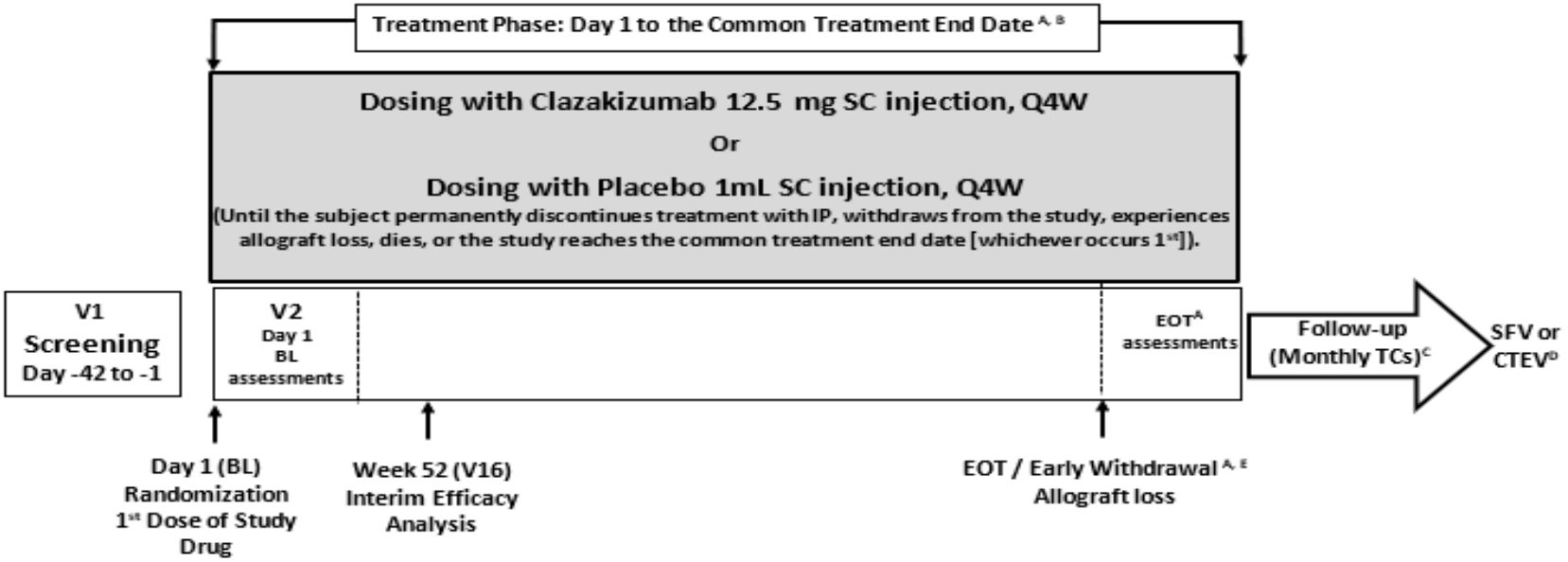
	Pharmacokinetic Analyses Serum PK concentration data will be summarized by nominal timepoint. The PK parameters (for those in the PK / PD Substudy) will be derived by noncompartmental analysis (NCA) using WinNonLin® version 5.2 (or higher) and will be summarized descriptively. **Exploratory Analyses** For subjects participating in the PK / PD Substudy, plasma IL-6 (total and free) and serum hsCRP will be listed and summarized by nominal timepoint. Exploratory analyses will be used to investigate the relationship between serum hsCRP, plasma IL-6 (total and free), and serum clazakizumab. HRQoL will be evaluated based on the domains and summary measures appropriate for the selected instruments included in the protocol by comparing the change from Baseline in scores between treatment groups. **Safety Endpoints** Safety endpoints will be presented using descriptive statistics. Additional details are documented in the Statistical Analysis Plan. Detailed procedures for maintaining the integrity of study blinding will be specified in the DSMB charter and / or Data Access Plan.
Rationale for Number of Subjects	**Primary Efficacy Analysis** The primary efficacy endpoint is the time to composite all-cause allograft loss or irreversible loss of allograft function, defined as time to first occurrence of any of the following components: • eGFR < 15 mL/min/1.73 m^2* • return to dialysis* • allograft nephrectomy • retransplantation • death from any cause, or • a sustained (≥60 days) 40% decline in eGFR from Baseline. (*total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days.) Assuming a rate of composite all-cause allograft loss or irreversible loss of allograft function survival of 24.7% for the placebo arm over a period of approximately 48 months, at least 221 composite all-cause allograft loss or irreversible loss of allograft function events (expected to accrue in 316 subjects) will be required to provide 80% power (two-sided alpha of 0.05) to detect a 31% reduction in the relative risk of allograft loss in the clazakizumab group compared to the placebo group, assuming clazakizumab can reduce the slope of eGFR decline by 50%. A relative risk reduction of 31% would improve the 4-year graft survival rate from 24.7% to 38.3%. Approximately 350 subjects will be enrolled to allow 10% for subjects lost to follow-up or withdrawals. **Interim Analysis for Sample Size Reestimation (IA #1)** Once approximately 100 subjects (50 per group) have been randomized and completed at least 52 weeks of study participation, reestimation (IA #1) of the planned sample size of 200 subjects will be conducted using the inverse normal method with prespecified

information rates (0.5556, 1) to control the Type I error rate. Observed data from subjects not completing / not reaching Week 52 will also be included in the analysis. The sample size reestimation ensures a power of 95.9%, when the assumed difference between treatment groups in the 52-week eGFR of 4.515 mL/min/1.73 m^2 and a common standard deviation of 9.252 mL/min/1.73 m^2 (effect size = 4.515/9.252 = 0.488). The average sample size under these assumptions is 202 subjects with at least 52 weeks of study participation data (corresponding to approximately 224 randomized subjects, assuming 10% for subjects lost to follow-up or withdrawals). When the assumed eGFR effect size is 0.368, then the power is 79.6% and the average sample size is 218 subjects (approximately 242 randomized subjects). The sample size for the interim efficacy analysis surrogate endpoint (IA #2) will not exceed a total of 250 subjects with at least 52 weeks of study participation (approximately 280 randomized subjects).

Interim Efficacy Analysis of Surrogate eGFR Week 52 Endpoint (IA #2)

A planned sample size of approximately 200 subjects (100 per group) has been determined for the IA #2 based on the following assumptions: The interim efficacy analysis surrogate endpoint is the change in mean eGFR (in mL/min/1.73 m^2) from Baseline to Week 52. A fixed sample size of 180 subjects (90 per group) will have 90% power (two-sided alpha of 0.05) to detect a minimum difference in the 52-week eGFR of 4.515 mL/min/1.73 m^2 between the treatment groups (assuming eGFR declines at a rate of 0.75 mL/min/1.73 m^2/month in the placebo treated group and that clazakizumab reduces eGFR decline by 50%). The sample size determination for the fixed design is based on a two-sided alpha of 0.05 and a common standard deviation of 9.252 mL/min/1.73 m^2 for the mean eGFR change from Baseline to Week 52 (effect size = 4.515/9.252 = 0.488). The planned sample size has been increased to a minimum of 200 subjects to allow 10% for subjects lost to follow-up or withdrawals.

SCHEMA



BL = Baseline; CTED = common treatment end date; CTEV = common treatment end visit; EOT = End of Treatment; Q4W = once every 4 weeks; SC = subcutaneous; SFV = safety follow-up visit; TCs = telephone calls; V = visit.

A Subjects will return to the clinic to receive treatment with IP (clazakizumab or placebo) by SC injection Q4W until the subject: permanently discontinues treatment with IP, withdraws from the study, experiences allograft loss, dies, or the study reaches the common treatment end date (CTED) (whichever occurs 1st). At some sites, home / work-place visits may be offered as an option instead of in-clinic visits for certain visits during the treatment phase. Dosing from randomization to the common treatment end date = approximately 260 weeks (on average).

B The CTED will occur when the pre-specified target number of allograft loss events (221) has been reached. The CTED will be communicated to study sites in advance to enable study sites to plan their subjects' common treatment end visit (CTEV).

C Subjects will be followed for 5 months after the last dose of IP.

D An in-clinic SFV is to be performed after the 5-month safety follow-up period. A CTEV will be performed for those subjects still receiving IP at the time the common treatment end date is reached.

E Subjects who discontinue IP will remain in the study and be followed for all-cause allograft loss and irreversible loss of allograft function events, or until the CTED is reached, whichever occurs first. Subjects who discontinue IP will undergo and EOT / Early Withdrawal Visit. They will remain on study and will be asked to return for 2 in-clinic safety follow-up visits, 3 and 5 months after the last dose of IP. In addition, all subjects will be contacted by telephone call 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data.

Schedule of Events

Table 1 Schedule of Events for Year 1 (Screening to Week 52 Inclusive)

Procedures	Screening[A]	Treatment Period: Clazakizumab Q4W SC Injection (Until Discontinuation of IP, Withdrawal from Study, Allograft Loss, Death, or Common Treatment End Date, whichever occurs first)[A]											
	Up to -42 Days +2 days	Day 1[A] BL	Wk 1[C] ±5 days	Wk 4[A] & 8 ±5 days	Wk 12[A] ±5 days	Wk 16 ±5 days	Wk 20 ±5 days	Wk 24[A], 28, 32, 36, 40, 44, 48[A] ±5 days	Wk 52[A] ±5 days	EOT / Early Withdrawal Visit[A,B]	SF Visits[B]	Q6M after DC of IP[B]	CTED Visit[B]
	Visit 1	Visit 2	Visit 3	Visit 4, 5	Visit 6	Visit 7	Visit 8	Visits 9 to 15	Visit 16				
Informed consent[D]	X												
Complete physical examination and vital signs[E]	X												
Medical history[E]	X												
Review historical serology for HIV, HBsAg, HCV, CMV, and EBV; and test for HIV and HBsAg if seronegative or unknown	X												
TB Screening (QuantiFERON-TB Gold and CXR)[E]	X												
HCV; COVID-19[F] rapid antigen test or PCR test	X												
Standard urinalysis dipstick[G]	X												
Inclusion / exclusion criteria review / check	X	X											

Procedures	Screening[A]	Treatment Period: Clazakizumab Q4W SC Injection (Until Discontinuation of IP, Withdrawal from Study, Allograft Loss, Death, or Common Treatment End Date, whichever occurs first)[A]											
	Up to -42 Days +2 days	Day 1[A] BL	Wk 1[C] ±5 days	Wk 4[A] & 8 ±5 days	Wk 12[A] ±5 days	Wk 16 ±5 days	Wk 20 ±5 days	Wk 24[A], 28, 32, 36, 40, 44, 48[A] ±5 days	Wk 52[A] ±5 days	EOT / Early Withdrawal Visit[A,B]	SF Visits[B]	Q6M after DC of IP[B]	CTED Visit[B]
	Visit 1	Visit 2	Visit 3	Visit 4, 5	Visit 6	Visit 7	Visit 8	Visits 9 to 15	Visit 16				
Randomization		X											
Abbreviated physical examination[H] and vital signs		X		X	X			Wks 24, 36 & 48 only (Visits 9, 12 & 15)		X			X
12-lead ECG	X				X			Wks 24 & 48 only (Visits 9 & 15)		X			X
Pregnancy test (for WOCBP)[I]	X	X		X	X	X	X	X	X	X	X		X
Safety laboratory tests (clinical chemistry, CBC, lipids, hsCRP)[J]	X	X		X	X		X	Wks 28, 36 & 44 only (Visits 10, 12 & 14)	X	X	X	X (minus hs-CRP)	X
BKV, CMV & EBV, DNA Viral PCR monitoring	X			X	X		X	Wks 28, 36 & 44 only (Visits 10, 12 & 14)	X	X			X
IgG monitoring	X				X			Wks 24, 36 & 48 only (Visits 9, 12 & 15)		X			X
DSA MFI scores	X Local testing[K]	X						Wk 24 only (Visit 9)	X	X	X	X (only Q12M)	X
DSA titers		X							X	X			

Procedures	Screening[A]	Treatment Period: Clazakizumab Q4W SC Injection (Until Discontinuation of IP, Withdrawal from Study, Allograft Loss, Death, or Common Treatment End Date, whichever occurs first)[A]											
	Up to -42 Days +2 days	Day 1[A] BL	Wk 1[C] ±5 days	Wk 4[A] & 8 ±5 days	Wk 12[A] ±5 days	Wk 16 ±5 days	Wk 20 ±5 days	Wk 24[A], 28, 32, 36, 40, 44, 48[A] ±5 days	Wk 52[A] ±5 days	EOT / Early Withdrawal Visit[A,B]	SF Visits[B]	Q6M after DC of IP[B]	CTED Visit[B]
	Visit 1	Visit 2	Visit 3	Visit 4, 5	Visit 6	Visit 7	Visit 8	Visits 9 to 15	Visit 16				
Renal biopsy	X[L]								X[M]	X[N]			
eGFR[O]	X	X		X	X	X	X	X	X	X	X	X	X
UACR[P]	X				X			Wks 24 & 48 only (Visits 9 & 15)		X	X	X	X
IL-6 levels (total and free)		X			X			Wks 24 & 48 only (Visits 9 & 15)		X	X		X
MPA levels[Q]		X	As clinically indicated per investigator discretion.							X			X
CNI levels[R]		X	X	X	X		X	Wks 28, 36 & 44 only (Visits 10, 12 & 14)	X	X			X
Adverse event / concomitant medication monitoring	X[S]	X		X	X	X	X	X	X	X	X		X
Clazakizumab drug levels and anti-clazakizumab antibodies[T]		X			X			Wks 24 & 48 only (Visits 9 & 15)		X	X		X
Prophylactic antibiotic[U]	X	X	X	X	X	X	X	X	X				X
EQ-5D-5L, KDQoL-36, and FACIT Fatigue Scale[V]		X						Wk 24 only (Visit 9)	X	X		X	X
Clazakizumab / placebo injection[W]		X		X	X	X	X	X	X				

AE = adverse event; AKI = acute kidney injury; BKV = polyoma BK virus; BL = Baseline; CBC = complete blood cell count; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CRO = contract research organization; CTED = common treatment end date; CTEV = common treatment end visit; CXR = chest X-ray; DSA = donor-specific antibodies; EBV = Epstein-Barr virus; ECG = electrocardiogram; eCOA = electronic clinical outcomes assessment; eGFR = estimated glomerular filtration rate; EOT = End of Treatment; EQ-5D-5L = EuroQol-5 Dimensions – 5 Levels; FACIT Fatigue Scale = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; hsCRP = high-sensitivity C-reactive protein; HRQoL = health-related quality of life; ICF = informed consent form; IgG = immunoglobulin G; IL-6 = interleukin 6; IP = investigational product; KDQoL36 = Kidney Disease Quality of Life Questionnaire 36; MDRD4 = Modification of Diet in Renal Disease 4; MFI = mean fluorescence intensity; MMF = mycophenolate mofetil; MPA = mycophenolate / mycophenolic acid; PCR = polymerase chain reaction; PJP = pneumocystis jiroveci pneumonia; Q4W = once every 4 weeks; Q6M = every 6 months; Q12M = every 12 months; RNA = ribonucleic acid; SAE = serious adverse event; SF= safety follow-up; SOE = schedule of events; TB = tuberculosis; UACR = urine albumin creatinine ratio; Wk = Week; WOCBP = women of childbearing potential.

Notes: During the Treatment Period, blood and urine samples should be collected prior to IP dosing at the clinic visit. Except where indicated otherwise, all samples will be analyzed by the central laboratory.

A. At some sites, home / workplace visits may be offered as an option instead of in-clinic visits for certain visits during the Treatment Period. This service may not be available for all subjects at all sites. In Year 1 of the study, in-clinic visits are mandatory at Visit 1 (Screening), Visit 2 (Baseline; Day 1), Visit 4 (Wk 4), Visit 6 (Wk 12), Visit 9 (Wk 24), Visit 15 (Wk 48), and Visit 16 (Wk 52). An in-clinic visit is required at EOT / Early Withdrawal; if a subject meets the primary efficacy endpoint (composite all-cause allograft loss or irreversible loss of allograft function); and, at the discretion of the Investigator, if clinically indicated (eg, because of an AE). Other scheduled visits can be home / workplace visits.

B. All early withdrawal subjects and subjects who permanently discontinued IP treatment due to loss of their allograft, will undergo all assessments per the EOT / Early Withdrawal Visit schedule. Subjects who permanently discontinued treatment with IP for any reason and who have not reached an endpoint of allograft loss, defined as an eGFR < 15 mL/min/1.73 m^{2*}, return to dialysis*, allograft nephrectomy, retransplantation, or death from any cause or subjects with a sustained (≥ 60 days) 40% decline in eGFR from Baseline who discontinued IP for any reason will not be withdrawn; they will remain in the study as described in Section 9.2.5.3. *total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days. Following the EOT / Early Withdrawal Visit, subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. (Note: DSA MFI Scores, UACR, and IL-6 levels are not required at the 3-month Safety Follow-up Visit). In addition, all subjects will be contacted by telephone call 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data. If a subject is unable to return for 6-monthly follow-up visits, he / she will be asked to agree to be contacted at CTED to collect allograft and survival status. The common treatment end visit (CTEV) will be performed within 4 weeks after the CTED is reached.

C. This visit is required only if the subject is taking a CNI.

D. Informed consent to be signed before any study-related procedures, including washout of prohibited medications. If consent is signed more than 30 days before Screening, it must be re-signed and re-dated at Screening to reaffirm the subject's continued interest to participate in the study. The Screening Period starts on the date the first Screening assessment is completed after signing the ICF.

E. A complete physical examination, including chest X-ray, and medical history, including historical serology for vital infections should be performed to evaluate exposure to TB and whether subjects with a history of latent TB (without active TB) completed a documented course of prophylactic treatment. If a positive result is obtained for the interferon-γ-release assay, the test should not be repeated. For an indeterminate result, the assay may be repeated 1 time. If the second test is positive or indeterminate, the result should be considered positive for that subject. A third test may not be performed. Note: local QuantiFERON-TB Gold testing is acceptable.

F. Subjects must have a negative rapid antigen test or PCR test result during the Screening Period as near to the Day 1 Baseline Visit (Visit 2) as possible. If the subject is unwell with symptoms suggestive of COVID-19 but rapid antigen test or PCR test result is negative, other causes for symptoms must be ruled out to determine subject eligibility. Subjects must be without symptoms attributable to COVID-19 for at least 1 month prior to the start of Screening. Additional testing during the trial may be performed at the discretion of the Investigator if clinically indicated.

G. Urinalysis dipstick (chemical profile) with optional microscopic profile if dipstick is abnormal.

H. Height will be included at Visit 1 only.

I. Urinary pregnancy test prior to every dose of IP. For subjects who permanently discontinued treatment with IP, this assessment will be conducted monthly for an additional 5 months following the last dose of IP. Positive urine tests will be confirmed by a serum pregnancy test that is analyzed at the central laboratory.

J. Fasting for a minimum of 10 hours is required for determination of fasting glucose and for lipids / triglycerides. If the subject failed to fast, samples should still be collected and processed with failure to fast recorded on the laboratory requisition and also recorded as a protocol deviation. Note: glucose and lipids / triglycerides will not be assessed at Visit 1. See Table 8 for details regarding the required assessments.

K. If the presence of HLA DSA has been confirmed within 6 months prior to the start of Screening, the test does not need to be repeated for eligibility. Rather, sites will submit the historical, local laboratory DSA results for review by the central HLA reviewer to confirm eligibility for entry into the study. If DSA has not been confirmed within 6 months prior to the start of Screening, local laboratory DSA testing should be performed, and the results submitted for review by the central HLA reviewer. If the central HLA reviewer disagrees with the local laboratory results, the central laboratory may repeat the Screening DSA test once; the repeat results must be reviewed by the central HLA reviewer to confirm DSA eligibility criteria. If local DSA testing is not available, a sample should be submitted to the central laboratory for analysis.

L. The local pathologist's diagnosis must be reviewed by a central pathologist to confirm eligibility for entry into the study. If treatment for ABMR (including CABMR) or TCMR (other than steroids*) was given between 3 to 12 months of Screening, a repeat kidney biopsy and DSA analysis are required at least 6 weeks after the end of treatment to confirm continuing CABMR and presence of HLA DSA and to determine eligibility.

M. At Wk 52 (Visit 16 [window -2 weeks to +6 weeks]). If clinically indicated, an unscheduled biopsy may be performed at any time. If a for-cause biopsy has been performed within 2 months of Wk 52, a repeat biopsy at Wk 52 is not required. Subjects who withdraw from the study on or after Visit 6 (Wk 12) and prior to Visit 16 (Wk 52; and the subject has not had a biopsy within this period) should have a biopsy performed as part of the EOT / Early withdrawal assessments.

N. EOT renal biopsy required if the subject withdraws on or after Visit 6 (Wk 12) and prior to Visit 16 (Wk 52), and the subject has not had a biopsy within this period.

O. The MDRD4 equation will be used for determination of eGFR. Baseline eGFR is defined as an average of 2 pre-treatment measurements up to 8 weeks apart. If the eGFR < 15 mL/min/1.73 m^2 is the only component reached, the value must be sustained over at least 60 days and must be confirmed by a repeat measurement after ≥60 days from the date of the first measurement.The confirmatory measurement of eGFR < 15 mL/min/1.73 m^2 done at least 60 days from the initial measurement must be processed by the central laboratory.

P. UACR determined using spot urine test. At Screening, if spot UACR is above the defined limits, a single repeat test can be performed on a separate day to confirm ineligibility.

Q. As clinically indicated per investigator discretion; only for subjects taking concomitant MMF / MPA. At relevant visits, treatment with MMF / MPA is to be withheld until after collection of the blood sample for determination of MPA levels.

R. Required only for subjects taking a concomitant CNI. CNI trough levels will be monitored at Year 1: Visits 2 (Baseline) through 6, 8, 10, 12, 14, and 16; Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit. CNIs will also be monitored every 2 weeks following a change in CNI dose, withholding, discontinuation, or restarting of IP, until target CNI trough levels are achieved. After Year 1, CNI levels may be checked per local practice through local laboratories, including being a part of evaluating any significant changes in creatinine. Locally drawn CNI levels may qualify for monitoring if drawn within the specified interval of ± 2 weeks. With prior alignment and permission from CSLB, CNI monitoring may be conducted locally during Year 1. If monitored locally during Year 1, CNI monitoring should be conducted at the same laboratory throughout the study, ie beginning from and including the Baseline CNI level. Also, if CNI monitoring is conducted locally in Year 1, a sample should be drawn and submitted to the central laboratory each time CNI levels are assessed as per the schedule described in the SOE. At relevant visits, CNIs are to be withheld until after collection of the blood sample for determination of CNI trough levels.

S. AEs occurring during the Screening Period are to be recorded as medical history. Any AE that meets the definition of an SAE must also be immediately reported to CSL Behring (or its delegate; eg, CRO) within 24 hours of site awareness.

T. Not required if the subject has been permanently discontinued from treatment with IP. For subjects participating in the PK / PD Substudy, additional samples will be collected as per Table 3. All PK samples will be drawn prior to administration of IP, except for those specified in the PK / PD Substudy. For subjects that go on to receive IVIG, additional PK samples will be collected (see Table 9).

U. All subjects will be required to take prophylactic treatment for PJP; these drugs will be prescribed and supplied by the investigational sites. For the first year of the study (ie, from Screening up to and including Wk 52), subjects should take trimethoprim / sulfamethoxazole as a single-strength pill (80 mg as trimethoprim) daily or double-strength pill (160 mg as trimethoprim) 3 times per week. It is recommended that treatment with trimethoprim / sulfamethoxazole should be started approximately 1 week before the Day 1 Baseline Visit (Visit 2) or dose should be stable at least 1 week before Screening if the subject is already taking it. If subject is already receiving a suitable Investigator-approved alternative therapy for PJP prophylaxis, the subject should remain on that therapy and not start trimethoprim / sulfamethoxazole. Subjects who are intolerant to trimethoprim / sulfamethoxazole and not already receiving an Investigator-approved alternative therapy should be started on atovaquone (mepron), inhaled pentamidine, or oral dapsone for approximately 1 week before the Day 1 Baseline Visit (Visit 2) based on consultation with the Medical Monitor. In the event of AKI (eg, interstitial nephritis) considered related to trimethoprim / sulfamethoxazole, prophylactic treatment with this drug should be discontinued, and the subject should be started on another antibiotic therapy for PJP prophylaxis (see Section 7.1.3.2). In the event of other serious adverse reactions, the Medical Monitor should be consulted with respect to discontinuing prophylactic treatment or switching to another prophylactic treatment.

V. EQ-5D-5L, KDQoL-36, and FACIT Fatigue questionnaires will be completed by subjects using an eCoA solution whether at the study site or during a home visit. Subjects who are randomized before the availability of the eCOA solution will not complete HRQoL questionnaires.

W. Throughout the Treatment Period, subjects will return to the clinic Q4W for investigational treatment with clazakizumab / placebo until the subject permanently discontinues IP, withdraws from the study, experiences allograft loss, dies, or reaches the CTED, whichever occurs first. Note: as detailed in Footnote A, home / workplace visits may be offered as an option instead of in-clinic visits for certain visits during the treatment phase (at some sites only).

Table 2 Schedule of Events for Year 2 to the Safety Follow-up Visit / Common Treatment End Visit[N]

Procedures	Clazakizumab Q4W SC Injection (Until Discontinuation of IP, Withdrawal from Study, Allograft Loss, Death, or Common Treatment End Date, whichever occurs first)[(A)]																		
Year 2 & Year 6	**Wk 56, 264 ±5 days (V17, V69)**	**Wk 60, 268[(A)] ±5 days (V18, V70)**	**Wk 64 +272 ±5 days (V19, V71)**	**Wk 68 + 276 ±5 days (V20, V72)**	**Wk 72[(A)] + 280 ±5 days (V21, V73)**	**Wk 76[(A)] + 284 ±5 days (V22, V74)**	**Wk 80 + 288 ±5 days (V23, V75)**	**Wk 84 + 292[(A)] ±5 days (V24, V76)**	**Wk 88 + 296 ±5 days (V25, V77)**	**Wk 92 + 300, ±5 days (V26, V78)**	**Wk 96 + 304 ±5 days (V27, V79)**	**Wk 100[(A)] + 308 ±5 days (V28, V80)**	**Wk 104 + 312 ±5 days (V29, V81)**				**EOT / Early With-drawal Visit (A,B)**	**SF Visits (B)**	**Q6M after DC[(B)]**	**CTED Visit[(B)]**
Year 3 & Year 7		**Wk 108, 316[(A)] ±5 days (V30, V82)**	**Wk 112 + 320 ±5 days (V31, V83)**	**Wk 116 + 324 ±5 days (V32, V84)**	**Wk 120 + 328 ±5 days (V33, V85)**	**Wk 124[(A)]+ 332 ±5 days (V34, V86)**	**Wk 128 + 336 ±5 days (V35, V87)**	**Wk 132 + 340[(A)] ±5 days (V36, V88)**	**Wk 136 + 344 ±5 days (V37, V89)**	**Wk 140 + 348 ±5 days (V38, V90)**	**Wk 144 + 352 ±5 days (V39, V91)**	**Wk 148[(A)] + 356 ±5 days (V40, V92)**	**Wk 152 +360 ±5 days (V41, V93)**	**Wk 156 + 364[(A)] ±5 days (V42, V94)**						
Year 4			**Wk 160 ±5 days (V43)**	**Wk 164 ±5 days (V44)**	**Wk 168 ±5 days (V45)**	**Wk 172[(A)] ±5 days (V46)**	**Wk 176 ±5 days (V47)**	**Wk 180 ±5 days (V48)**	**Wk 184 ±5 days (V49)**	**Wk 188 ±5 days (V50)**	**Wk 192 ±5 days (V51)**	**Wk 196[(A)] ±5 days (V52)**	**Wk 200 ±5 days (V53)**	**Wk 204 ±5 days (V54)**	**Wk 208 ±5 days (V55)**					
Year 5				**Wk 212 ±5 days (V56)**	**Wk 216 ±5 days (V57)**	**Wk 220[(A)] ±5 days (V58)**	**Wk 224 ±5 days (V59)**	**Wk 228 ±5 days (V60)**	**Wk 232 ±5 days (V61)**	**Wk 236 ±5 days (V62)**	**Wk 240 ±5 days (V63)**	**Wk 244[(A)] ±5 days (64)**	**Wk 248 ±5 days (V65)**	**Wk 252 ±5 days (V66)**	**Wk 256 ±5 days (V67)**	**Wk 260 ±5 days (V68) [(N)]**				
Clazakizumab / placebo injection[(C)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Abbreviated physical examination[(D)] and vital signs		X				X				X				X			X			X
12-lead ECG												Wk 100 (V28) Wk 308 (V80)		Wk 156 (V42) Wk 204 (V54) Wk 364 (V94)		X	X			X
Pregnancy test (for WOCBP)[(E)]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Procedures	**Clazakizumab Q4W SC Injection (Until Discontinuation of IP, Withdrawal from Study, Allograft Loss, Death, or Common Treatment End Date, whichever occurs first)[A]**																		
Year 2 & Year 6	**Wk 56, 264 ±5 days (V17, V69)**	**Wk 60, 268[A] ±5 days (V18, V70)**	**Wk 64 +272 ±5 days (V19, V71)**	**Wk 68 + 276 ±5 days (V20, V72)**	**Wk 72[A] + 280 ±5 days (V21, V73)**	**Wk 76[A] + 284 ±5 days (V22, V74)**	**Wk 80 + 288 ±5 days (V23, V75)**	**Wk 84 + 292[A] ±5 days (V24, V76)**	**Wk 88 + 296 ±5 days (V25, V77)**	**Wk 92 + 300, ±5 days (V26, V78)**	**Wk 96 + 304 ±5 days (V27, V79)**	**Wk 100[A] + 308 ±5 days (V28, V80)**	**Wk 104 + 312 ±5 days (V29, V81)**				**EOT / Early With-drawal Visit [A,B]**	**SF Visits [B]**	**Q6M after DC[B]**	**CTED Visit[B]**
Year 3 & Year 7		**Wk 108, 316[A] ±5 days (V30, V82)**	**Wk 112 + 320 ±5 days (V31, V83)**	**Wk 116 + 324 ±5 days (V32, V84)**	**Wk 120 + 328 ±5 days (V33, V85)**	**Wk 124[A]+ 332 ±5 days (V34, V86)**	**Wk 128 + 336 ±5 days (V35, V87)**	**Wk 132 + 340[A] ±5 days (V36, V88)**	**Wk 136 + 344 ±5 days (V37, V89)**	**Wk 140 + 348 ±5 days (V38, V90)**	**Wk 144 + 352 ±5 days (V39, V91)**	**Wk 148[A] + 356 ±5 days (V40, V92)**	**Wk 152 +360 ±5 days (V41, V93)**	**Wk 156 + 364[A] ±5 days (V42, V94)**						
Year 4			**Wk 160 ±5 days (V43)**	**Wk 164 ±5 days (V44)**	**Wk 168 ±5 days (V45)**	**Wk 172[A] ±5 days (V46)**	**Wk 176 ±5 days (V47)**	**Wk 180 ±5 days (V48)**	**Wk 184 ±5 days (V49)**	**Wk 188 ±5 days (V50)**	**Wk 192 ±5 days (V51)**	**Wk 196[A] ±5 days (V52)**	**Wk 200 ±5 days (V53)**	**Wk 204 ±5 days (V54)**	**Wk 208 ±5 days (V55)**					
Year 5				**Wk 212 ±5 days (V56)**	**Wk 216 ±5 days (V57)**	**Wk 220[A] ±5 days (V58)**	**Wk 224 ±5 days (V59)**	**Wk 228 ±5 days (V60)**	**Wk 232 ±5 days (V61)**	**Wk 236 ±5 days (V62)**	**Wk 240 ±5 days (V63)**	**Wk 244[A] ±5 days (64)**	**Wk 248 ±5 days (V65)**	**Wk 252 ±5 days (V66)**	**Wk 256 ±5 days (V67)**	**Wk 260 ±5 days (V68) [N]**				
Safety laboratory tests (clinical chemistry, CBC, lipids, hsCRP)[F]		X		X		X		X		X		X		X		X	X	X	X	X
BKV, CMV & EBV, DNA Viral PCR monitoring						X						X				X	X			X
IgG monitoring		X				X				X				X			X			X
DSA MFI scores												Wk 100 (V28), Wk 308 (V80)		Wks 156, 204, & 364 (V42, 54, & 94)		X	X	X	X (only Q12M)	X

Procedures	**Clazakizumab Q4W SC Injection (Until Discontinuation of IP, Withdrawal from Study, Allograft Loss, Death, or Common Treatment End Date, whichever occurs first)[A]**																		
Year 2 & Year 6	**Wk 56, 264 ±5 days (V17, V69)**	**Wk 60, 268[A] ±5 days (V18, V70)**	**Wk 64 +272 ±5 days (V19, V71)**	**Wk 68 + 276 ±5 days (V20, V72)**	**Wk 72[A] + 280 ±5 days (V21, V73)**	**Wk 76[A] + 284 ±5 days (V22, V74)**	**Wk 80 + 288 ±5 days (V23, V75)**	**Wk 84 + 292[A] ±5 days (V24, V76)**	**Wk 88 + 296 ±5 days (V25, V77)**	**Wk 92 + 300, ±5 days (V26, V78)**	**Wk 96 + 304 ±5 days (V27, V79)**	**Wk 100[A] + 308 ±5 days (V28, V80)**	**Wk 104 + 312 ±5 days (V29, V81)**				**EOT / Early With-drawal Visit [A,B]**	**SF Visits [B]**	**Q6M after DC[B]**	**CTED Visit[B]**
Year 3 & Year 7		**Wk 108, 316[A] ±5 days (V30, V82)**	**Wk 112 + 320 ±5 days (V31, V83)**	**Wk 116 + 324 ±5 days (V32, V84)**	**Wk 120 + 328 ±5 days (V33, V85)**	**Wk 124[A]+ 332 ±5 days (V34, V86)**	**Wk 128 + 336 ±5 days (V35, V87)**	**Wk 132 + 340[A] ±5 days (V36, V88)**	**Wk 136 + 344 ±5 days (V37, V89)**	**Wk 140 + 348 ±5 days (V38, V90)**	**Wk 144 + 352 ±5 days (V39, V91)**	**Wk 148[A] + 356 ±5 days (V40, V92)**	**Wk 152 +360 ±5 days (V41, V93)**	**Wk 156 + 364[A] ±5 days (V42, V94)**							
Year 4			**Wk 160 ±5 days (V43)**	**Wk 164 ±5 days (V44)**	**Wk 168 ±5 days (V45)**	**Wk 172[A] ±5 days (V46)**	**Wk 176 ±5 days (V47)**	**Wk 180 ±5 days (V48)**	**Wk 184 ±5 days (V49)**	**Wk 188 ±5 days (V50)**	**Wk 192 ±5 days (V51)**	**Wk 196[A] ±5 days (V52)**	**Wk 200 ±5 days (V53)**	**Wk 204 ±5 days (V54)**	**Wk 208 ±5 days (V55)**					
Year 5				**Wk 212 ±5 days (V56)**	**Wk 216 ±5 days (V57)**	**Wk 220[A] ±5 days (V58)**	**Wk 224 ±5 days (V59)**	**Wk 228 ±5 days (V60)**	**Wk 232 ±5 days (V61)**	**Wk 236 ±5 days (V62)**	**Wk 240 ±5 days (V63)**	**Wk 244[A] ±5 days (64)**	**Wk 248 ±5 days (V65)**	**Wk 252 ±5 days (V66)**	**Wk 256 ±5 days (V67)**	**Wk 260 ±5 days (V68) [N]**				
eGFR[G]		X		X		X		X		X		X		X		X	X	X	X	X
UACR[H]				X						X						X	X	X	X	X
IL-6 levels (total and free)				X						X						X	X	X		X
MPA levels[I]	As clinically indicated as per investigator discretion.																X			X
CNI levels[J]		X		X		X		X		X		X		X		X	X			X
Adverse event / concomitant medication monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Procedures	**Clazakizumab Q4W SC Injection (Until Discontinuation of IP, Withdrawal from Study, Allograft Loss, Death, or Common Treatment End Date, whichever occurs first)[A]**																		
Year 2 & Year 6	**Wk 56, 264 ±5 days (V17, V69)**	**Wk 60, 268[A] ±5 days (V18, V70)**	**Wk 64 +272 ±5 days (V19, V71)**	**Wk 68 + 276 ±5 days (V20, V72)**	**Wk 72[A] + 280 ±5 days (V21, V73)**	**Wk 76[A] + 284 ±5 days (V22, V74)**	**Wk 80 + 288 ±5 days (V23, V75)**	**Wk 84 + 292[A] ±5 days (V24, V76)**	**Wk 88 + 296 ±5 days (V25, V77)**	**Wk 92 + 300, ±5 days (V26, V78)**	**Wk 96 + 304 ±5 days (V27, V79)**	**Wk 100[A] + 308 ±5 days (V28, V80)**	**Wk 104 + 312 ±5 days (V29, V81)**				**EOT / Early With-drawal Visit [A,B]**	**SF Visits [B]**	**Q6M after DC[B]**	**CTED Visit[B]**
Year 3 & Year 7		**Wk 108, 316[A] ±5 days (V30, V82)**	**Wk 112 + 320 ±5 days (V31, V83)**	**Wk 116 + 324 ±5 days (V32, V84)**	**Wk 120 + 328 ±5 days (V33, V85)**	**Wk 124[A]+ 332 ±5 days (V34, V86)**	**Wk 128 + 336 ±5 days (V35, V87)**	**Wk 132 + 340[A] ±5 days (V36, V88)**	**Wk 136 + 344 ±5 days (V37, V89)**	**Wk 140 + 348 ±5 days (V38, V90)**	**Wk 144 + 352 ±5 days (V39, V91)**	**Wk 148[A] + 356 ±5 days (V40, V92)**	**Wk 152 +360 ±5 days (V41, V93)**	**Wk 156 + 364[A] ±5 days (V42, V94)**						
Year 4			**Wk 160 ±5 days (V43)**	**Wk 164 ±5 days (V44)**	**Wk 168 ±5 days (V45)**	**Wk 172[A] ±5 days (V46)**	**Wk 176 ±5 days (V47)**	**Wk 180 ±5 days (V48)**	**Wk 184 ±5 days (V49)**	**Wk 188 ±5 days (V50)**	**Wk 192 ±5 days (V51)**	**Wk 196[A] ±5 days (V52)**	**Wk 200 ±5 days (V53)**	**Wk 204 ±5 days (V54)**	**Wk 208 ±5 days (V55)**					
Year 5				**Wk 212 ±5 days (V56)**	**Wk 216 ±5 days (V57)**	**Wk 220[A] ±5 days (V58)**	**Wk 224 ±5 days (V59)**	**Wk 228 ±5 days (V60)**	**Wk 232 ±5 days (V61)**	**Wk 236 ±5 days (V62)**	**Wk 240 ±5 days (V63)**	**Wk 244[A] ±5 days (64)**	**Wk 248 ±5 days (V65)**	**Wk 252 ±5 days (V66)**	**Wk 256 ±5 days (V67)**	**Wk 260 ±5 days (V68) [N]**				
Clazakizumab drug levels and anti-clazakizumab antibodies[K]				X						X						X	X	X		X
Prophylactic antibiotic[L]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
EQ-5D-5L, KDQoL-36, and FACIT Fatigue Scale [M]							Wk 80 only (V23)						Wk 104 (V29) + Wk 312 (V81)	Wk 156 (V42) + Wk 364 (V94)	Wk 208 (V55)	X	X		X	X

AE = adverse event; BKV = polyoma BK virus; CBC = complete blood cell count; CMV = cytomegalovirus; CNI= calcineurin inhibitor;CTED = common treatment end date; CTEV = common treatment end visit; DNA = deoxyribonucleic acid; DSA = donor-specific antibodies; EBV = Epstein-Barr virus; ECG = electrocardiogram; eCOA = electronic clinical outcomes assessment; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOT = End of Treatment; EQ-5D-5L = EuroQol-5 Dimensions – 5 Levels; FACIT Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; hsCRP = high-sensitivity C-reactive protein; HRQoL = health-related quality of life; IgG = Immunoglobulin G; IL6 = Interleukin 6; IP = investigational product; KDQoL36 = Kidney Disease Quality of Life Questionnaire 36; MDRD4=Modification of Diet in Renal Disease 4; MFI = Mean fluorescence intensity; MMF = Mycophenolate mofetilt; MPA = mycophenolate / mycophenolic acid; PCR = polymerase chain reaction; PJP = pneumocystis jiroveci pneumonia; Q4W = once every 4 weeks; Q6M = every 6 months; Q12M = every 12 months; SAE = serious adverse event; SF= safety follow-up; SFV = safety follow-up visit; SOE = schedule of events; UACR = urine albumin creatinine ratio; V = visit; Wk = Week; WOCBP = women of childbearing potential.

Notes: During the Treatment Period, blood and urine samples should be collected prior to dosing at the clinic visit. Unscheduled visits may be performed during the course of the study for safety reasons.

A. At some sites, home / workplace visits may be offered as an option instead of in-clinic visits for certain visits during the Treatment Period. This service may not be available for all subjects at all sites. In Year 2 to SFV, in-clinic visits are required approximately every 6 months (ie, at Visit 22 [Wk 76], Visit 28 [Week 100], Visit 34 [Week 124], Visit 40 [Week 148], Visit 46 [Week 172], Visit 52 [Week 196], Visit 58 [Week 220], Visit 64 [Week 244], Visit 70 [Week 268], Visit 76 [Week 292], Visit 82 [Week 316], Visit 88 [Week 340], and Visit 94 (Week 364]). An in-clinic visit is required at EOT / Early Withdrawal; if a subject meets the primary efficacy endpoint (composite all-cause allograft loss or irreversible loss of allograft function); and, at the discretion of the Investigator, if clinically indicated (eg, because of an AE). Other scheduled visits can be home / workplace visits.
B. All early withdrawal subjects and subjects who permanently discontinued IP treatment due to loss of their allograft, will undergo all assessments per the EOT / Early Withdrawal Visit schedule. Subjects who permanently discontinued treatment with IP for any reason and who have not reached an endpoint of allograft loss, defined as an eGFR < 15 mL/min/1.73 m^{2*}, return to dialysis*, allograft nephrectomy, retransplantation, or death from any cause or subjects with a sustained (≥ 60 days) 40% decline in eGFR from Baseline who discontinue IP for any reason, will not be withdrawn; they will remain in the study as described in Section 9.2.5.3. *total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days. Following the EOT / Early Withdrawal Visit, subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. (Note: DSA MFI Scores, UACR, and IL-6 levels are not required at the 3-month Safety Follow-up Visit). In addition, all subjects will be contacted by telephone call (TC) 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data. If a subject is unable to return for 6-monthly follow-up visits, he / she will be asked to agree to be contacted at CTED to collect allograft and survival status. The CTEV will be performed within 4 weeks after the CTED is reached.
C. Throughout the Treatment Period, subjects will return to the clinic Q4W for treatment with IP until the subject discontinues IP, withdraws from the study, experiences allograft loss, dies, or the reached CTED, whichever occurs first. Note: as detailed in Footnote A, home / workplace visits may be offered as an option instead of in-clinic visits for certain visits during the treatment phase (at some sites only).
D. Height will be included at Visit 1 only.
E. Urinary pregnancy test prior to every dose of IP. For subjects who permanently discontinued investigational treatment with clazakizumab / placebo, this assessment will be conducted monthly for an additional 5 months following the last dose of IP. Positive urine tests will be confirmed by a serum pregnancy test that is analyzed at the central laboratory.
F. Fasting for a minimum of 10 hours is required for the determination of fasting glucose and for lipids / triglycerides. If the subject failed to fast, samples should still be collected and processed with failure to fast recorded on the laboratory requisition and also recorded as a protocol deviation. See Table 8 for details regarding the required assessments.
G. The MDRD4 equation will be used for determination of eGFR. Baseline eGFR is defined as an average of 2 pre-treatment measurements up to 8 weeks apart. If the eGFR < 15 mL/min/1.73 m^2 is the only component reached, the value must be sustained over at least 60 days and must be confirmed by a repeat measurement after ≥60 days from the date of the first measurement. The confirmatory measurement of eGFR < 15 mL/min/1.73 m^2 done at least 60 days from the initial measurement must be processed by the central laboratory.
H. UACR determined using spot urine test.
I As clinically indicated per investigator discretion; only for subjects taking concomitant MMF / MPA. At relevant visits, treatment with MMF / MPA is to be withheld until after collection of the blood sample for determination of MPA levels.
J. Required only for subjects taking a concomitant CNI. CNI trough levels will be monitored at Year 1: Visits 2 (Baseline) through 6, 8, 10, 12, 14, and 16; Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit. CNIs will also be monitored every 2 weeks following a change in CNI dose, withholding, discontinuation, or restarting of IP, until target CNI trough levels are achieved. With prior alignment and permission from CSLB, CNI monitoring may be conducted locally during Year 1. If monitored locally during Year 1, CNI monitoring should be conducted at the same laboratory throughout the study, ie beginning from and including the Baseline CNI level. Also, if CNI monitoring is conducted locally in Year 1, a sample should be drawn and submitted to the central laboratory each time CNI levels are assessed as per the schedule described in the SOE. After Year 1, CNI levels may be checked per local practice through local laboratories, including being a part of evaluating any significant changes in creatinine. Locally drawn CNI levels may qualify for monitoring if drawn within the specified interval of ± 2 weeks. At relevant visits, CNIs are to be withheld until after collection of the blood sample for determination of CNI trough levels.
K. Not required if the subject has been permanently discontinued from treatment with IP. For subjects that go on to receive IVIG, additional PK samples will be collected (see Table 9).

L. PJP prophylaxis should be continued at the discretion of the Investigator.
M. EQ-5D-5L, KDQoL-36, and FACIT Fatigue questionnaires will be completed by subjects using an eCoA solution whether at the study site or during a home visit. Subjects who are randomized before the availability of the eCOA solution will not complete HRQoL questionnaires.
N. For those subjects who complete the SOE (through Year 5) and remain on study, the SOE schedule for Year 2 through 5 will repeat ie, Year 6 follows the Year 2 SOE, Year 7 follows the Year 3 SOE, etc. The first visit in Year 6 is Visit 69 (Week 264).

Table 3 Pharmacokinetic / Pharmacodynamic Substudy Schedule of Sample Collection[A,B]

Activity	Analyte	Sampling Timepoint	Timepoint Window
Week 1 (Day 8)			
Blood Draw	hsCRP, IL-6, Clazakizumab	168 hours	± 24 hours
Week 4 / Visit 4 (± 1 day)			
Blood Draw	hsCRP[C], IL-6, Clazakizumab	Predose	-30 minutes
SC Administration of Clazakizumab		0 minutes	NA
Week 24 / Visit 9 (± 5 days)			
Blood Draw	hsCRP	Predose	-30 minutes
SC Administration of Clazakizumab		0 minutes	NA
Blood Draw	hsCRP, IL-6, Clazakizumab	72 hours (3 days) after dosing	± 12 hours
Blood Draw	hsCRP, IL-6, Clazakizumab	120 hours (5 days) after dosing	± 12 hours
Week 25			
Blood Draw	hsCRP, IL-6, Clazakizumab	168 hours (7 days) after dosing	± 24 hours
Week 26			
Blood Draw	hsCRP, IL-6, Clazakizumab	336 hours (14 days) after dosing	± 2 days
Week 27			
Blood Draw	hsCRP, IL-6, Clazakizumab	504 hours (21 days) after dosing	± 2 days

hsCRP = High-sensitivity C-reactive protein; IL-6 = Interleukin 6; SC = subcutaneous.

A. Participation in the PK / PD Substudy is optional. Subjects participating in the PK / PD Substudy will have these blood samples drawn, in addition to the blood samples drawn in the main study. Refer to the Laboratory Manual for additional details on the PK / PD Substudy.

B. Not required if a subject has been permanently discontinued from treatment with IP.

C. hsCRP is included in the safety laboratory tests in Week 4 as described in Table 1.

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List of Abbreviations

Abbreviation	Term
ABMR	Antibody-mediated rejection
ACEI	Angiotensin-converting enzyme inhibitor
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
AZA	Azathioprine
BKV	Polyoma BK virus
C4d	Complement component 4d
CABMR	Chronic active antibody-mediated rejection
CBC	Complete blood count
CFR	Code of Federal Regulations
CTFG	Clinical Trial Facilitation Group
cg	Chronic glomerulopathy
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CRP	C-reactive protein
CSLB	CSL Behring
CTCAE	Common Toxicity Criteria for Adverse Events
CTED	Common treatment end date
CTEV	Common treatment end visit
CYP	Cytochrome P450
DMARD	Disease-modifying antirheumatic drug
DSA	Donor-specific antibodies
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus

EC	Ethics Committee
ECG	Electrocardiogram
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of Treatment
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
FACIT Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GVHD	Graft-versus-host disease
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
hsCRP	High-sensitivity C-reactive protein
IA #1	Interim analysis #1
IA #2	Interim analysis #2
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IIT	Investigator-initiated trial
IL-6	Interleukin 6
IL-6R	Interleukin 6 receptor
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intention-to-treat
IU	International units

IV	Intravenous
IVIG	Intravenous immunoglobulin
KDIGO	Kidney Disease: Improving Global Outcomes
KDQoL-36	Kidney Disease Quality of Life Questionnaire – 36
LC-MS / MS	Liquid chromatography-tandem mass spectrometry
LFT	Liver function test
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MDRD4	Modification of Diet in Renal Disease 4
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean fluorescence intensity
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
mRNA	Messenger ribonucleic acid
mTOR	Mechanistic target of rapamycin
MTX	Methotrexate
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PJP	Pneumocystis jiroveci pneumonia
PK	Pharmacokinetic
PLEX	Plasma exchange
PP	Per-protocol
PsA	Psoriatic arthritis
PT	Preferred Term
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
QIU	Qualified Investigator Undertaking
QW	Once a week
RA	Rheumatoid arthritis
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SFV	Safety Follow-up Visit
SOC	System Organ Class
SOE	Schedule of Events

STAT3	Signal transducer and activator of transcription 3
$t_{1/2}$	Terminal or elimination half-life
TB	Tuberculosis
TC	Telephone call
TCMR	T cell-mediated rejection
TCZ	Tocilizumab
TEAE	Treatment-emergent adverse event
TG	Transplant glomerulopathy
Th	T helper (cell)
Treg	Regulatory T (cell)
UACR	Urine albumin creatinine ratio
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

1. Introduction and Background

1.1 IL-6 and Antibody-mediated Rejection in Kidney Transplant Recipients

A detailed discussion of the role of interleukin 6 (IL-6) in the pathogenesis of antibody-mediated rejection (ABMR) and preliminary evidence that blocking the activity of this cytokine may benefit patients with active antibody-mediated rejection (ABMR) is provided in Appendix 3. The clinical setting and unmet medical need are also discussed.

IL-6 is a pleiotropic cytokine that regulates the immune response, inflammation, hematopoiesis, and bone metabolism [Keller et al, 1996]. IL-6 also has a range of effects on the adaptive immune response. It stimulates B cell differentiation and secretion of antibodies and prevents apoptosis of activated B cells [Hirano et al, 1985; Muraguchi et al, 1988; Kawano et al, 1995]. IL-6 also activates and induces proliferation of T cells and, in the presence of interleukin 2, induces differentiation of mature and immature T cells into cytotoxic T cells [Lotz et al, 1988; Okada et al, 1988].

IL-6 appears to be a critical cytokine involved in the humoral rejection of kidney allografts (ie, ABMR). IL-6 promotes the development and maturation of B cells to plasma cells that produce donor-specific antibodies (DSA) targeting the allograft. These donor-specific antibodies (DSA) damage the allograft via complement and non-complement mediated pathways and induce graft endothelial cells to produce inflammatory (eg, p-selectin, vascular cell adhesion molecule [VCAM-1]) and pro-thrombotic (eg, von Willebrand factor) molecules [Gaston et al, 2010; Thomas et al, 2015; Jordan et al, 2017]. Furthermore, IL-6 shapes the T cell immune response resulting in promotion of long-lived pro-inflammatory T helper (Th) cells (eg, follicular Th cells, Th17, Th1, and Th2 cells) and inhibition of immune regulatory T (Treg) cells that promote allograft tolerance.

Active ABMR, especially chronic active antibody-mediated rejection (CABMR), is now recognized as the most common cause of allograft failure after a successful kidney transplant. Active ABMR and CABMR are part of a continuum of injury which, left untreated, results in the loss of the transplanted allograft. The continuum of injury produced by active ABMR is triggered by inflammation following interaction between complement-activating recipient DSA and donor human leukocyte antigen (HLA) expressed on the surface of the transplant vascular endothelium. Active ABMR is the pathological expression of a repetitive pattern of cellular injury and repair. Regardless of how the process is initiated, this ongoing injury eventually manifests as CABMR with its hallmark chronic tissue injury pathology (ie,

transplant glomerulopathy [TG]) and loss of functional renal mass that leads to a decline in renal function.

In kidney transplant recipients with CABMR, a progressive decline in renal function is, by definition, on the pathway to graft loss. Numerous studies in kidney transplant recipients, and specifically in post-transplant patients with ABMR, have shown that progressive renal function decline (as measured by estimated glomerular filtration rate [eGFR]) is significantly correlated with graft loss and patient survival [Hariharan et al, 2002; Kasiske et al, 2011; Wiebe et al, 2012; Eskandary et al, 2014; Wiebe et al, 2015; Clayton et al, 2016]. Indeed, measures of renal function (eg, serum creatinine or eGFR) are commonly used in clinical practice to make decisions on the need and timing of re-initiating dialysis in kidney transplant recipients with imminent graft loss.

Although effective treatment of acute cellular rejections has led to high short-term survival of kidney allografts (ie, > 95% in the first year post-transplant), long-term graft survival has not improved. Death-censored graft failure rates beyond the first year have remained relatively unchanged since the late 1980s, and by 10 years, 20% to 30% of all kidney allografts will have failed [Stegall et al, 2014]. Current standard of care antirejection treatments target cellular-mediated (ie, T cell-mediated rejection [TCMR]) processes and do not affect this antibody-mediated process.

Currently, there are no approved or effective treatments for active ABMR, including CABMR. The Kidney Disease: Improving Global Outcomes (KDIGO) 2009 guideline [Kidney Disease: Improving Global Outcomes, 2009] recognizes the lack of good quality data and suggests the use of one or more of the following alternatives, with or without corticosteroids, to treat acute humoral rejections due to DSA: PLEX; intravenous immunoglobulin (IVIG); anti-CD20 antibody; and lymphocyte-depleting antibody. Recent systematic reviews of treatments for ABMR have shown that the situation remains unchanged, even with novel agents targeting B cells, plasma cells and the complement system [Roberts et al, 2012; Wan et al, 2018]. In the RITUX ERAH study, there was not early or late (up to 5 years) benefit with rituximab (an anti-CD20 monoclonal antibody [mAb]) administered with IVIG, PLEX and corticosteroids in kidney transplant recipients with early acute ABMR [Sautenet et al, 2016; Bailly et al, 2017]. More specifically, no evidence of efficacy was seen in studies in CABMR with eculizumab (a complement inhibitor), bortezomib (a proteasome inhibitor), IVIG, rituximab and PLEX [Kulkarni et al, 2017; Piñeiro et al, 2017; Eskandary et al, 2018; Moreso et al, 2018].

Blocking the activity of IL-6 in kidney transplant recipients with ABMR has been investigated in a number of small uncontrolled clinical trials with promising results. In a study in 36 HLA-sensitized kidney transplant recipients with CABMR and TG who had failed treatment with IVIG plus rituximab with / without PLEX, Choi et al. showed that treatment with tocilizumab (TCZ) 8 mg/kg intravenous (IV) administered monthly, was able to significantly reduce immunodominant DSA levels and stabilize long-term renal function (eGFR) in these patients [Choi et al, 2017a]. Improvements in microvascular inflammation and complement component 4d (C4d) staining scores were also seen in the allograft biopsies. Promising graft survival (80%) and patient survival (91%) rates were observed over 6 years. Extended experience with a larger cohort of 65 kidney transplant recipients with CABMR and TG, treated monthly with TCZ 4 to 8 mg/kg, demonstrated similar promising results [Choi et al, 2017b]. Puliyanda et al. showed that the administration of TCZ 4 to 8 mg/kg monthly for 4 to 12 doses in 6 pediatric kidney transplant recipients with severe CABMR refractory to B cell immunotherapy was able to stabilize the progression of ABMR, resulting in no graft loss and no decline in renal function [Puliyanda et al, 2017]. In a small cohort of highly sensitized kidney transplant recipients with acute ABMR, Venkatachalam et al. showed that the addition of TCZ 8 mg/kg IV monthly for 3 to 6 months appeared to be effective, resulting in improved renal function and reduced DSAs [Venkatachalam et al, 2017]. In a small randomized controlled study in kidney transplant recipients with biopsy evidence of subclinical inflammation within Year 1 of their transplant, Chandran et al. showed that treatment with TCZ 8 mg/kg IV monthly for 6 months was well tolerated and was associated with a significant increase in circulating Treg cells, a significant decrease in $CD4^+$ T cell cytokine (interleukin 17) production, and a trend towards decreased graft inflammation [Chandran et al, 2017]. In a group of kidney transplant recipients with CABMR refractory to other treatments, Patel et al. showed that the addition of TCZ 8 mg/kg IV monthly to a regimen of tacrolimus, mycophenolate and prednisone stabilized eGFR, despite persistent DSA and with few infectious complications [Patel et al, 2017]. Finally, in a study by Vo et al., mean wait time to renal transplant in highly HLA-sensitized patients (resistant to desensitization standard of care [ie, IVIG + rituximab +/- PLEX]) was shortened following treatment with TCZ (+ IVIG) 8 mg/kg IV administered on Day 15, then monthly for 6 months [Vo et al, 2015]. Significant reductions in immunodominant DSAs were seen in all transplanted patients with no biopsy evidence of ABMR at 6 months. In all these trials, the safety profile of TCZ was acceptable.

In summary, the current treatments commonly being used for the treatment of CABMR are not evidenced-based. Considering the cost and potential for serious toxicity with the current treatments, this highlights the need for well-designed randomized controlled studies to

investigate the safety and efficacy of any new drugs for the treatment of CABMR – a serious and rare condition with an unmet clinical need. Promising signals of efficacy have been seen with an anti-IL-6 approach.

1.2 Clazakizumab – Properties and Mechanism of Action

Clazakizumab is a genetically engineered humanized immunoglobulin G1 (IgG1) mAb that binds to human IL-6. Using multiple assays for signaling and cellular functions in response to IL-6 alone (to measure classical signaling) and a combination of IL-6 and soluble IL-6 receptor (IL-6R) (to measure trans-signaling), it was demonstrated that clazakizumab is a potent and full antagonist of IL-6-induced signaling as measured by phosphorylation of signal transducer and activator of transcription 3 (STAT3), as well as cellular functions such as cell proliferation, differentiation, activation, B cell production of immunoglobulins, and hepatocyte production of acute phase proteins (C-reactive protein [CRP] and fibrinogen). In addition, clazakizumab is shown to be a competitive antagonist of IL-6-induced cell proliferation. This in vitro pharmacological profile supports the potential of clazakizumab to impact multiple immune and non-immune cellular processes that are central to the pathogenesis of ABMR in kidney transplant recipients.

1.3 Clazakizumab Development Program – Overview

The clazakizumab development program includes a comprehensive nonclinical development program and clinical studies (conducted by previous Sponsors of the drug) in healthy subjects and in subjects with rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn's disease, graft-versus-host disease (GVHD), and oncology. To date, no studies with clazakizumab have been completed in kidney transplant recipients, although supporting safety data are available from the previous clinical studies. Preliminary safety data are also available from 3 Investigator-initiated trials (IITs) in the kidney transplant setting.

1.3.1 Nonclinical Studies

A comprehensive nonclinical development program has been completed (see the CSL300 Investigator's Brochure for details). Clazakizumab was shown to be a potent inhibitor of IL-6-induced acute phase proteins. In pharmacokinetic (PK) / pharmacodynamic (PD) studies, a single dose of clazakizumab resulted in full inhibition of IL-6 activity as measured by the inhibition of IL-6-induced phosphorylated STAT3 activity in whole blood treated ex vivo with IL-6. The results of this functional PD assay correlated with drug exposures where full inhibition of phosphorylated STAT3 activity was observed when drug levels exceeded 50 ng/mL (approximately 0.3 nM). In a tissue cross-reactivity study, tissue binding

of clazakizumab was observed in multiple tissues in both human and cynomolgus monkey, was generally cytoplasmic in nature, and was consistent with the known expression of IL-6 by cells and tissues. Results from both single- and repeat-dose nonclinical toxicology studies of up to 6 months in cynomolgus monkeys demonstrated an acceptable safety profile for clazakizumab. In a preliminary enhanced pre- and post-natal development study conducted in cynomolgus monkeys, an increase in the number of monkeys with retention of the placenta at parturition was observed at clazakizumab doses of 3 mg/kg (n=2) and 30 mg/kg (n=3), corresponding to doses 34 and 340 times the planned human dose of 12.5 mg once every 4 weeks (Q4W) in the current study. There were no other safety findings of clinical concern.

For further details regarding the nonclinical studies with clazakizumab, please consult the CSL300 Investigator's Brochure.

1.3.2 Clinical Studies

Clinical studies have been conducted in healthy subjects and in the following patient populations: RA, PsA, Crohn's disease, GVHD, and oncology. These completed clinical studies include a total of 1223 subjects, of which 1056 subjects were exposed to clazakizumab for up to 175 weeks (including open-label, long-term extension phases) with doses ranging from 1 to 640 mg, given by either IV or subcutaneous (SC) injection. Preliminary safety data from ongoing IITs are discussed in Appendix 4.

Clinical Pharmacology

Following the administration of clazakizumab as a 1-hour IV infusion, the PK of clazakizumab were linear over the dose ranges of 30 to 640 mg in healthy subjects and 80 to 320 mg in subjects with RA, as indicated by consistent clearance at these dose levels. The terminal elimination half-life ($t_{1/2}$) of clazakizumab at all doses was very similar in healthy male subjects and in subjects with RA and was consistent with that expected for a humanized IgG1 antibody. Across the doses studied, the mean $t_{1/2}$ of clazakizumab ranged from 19.5 to 31.0 days in healthy male subjects and from 26.4 to 30.9 days in subjects with RA. The $t_{1/2}$ of clazakizumab after SC administration in healthy male subjects was comparable to the IV administration. In a phase 1 study comparing IV and SC dosing in healthy male subjects, the mean $t_{1/2}$ of clazakizumab was 30.7 days after a single IV dose and 31.1 to 33.6 days after SC administration. The bioavailability of clazakizumab after SC administration was 60% of the IV formulation. As expected, the maximum observed concentration was lower and time to maximum observed concentration was longer for the SC administration relative to IV administration.

Clinical Efficacy and Safety Studies

Efficacy and safety data for clazakizumab are available from clinical studies conducted in healthy subjects, and in subjects with RA, PsA, and oncology. Studies conducted in GVHD and Crohn's disease were prematurely terminated due to safety concerns and therefore no efficacy conclusions are available for these studies.

In phase 2 studies in RA and PsA, doses from 5 mg SC Q4W up to 320 mg IV once every 8 weeks were significantly effective with clinical response evident as early as 2 weeks post-treatment. One study in RA also demonstrated that the efficacy of clazakizumab is comparable or may be better than the standard of care treatment in RA (ie, adalimumab + methotrexate [MTX]).

Efficacy with clazakizumab was not shown in the 2 phase 2 studies in oncology (head and neck cancer and non-small cell lung cancer).

Two studies were terminated prematurely due to safety concerns. A phase 2 study in Crohn's disease was terminated early because of gastrointestinal (GI) perforation in 3 subjects who had received clazakizumab, and this indication is no longer being studied. Although these subjects had multiple confounding medical issues, and the disease itself has an inherent risk of mucosal perforation, GI perforations were also observed during the clinical studies with TCZ in patients with RA. Gastrointestinal perforation is a recognized risk of anti-IL-6 mAbs. After only 3 subjects were enrolled, a study in subjects with GVHD was also prematurely terminated due to 2 subjects experiencing similar serious adverse events (SAEs) (ie, acute renal failure) which led to death. Both subjects had severe GVHD disease at the time of death.

Overall, the safety findings from the completed clinical studies conducted with clazakizumab to date are consistent with the known effects of blocking the IL-6 pathway [Actemra® Prescribing Information (USA), 2017; Actemra® Product Monograph (Canada), 2018; RoActemra® Summary of Product Characteristics (EU), 2018]. Identified risks associated with clazakizumab administration include the following: infections, liver function test (LFT) abnormalities, changes in hematology parameters (ie, neutropenia and thrombocytopenia), dyslipidemia (ie, hypercholesterolemia and hypertriglyceridemia), GI perforations, and injection site reactions (see Section 8.1).

For further details regarding clinical studies with clazakizumab, please consult the CSL300 Investigator's Brochure.

2. Rationale

A detailed discussion of the role of IL-6 in the pathogenesis of ABMR and preliminary evidence that blocking the activity of this cytokine may benefit patients with ABMR is provided in Appendix 3.

This multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3 trial investigates whether clazakizumab (an anti-IL-6 mAb) may be beneficial for the treatment of CABMR in kidney transplant recipients by inhibiting the production of DSA and re-shaping T cell alloimmune responses. Subjects will be administered clazakizumab at a target dose of 12.5 mg (or placebo) by SC injection, Q4W until the subject permanently discontinues IP, withdraws from the study, experiences allograft loss, dies, or reaches the common treatment end date (CTED), whichever occurs first. This "event-driven" trial has been designed to evaluate the benefits of clazakizumab in prolonging the time to composite all-cause allograft loss or irreversible loss of allograft function (primary efficacy endpoint) in subjects with CABMR. A total of 221 composite all-cause allograft loss or irreversible loss of allograft function events (expected to accrue in 316 kidney transplant recipients with CABMR) is estimated to be required to show a relative risk reduction of 31%, which would improve the 4-year graft survival rate from 24.7% to 38.3% (see Section 12.2). An interim efficacy analysis (Interim Analysis #2 [IA #2]) will be conducted to evaluate the benefits of clazakizumab in reducing the slope of decline in eGFR when an initial cohort of approximately 200 subjects have completed at least 52 weeks of study participation. If this interim analysis shows a significant positive effect of clazakizumab on eGFR decline, a submission for expedited regulatory approval will be sought while the study continues to its final allograft loss endpoint. If this interim endpoint does not reach statistical significance, the study will continue as planned until its final allograft loss endpoint is completed.

Relationship Between Change in eGFR and Risk of Allograft Failure

To inform the study design and demonstrate the suitability of the Week 52 eGFR as a surrogate endpoint reasonably likely to predict clinical benefit, a data modeling exercise was conducted to evaluate the functional relationship between rate of eGFR decline following diagnosis of acute / active ABMR or CABMR and risk of allograft failure (death-censored composite all-cause allograft loss), to enable quantification of a clinically meaningful change in eGFR as it relates to a clinically meaningful change in allograft survival. Results of the modeling exercise were also used for sample size estimation (see Section 12.2).

The data modeling exercise was a non-interventional historical, prospective cohort study that evaluated the relationship between change in eGFR (estimated using the Modification of Diet

in Renal Disease 4 [MDRD4] equation) and risk of allograft failure in patients diagnosed with acute / active ABMR or CABMR following kidney transplantation. The primary analysis set of the study used existing data from 91 patients with biopsy-proven active ABMR (according to the Banff 2015 criteria [Loupy et al, 2017]), anti-HLA DSA, Baseline eGFR ≥ 25 mL/min/1.73 m^2 (at time of diagnosis of ABMR), and a minimum of 3 years follow-up data. The primary outcome variable was death-censored allograft failure / loss (defined as the need for permanent dialysis, allograft nephrectomy, retransplantation, or eGFR < 15 mL/min/1.73 m^2) occurring at any time over the course of subject follow-up post-diagnosis of active ABMR. All-cause allograft failure / loss was examined as the key secondary outcome variable (defined as the need for permanent dialysis, allograft nephrectomy, retransplantation, eGFR < 15 mL/min/1.73 m^2, or death from any cause).

Results involving the primary and key secondary outcome variables of death-censored and all-cause- allograft failure, respectively, are summarized in Table 4. As expected, both death-censored and all-cause allograft loss event rates were high (59.3% and 68.1%, respectively) over the 60-month observation period. For both endpoints, most allograft loss events were defined by eGFR falling below 15 mL/min/1.73 m^2 while the remaining subjects met one or more of the other criteria for allograft loss (need for permanent dialysis, allograft nephrectomy, or retransplantation) or death (for all-cause allograft failure). The median time to reach the composite endpoint of death-censored allograft failure and all-cause allograft failure was 46.2 months and 40.7 months, respectively.

Table 4 Summary of Number of Patients Included in Analysis, Allograft Loss Rates and Median Times to Allograft Loss: Primary Analysis Set

Primary Outcome Variables	Category or Statistic	Death-Censored Allograft Loss Primary Endpoint	All-Cause Allograft Loss Key Secondary Endpoint
		Pooled Data (N=91)	Pooled Data (N=91)
Allograft failure / loss composite endpoint	n (%)	54 (59.3%)	62 (68.1%)
Need for permanent dialysis, allograft nephrectomy, or retransplantation	n (%)	18 (19.8%)	18 (19.8%)
eGFR < 15 mL/min/1.73 m^2	n (%)	36 (39.6%)	36 (39.6%)
Death	n (%)	N/A	8 (8.8%)
Time to allograft loss composite endpoint (months)	Median (25^{th}–75^{th})	46.2 (20.6–109.4)	40.7 (18.0–109.4)
Allograft survival post-diagnosis of ABMR[(a)]:			
12 months	Estimate [95% CI]	88.9% [80.4–93.9%]	87.9% [79.2–93.1]
24 months	Estimate [95% CI]	66.0% [55.0–74.8%]	62.6% [51.9–71.7]

Primary Outcome Variables	Category or Statistic	Death-Censored Allograft Loss Primary Endpoint	All-Cause Allograft Loss Key Secondary Endpoint
		Pooled Data (N=91)	Pooled Data (N=91)
36 months	Estimate [95% CI]	58.9% [47.9–68.4%]	53.8% [43.1–63.4]
48 months	Estimate [95% CI]	47.5% [36.5–57.7%]	42.4% [32.1–52.3]
60 months	Estimate [95% CI]	36.4% [25.3–47.6%]	30.7% [20.7–41.3]
Follow-up (months)[b]	Median (25–75th)	61.7 (47.7–91.8)	67.9 (49.1-95.7)

ABMR = antibody-mediated rejection; CI = confidence interval; eGFR = estimated glomerular filtration rate; N / A = not applicable.
Notes:
[a] Kaplan-Meier method.
[b] Reverse Kaplan-Meier method.
Source: Modeling Report, Section 10, Table 4.

To address the objective of the modeling exercise, both a linear mixed effects model to describe eGFR decline and a joint model involving longitudinal eGFR and time-to-event data were constructed. The joint model predicted that the Baseline eGFR and its rate of decline (slope change per month) following active ABMR diagnosis significantly predicts the risk of death-censored allograft failure and all-cause allograft failure, especially in patients with CABMR. As expected, a lower Baseline eGFR and a higher rate of decline of eGFR were significantly associated with a greater risk of allograft loss. Increasing donor age was consistently associated with a lower Baseline eGFR.

Using the modeling results for all-cause allograft loss, the mean eGFR declined from Baseline (ABMR diagnosis) to Month 12 post ABMR diagnosis (timing of IA #2, see Section 12.11) by 19.8% (-0.75 mL/min/1.73 m^2 per month change) and was associated with predicted event-free survival rates of 80.0%, 58.7%, 44.4%, and 23.3% at 2, 3, 4, and 5 years after ABMR diagnosis, respectively.

In this study, a 50% reduction in the rate of eGFR decline with clazakizumab (compared to placebo) is considered a reasonable and realistic assumption considering that treatment with TCZ (an anti-IL-6R mAb) was able to stabilize eGFR decline in kidney transplant recipients with CABMR [Choi et al, 2017a; Choi et al, 2017b; Patel et al, 2017; Puliyanda et al, 2017; Venkatachalam et al, 2017]. Furthermore, conducting the interim efficacy analysis on the 52-week eGFR surrogate endpoint is considered appropriate given the relatively rapid rate of decline in eGFR that would be expected in the placebo-control group, as reflected in the mean rate of eGFR decline seen in the modeling exercise (-0.75 mL/min/1.73 m^2/month). As summarized in Section 12.2, using data from the modeling exercise, sample sizes based on

eGFR data collected for a period of up to 52 weeks after diagnosis of ABMR, and assuming a 50% reduction in the rate of eGFR decline, were estimated for the risk of composite all-cause allograft loss, and "working backwards", for the interim analysis of the surrogate 52-week eGFR endpoint.

In summary, the results of this data modeling exercise support the clinical trial design. The joint modeling of the clinical data meets statistical and clinical expectations: it predicted the Baseline eGFR, and its rate of decline (slope change per month) following active ABMR diagnosis significantly predicted risk of all-cause allograft failure. The exercise provided good evidence that the surrogate 52-week eGFR endpoint to be used in the interim efficacy analysis (IA #2), if positive, is reasonably likely to predict clinical benefit based on the final clinical endpoint of composite all-cause allograft loss.

3. Objectives

3.1 Primary Objectives

1. To evaluate the efficacy of clazakizumab in preventing all-cause allograft loss (including death) or irreversible loss of allograft function due to CABMR.
2. To evaluate the efficacy of clazakizumab in slowing / preventing the progressive loss of kidney function (as measured by eGFR using the MDRD4 equation [IA #2]).
3. To evaluate the safety of clazakizumab.

3.2 Secondary Objectives

1. To evaluate the efficacy of clazakizumab in preventing all-cause allograft loss (including death) due to CABMR.
2. To evaluate the effects of clazakizumab on loss of allograft function (defined as a 40% decline in eGFR from Baseline that is sustained for at least 60 days).
3. To evaluate the effects of clazakizumab on death-censored allograft loss.
4. To evaluate the effects of clazakizumab on albuminuria.
5. To evaluate the effects of clazakizumab on DSA titers and mean fluorescence intensity (MFI) scores.
6. To evaluate the effects of clazakizumab on the histology of kidney biopsies according to the Banff 2015 [Loupy et al, 2017] lesion grading scores.
7. To evaluate the effects of clazakizumab on incidence of acute rejection episodes (TCMR and ABMR).
8. To evaluate the effects of clazakizumab on overall subject survival.
9. To evaluate the PK of clazakizumab following SC injection in kidney transplant recipients with CABMR (for those subjects in the PK / PD Substudy only).
10. To evaluate the immunogenicity of clazakizumab in kidney transplant recipients with CABMR.

3.3 Exploratory Objectives

1. To evaluate the PD of clazakizumab (serum IL-6 (total and free) and / or high-sensitivity C-reactive protein [hsCRP]) following SC injection in kidney transplant recipients with CABMR (for those in the PK / PD Substudy only).

2. To explore the relationship between clazakizumab PK and PD parameters (serum IL-6 [total and free] and / or hsCRP [for those in the PK / PD Substudy only]).

3. To evaluate the effects of clazakizumab on health-related quality of life (HRQoL) associated with the treatment of antibody-mediated rejection to Week 52 as well as to the Safety Follow-up Visit (SFV).

4. To evaluate the efficacy of clazakizumab in slowing / preventing the progressive loss of kidney function up to the EOT (as measured by eGFR using the MDRD4 equation).

4. Investigational Plan

4.1 Overall Study Design

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3 trial in which subjects receive treatment with either 12.5 mg clazakizumab (n = 175) or placebo (n = 175) by SC injection Q4W until the subject permanently discontinues IP, withdraws from the study, experiences allograft loss, dies, or reaches the CTED, whichever occurs first. The CTED is the date when the primary efficacy endpoint (composite all-cause allograft loss or irreversible loss of allograft function) is achieved, ie, the date the target number of primary composite all-cause allograft loss or irreversible loss of allograft function events (221) has been reached. The primary efficacy endpoint of this "event-driven" study is the time to composite all-cause allograft loss or irreversible loss of allograft function, defined as the occurrence of any of the following components:

- eGFR < 15 mL/min/1.73 m^2*
- return to dialysis*
- allograft nephrectomy
- retransplantation
- death from any cause, or
- a sustained (≥ 60 days) 40% decline in eGFR from Baseline.

(*total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days.)

If the eGFR < 15 mL/min/1.73 m^2 is the only component reached, the value must be sustained over at least 60 days and must be confirmed by a repeat measurement after ≥ 60 days from the date of the first measurement. The confirmatory measurement of eGFR < 15 mL/min/1.73 m^2 done at least 60 days from the initial measurement must be processed by the central laboratory.

Subjects who reach the endpoint of sustained 40% decline in eGFR from Baseline (but did not reach any of the non-fatal endpoint components of allograft failure) will continue to receive double-blind medication until they reach any of the other primary endpoints of allograft loss. The subject will remain in the study attending all regular clinic visits and undergoing all assessments per the SOE. IVIG and PLEX may be administered at the discretion of the PI to these subjects if they have completed the Week 52 visit. Double-blind medication and IVIG should be administered 2 weeks apart due to potential binding of IVIG

to clazakizumab. For treatment with IVIG, subjects may be called in for unscheduled visits between regularly scheduled dosing with IP according to the SOE.

The CTED will be communicated to study sites when the target number of primary composite all-cause allograft loss or irreversible loss of allograft function events (221) has been reached to enable study sites to plan their subjects' final visit(s) (CTEV). Further details on procedures for subject follow-up can be found in Section 9.2.5.

An interim efficacy analysis (IA #2), using a surrogate endpoint (change in mean eGFR from Baseline to Week 52) will be conducted to evaluate the benefits of clazakizumab in slowing the decline in eGFR when an initial cohort of approximately 200 subjects (100 per group) have completed at least 52 weeks of study participation. The adequacy of the planned sample size for this analysis will be reevaluated once approximately 100 subjects have been randomized and have completed at least 52 weeks of study participation (Interim Analysis #1 [IA #1]). If the interim analysis of the 52-week eGFR surrogate endpoint shows a statistically significant ($p \leq 0.05$) positive effect of clazakizumab on eGFR decline, CSL Behring (CSLB) will seek expedited approval, where applicable. In the meantime, the trial will continue as planned until its final composite allograft loss endpoint is completed. The composite allograft loss endpoint data will be used to convert the expedited approval to regular approval. An overview of the study design is depicted in the Study Schema. A Schedule of Events (SOE) is provided in Table 1 (Year 1) and Table 2 (Year 2 to SFV / CTEV). An overall summary table of all scheduled study visits is provided in Appendix 2.

A Screening Visit (Visit 1) will be conducted up to 42 days before Day 1 (Baseline, Visit 2). Subjects who satisfy the inclusion and exclusion criteria will be randomized using an Interactive Response Technology (IRT) to treatment with either clazakizumab or placebo until the subject permanently discontinues IP, withdraws from the study, experiences allograft loss, dies, or reaches the CTED, whichever occurs first. Baseline assessments will be performed before the first dose of IP at Visit 2. Subjects will return Q4W for administration of IP. Safety monitoring, including eGFR, concomitant medication monitoring, and pregnancy testing (for women of childbearing potential [WOCBP]), will be conducted at dosing visits. eGFR will be assessed every other visit. Additional assessments of efficacy and safety will occur at Week 1, Q4W between Week 4 and Week 12, every 8 to 12 weeks up to Week 52, and then every 8 to 24 weeks until the EOT as detailed in Table 1 and Table 2.

Prior to dosing at each visit, the most recent LFT and complete blood count (CBC) analyses and viral monitoring results (for polyoma BK virus [BKV], cytomegalovirus [CMV], and Epstein-Barr virus [EBV]) from a prior visit (scheduled or otherwise) will be reviewed for

safety considerations. At a minimum, these safety assessments will be performed per the SOE in Table 1 and Table 2. Based on the results of these safety assessments, the dose of IP may be reduced to 6.25 mg SC Q4W, temporarily withheld, or permanently discontinued as detailed in Section 7.5. A modification of the dose of background immunosuppression may also be recommended.

All subjects, completed (ie, subjects who met any of the composite non-fatal all-cause allograft loss endpoints), or discontinued treatment with the intent to withdraw will complete an in-clinic visit for EOT assessments at the time of completion as described in the SOE. After the EOT Visit, subjects will be monitored for safety with monthly follow-up TCs for 5 months after their last dose of IP if not withdrawn. During the 5-month safety follow-up period, subjects may be called in for a clinic visit at the discretion of the Investigator. An in-clinic SFV is to be completed after the last of the 5-month TCs. Further details on SFV procedures for subjects who have completed or withdrew from the study can be found in Section 9.2.5.2 and 9.2.5.4, respectively.

Subjects who permanently discontinued treatment with IP for any reason and who have not reached an endpoint of allograft loss or death, will continue in the study as described in Section 9.2.5.3. Following the in-clinic EOT / Early Withdrawal Visit within 4 weeks of receiving the last dose of IP, all subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. In addition, all subjects will be contacted by telephone call 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data. If a subject is unable to return for 6-monthly follow-up visits, he / she will be asked to agree to be contacted at CTED to collect allograft and survival status.

Depending on the timing of early treatment discontinuation, this follow-up may consist of assessments conducted at regularly scheduled visits per-protocol and / or monthly follow-up TCs as needed and the in-clinic SFV to complete 5 months of safety monitoring following their last dose of IP. Subjects who permanently discontinued treatment with IP ≥ 5 months before their EOT Visit (and complete the remainder of the study visits) will not require any follow-up TCs. Further details on SFV procedures for subjects who permanently discontinued IP can be found in Section 9.2.5.3.

Subjects who are receiving IP treatment at the time the target number or primary composite all-cause allograft loss or irreversible loss of allograft function events (221) has been reached

(ie, the CTED) will return for a CTEV. Further details on CTEV procedures for subjects receiving IP at the time the CTED is reached can be found in Section 9.2.5.5.

4.1.1 PK / PD Substudy

A subset of 44 subjects (out of the 350 enrolled in the main study) will have the option to participate in a PK / PD Substudy. The purpose of the PK / PD Substudy is to characterize the PK profile of clazakizumab in CABMR subjects and explore the relationship between clazakizumab concentration with IL-6 or hsCRP. Subjects enrolled in the PK / PD Substudy will provide consent for additional blood samples for the purpose of PK / PD analyses.

4.2 Dose Selection

A full discussion for the dose selection rationale is provided in Appendix 4.

CSLB has selected 12.5 mg SC injection Q4W as the target dose to be investigated in this pivotal trial. However, if required to manage any AEs that may be related to IP, the dose may be reduced to 6.25 mg SC Q4W. This dosing regimen is based on a rational dose justification considering the results of the clazakizumab nonclinical program and the safety and efficacy data from completed clinical trials where repeat dosing was studied, as well as comparison with the reported experience with TCZ (an anti-IL-6R mAb approved for use in RA and other indications) used in studies for the treatment of patients with ABMR and highly HLA-sensitized patients awaiting kidney transplant. Preliminary safety data from 1 completed and 2 ongoing IITs in the kidney transplant setting were also considered.

An extensive nonclinical program has been completed with clazakizumab. Further details of the nonclinical toxicology and safety pharmacology studies are provided in the CSL300 Investigator's Brochure. Results from both single- and repeat-dose SC (up to 4 weeks once a week [QW]) or 6 months once every 2 weeks (Q2W) or IV (up to 3 months QW) toxicology studies of clazakizumab in cynomolgus monkeys have demonstrated an acceptable safety profile, supporting its planned clinical use at 12.5 mg SC injection, Q4W. Results from an enhanced pre- and post-natal development study conducted in cynomolgus monkeys (DN13073) showed an increase in the number of monkeys with retention of the placenta at parturition at clazakizumab doses of 3 mg/kg Q2W (n = 2) and 30 mg/kg Q2W (n = 3), corresponding to doses 34 and 340 times a human dose of 12.5 mg Q4W (based on a 70 kg adult). These doses are expected to generate exposures approximately 48 and 480 times higher, respectively, than a human dose of 12.5 mg SC injection, Q4W. Regular pregnancy testing will be undertaken in WOCBP prior to every dose during the trial, and if positive, the

subject will discontinue treatment with IP and continue in the trial per-protocol (see Section 10.3.3).

The completed clinical trials with clazakizumab provide an extensive safety database and drug exposure experience to define its safety profile, which is primarily associated with its IL-6 blocking effects. The AEs observed with clazakizumab have been described with other mAbs that block IL-6 signaling, such as TCZ and sarilumab. Clazakizumab has been studied in clinical trials in multiple subject populations including healthy subjects, patients with RA, PsA, advanced cancer, GVHD, and Crohn's disease. These trials include 1056 subjects who received at least a single dose of clazakizumab with doses ranging from 1 mg to 640 mg, given by either IV or SC injection for up to 175 weeks (including long-term extension phases), corresponding to a maximum duration of exposure of 196 weeks. A detailed description of these trials is given in the CSL300 Investigator's Brochure.

In addition, preliminary safety data from 1 completed and 2 ongoing IITs in the kidney transplant setting are provided in the CSL300 Investigator's Brochure.

Selection of the proposed clazakizumab doses also takes into consideration the comparability of doses of clazakizumab and TCZ used in RA. Levels of CRP suppression seen with clazakizumab 5 mg and 25 mg SC injection Q4W are comparable to levels seen with TCZ 8 mg/kg IV injection Q4W [Tocilizumab Arthritis Advisory Report, 2008]. Doses of clazakizumab 5 mg and 25 mg SC injection Q4W showed comparable efficacy to TCZ (4 mg/kg and 8 mg/kg IV injection Q4W) with respect to the American College of Rheumatology response rates and the Disease Activity Scores 28 (DAS-28) based on CRP [Tocilizumab Arthritis Advisory Report, 2008]. The comparability of the clazakizumab 5 mg and 25 mg SC doses to TCZ 4 mg/kg and 8 mg/kg IV doses, is consistent with the 3 to 120 times higher potency of clazakizumab versus TCZ demonstrated in in vitro IL-6 signaling assays [Zhao et al, 2013].

As summarized in Section 1.1, TCZ has also been used in several small, uncontrolled clinical trials for the treatment of kidney transplant recipients with ABMR [Chandran et al, 2017; Choi et al, 2017a; Choi et al, 2017b; Patel et al, 2017; Puliyanda et al, 2017; Venkatachalam et al, 2017] and in highly HLA-sensitized patients awaiting kidney transplant [Vo et al, 2015]. These trials mainly used the approved TCZ dose of 8 mg/kg IV monthly. Promising signals of efficacy with acceptable safety were seen in these trials.

In conclusion, the proposed clazakizumab dose regimen balances the need to ensure subject safety and the potential for demonstrating a meaningful positive clinical response.

Nonclinical and clinical studies have shown clazakizumab to be a potent and full antagonist of IL-6 with similar pharmacological properties and clinical effects to TCZ. The target dose of clazakizumab 12.5 mg SC Q4W is comparable to the dose of TCZ that has been used in clinical trials in kidney transplant recipients with ABMR and in highly HLA-sensitized patients awaiting kidney transplant. Given that a dose of clazakizumab as low as 5 mg SC Q4W showed comparable CRP suppression and clinical efficacy to TCZ 8 mg IV Q4W and considering the AEs / SAEs reported in the ongoing IITs with the higher clazakizumab dose (25 mg SC Q4W), 12.5 mg SC Q4W was chosen as the target dose for Study VKTX01. A higher rate of reported SAEs with TCZ 8 mg/kg (versus 4 mg/kg) IV Q4W was also considered [Actemra® Product Monograph (Canada), 2018]. The protocol has been designed to exclude subjects with known and potential risk factors to anti-IL-6 blockade and will include safety monitoring procedures during the trial to minimize these risks.

4.3 Duration of Subject Participation and Study

The average study duration for an individual subject will be approximately 5.5 years. This includes a Screening Period of up to 42 days, a Treatment Period from Day 1 until the subject permanently discontinues IP, withdraws from the study, experiences allograft loss, dies, or reaches the CTED, whichever occurs first (approximately 260 weeks on average), and a Follow-up period of 5 months after the last dose of IP (completion or early termination). The CTED will be communicated to study sites when the target number of primary composite all-cause allograft loss or irreversible loss of allograft function events (221) has been reached to enable study sites to plan their subjects'final visit (CTEV).

4.4 Access to Study Product After the End of Study

After completion of the study, clazakizumab will, at the discretion of the treating physician, be offered to subjects as agreed upon in their respective country and provided via country-specific access program(s). Subjects who withdraw from the study and / or permanently discontinued treatment before the CTED are not eligible.

5. Selection and Withdrawal of Subjects

5.1 Number of Subjects

Approximately 350 subjects will be randomized 1:1 into 2 treatment arms using a stratified block randomization scheme: 175 subjects in the clazakizumab group and 175 subjects in the placebo group. Subjects will be enrolled at approximately 155 study sites worldwide.

5.2 Inclusion Criteria

Unless specified otherwise, all inclusion criteria time intervals are assessed with respect to the Screening Visit. In order to be eligible to participate in the trial, a subject must meet all of the following inclusion criteria:

1.A8 Age 18 to 75 years.

2. Living donor / deceased donor kidney transplant recipients ≥ 6 months from time of transplant.

3.A9 Diagnosis of CABMR determined by kidney biopsy and the presence of HLA DSA using single-antigen bead-based assays. For eligibility, kidney biopsy must not be older than 12 months and DSA analysis must be performed no longer than 6 months prior to the start of Screening.

NOTE:

- Within 3 months prior to the start of Screening, treatments for ABMR or TCMR, with the exception of steroids*, are not allowed (see Exclusion Criterion 3).

- If treatment for ABMR (including CABMR) or TCMR (other than steroids*) was given between 3 to 12 months of Screening, a repeat kidney biopsy and DSA analysis are required at least 6 weeks after the end of treatment to confirm continuing CABMR and presence of HLA DSA and to determine eligibility.

* A maximum dose of 2g of methylprednisolone intravenously (or dose equivalent of other steroids), followed by a taper to the original maintenance steroid dose is allowed.

The following histopathologic and serologic diagnostic criteria (based on Banff 2015 criteria [Loupy et al, 2017]) must be met for inclusion:

a. Morphologic evidence of chronic tissue injury, as demonstrated by TG (chronic glomerulopathy [cg] > 0). Biopsies without evidence of chronic tissue injury on light microscopy, but with glomerular basement membrane double contours on electron microscopy (cg1a) are eligible.

b. Evidence of current / recent antibody interaction with vascular endothelium, including 1 or more of the following:

i. Linear C4d staining in peritubular capillaries or medullary vasa recta (Banff scores C4d2 or C4d3 by immunofluorescence on frozen sections, or C4d > 0 by immunohistochemistry on paraffin sections).

ii. At least moderate microvascular inflammation ([glomerulitis score, g + peritubular capillaritis score, ptc] ≥ 2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥ 1.

NOTE: The local pathologist's diagnosis must be reviewed by a central pathologist to confirm eligibility for entry into the study. Biopsies with other histopathologic changes (eg, BKV nephropathy or recurrent glomerulonephritis) may be eligible if concurrent CABMR changes (as detailed above) are present and determined to be the predominant cause of renal dysfunction.

c. Serologic evidence of circulating HLA DSA.

NOTE: The local laboratory DSA results must be reviewed and confirmed by the central HLA reviewer during the Screening Period.

4. Written informed consent obtained from the subject (or legally acceptable representative) before any trial-related procedures.

5.3 Exclusion Criteria

Unless specified otherwise, all exclusion criteria time intervals are assessed with respect to the Screening Visit.

1.A8 Subject is unable or unwilling to comply with study procedures in the opinion of the Investigator.

2.A6 Multi-organ transplant recipient (except for simultaneous kidney-pancreas or previous multiple kidney transplants) or cell transplant (islet, bone marrow, stem cell) recipient.

3. Treatment for ABMR (including CABMR) or TCMR within 3 months prior to the start of Screening with the exception of steroids.

4. Received T cell depleting agents (eg, alemtuzumab, anti-thymocyte globulin) within 3 months prior to the start of Screening.

5. Treatment with mechanistic target of rapamycin (mTOR) inhibitors within 4 weeks prior to the start of Screening (see Section 7.6.1).

6.A9 Biopsy indicating predominant cause of renal dysfunction caused by pathology other than CABMR, within 12 months prior to the start of Screening.

7.A8 Impaired renal function due to disorders in the transplanted allograft (eg, renal artery stenosis, significant vascular disease of the donor, hydronephrosis).

8. eGFR < 25 mL/min/1.73 m^2 or > 65 mL/min/1.73 m^2 (MDRD4).

9.A8 Nephrotic range proteinuria defined as spot UACR ≥ 2200 mg/g (≥ 248.4 mg/mmol). If spot UACR is above the defined limits, a single repeat test can be performed on a separate day to confirm ineligibility.

10.A9 Pregnant, breastfeeding, or unwillingness to practice adequate contraception (eg, a highly effective method of contraception) during the study and for 5 months after the last dose of IP.

11.A9 History of anaphylaxis or known hypersensitivity related to clazakizumab or to any constituent of the drug product.

12.A8 Abnormal LFTs (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] or bilirubin > 1.5 x upper limit of normal [ULN]) or other significant liver disease. Subjects with an established diagnosis of Gilbert's syndrome are allowed.

13.A8 Active tuberculosis (TB) or history of active TB.

14.A8 History of latent TB (eg, positive QuantiFERON-TB test) without history of active TB unless the subject has completed a documented course of prophylactic treatment.

15. History of HIV infection or positive for HIV.

16. Seropositive for hepatitis B surface antigen (HBsAg).

17. HCV RNA positive.

18.A8 Known EBV mismatch (at time of transplant): donor seropositive, recipient seronegative. Seroconversion to EBV IgG-positive post-transplant is allowed, if documented.

19.A8 History of GI perforation; diverticular disease defined as clinically significant diverticulosis (except if disease has been fully excised and the subject has recovered from surgery) or diverticulitis (except if disease has been fully excised and the subject has recovered from surgery); or inflammatory bowel disease (except fully excised ulcerative colitis and the subject has recovered from surgery).

20.A8 Neutropenia (< 1500/mm^3) or thrombocytopenia (< 75,000/mm^3).

21. Active infections requiring systemic antimicrobial agents and unresolved prior to Screening.

22.A8 History of or current invasive fungal infection or other opportunistic infection, including (but not limited to) the following: a nontuberculous mycobacterial infection, aspergillosis, pneumocystosis, and toxoplasmosis, etc.

23.A8 Active viral infections such as BKV, CMV, or EBV based on plasma PCR testing. Active infection is defined as a test result ≥ LLOQ – see definition in Table 6.

24. Current or recent (within 3 months) participation in an interventional trial.

25. Administration of a live vaccine within 6 weeks prior to the start of Screening, including but not limited to the following:

a. Adenovirus.
b. Measles, mumps, and rubella.
c. Oral polio.
d. Oral typhoid.
e. Rotavirus.
f. Varicella zoster.
g. Yellow fever.

26.A8 History of alcohol or illicit substance (including marijuana) abuse < 5 years before Screening.

27.A8 Present or previous (within 3 years) malignancy except for basal cell carcinoma, fully excised squamous cell carcinoma of the skin; other malignancies or those that required significant therapy may require longer duration documented cancer-free (5 years) such as non-recurrent cervical carcinoma in-situ or malignancy treated with resection and chemotherapy. These cases should be discussed with the Medical Monitor and Sponsor on a case-by-case basis.

28. The presence of a condition or abnormality (ie, clinically significant endocrine, autoimmune, metabolic, neurological, psychiatric / psychological, renal, GI, hepatic, and hematological or any other system abnormalities that are uncontrolled with standard treatment) that in the opinion of the Investigator would compromise the safety or life expectancy of the subject or the quality of the data.

29.A9 History of intolerance to trimethoprim and / or sulfamethoxazole. This criterion does not apply if the subject is already taking another suitable Investigator-approved alternative therapy for Pneumocystis jiroveci pneumonia (PJP) prophylaxis, or if the subject is willing to begin taking a suitable Investigator-approved alternative prophylactic therapy approximately 1 week prior to the Day 1 Baseline Visit (Visit 2).

30. Prior exposure to clazakizumab, TCZ, or other IL-6 / IL-6R blockers.

31. ABO-incompatible transplant recipient.

32. Severe hypogammaglobulinemia (defined as immunoglobulin G [IgG] < 400 mg/dL).

33. Prior (within 2 years prior to the start of Screening) exposure to proteasome inhibitors (eg, bortezomib).

34.A9 Active infection with coronavirus disease 2019 (COVID-19). Subjects must have a negative rapid antigen test or PCR test result during the Screening Period as near to the Day 1 Baseline Visit (Visit 2) as possible. If the subject is unwell with symptoms suggestive of COVID-19 but rapid antigen test or PCR test result is negative, other causes for symptoms must be ruled out to determine subject eligibility. Subjects must be without symptoms attributable to COVID-19 for at least 1 month prior to the start of Screening.

35.A9 For subjects receiving anti-hypertensive agents (eg, Angiotensin-converting enzyme inhibitor [ACEIs] or angiotensin II receptor blockers [ARBs]), the dose of the agent has been stable for at least 2 months prior to the start of Screening.

5.4 Adequate Contraception

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise these subjects on the use of adequate methods of contraception and will check for adherence during study visits.

The Clinical Trials Facilitation and Coordination Group (CTFG) provides recommendations related to contraception and pregnancy testing in clinical trials. The following methods of contraception are considered adequate for this study:

Highly effective methods of contraception: Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly. The following methods are considered highly effective:

- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices such as Mirena® by female subject or male subject's female partner. Administration of clazakizumab may decrease the efficacy of hormonal contraceptive methods. A WOCBP subject using a hormonal contraceptive method must also supplement with a barrier method of contraception (preferably male condom).
- Nonhormonal intrauterine devices, such as ParaGard®.
- Tubal ligation.
- Vasectomy.
- Complete abstinence: Complete abstinence is defined as complete avoidance of heterosexual intercourse and is a highly effective method form of contraception for all IPs. However, WOCBP must continue to have pregnancy tests.

Subjects must agree to use adequate contraception during the study and for 5 months after the last dose of IP.

5.5 Withdrawal from Study

It is the subject's right to withdraw consent from study participation at any time without having to provide a reason. In this case, the source documents and the eCRF should document the reason for discontinuation as "withdrawal of consent." Withdrawn subjects will not be replaced. No further assessments will be performed after withdrawal of consent.

Subjects may also be withdrawn at the Investigator's discretion if it is in the subject's best interest.

Every effort should be made before the subject withdraws from the study, either voluntarily or at the Investigator's discretion, to undergo EOT assessments and safety follow-up as it is in the best interest of the subject. If possible, the subject will return for an in-clinic EOT / Early withdrawal visit within 4-weeks of the subject's last dose of IP. If the subject agrees to

the safety follow-up following the EOT/ Early withdrawal visit, all subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. In addition, all subjects will be contacted by TC 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies.

If a subject refuses the EOT / Early withdrawal visit, safety follow-up TCs, and / or SFV(s), the reason for refusal should be fully documented in the subject's source document and recorded in the electronic case report form (eCRF).

5.6 Withholding or Permanent Discontinuation of Investigational Product

Subjects considered for withholding or discontinuation of IP should be discussed with the Medical Monitor where possible. If IP is withheld or discontinued, an explanation of this clinical decision will be documented on the eCRF and the subject may be called into the clinic for an unscheduled visit, at the discretion of the Investigator. If the reason for withholding or discontinuing IP is an AE or an abnormal laboratory test result, the specific event or test will be recorded as an AE in the eCRF.

Withholding of Investigational Product

While IP is withheld, subjects will continue in the study, attend all regular clinic visits and undergoing all study assessments per Table 1 and Table 2, and comply with all aspects of the protocol. If IP is withheld for ≥ 3 consecutive doses because of an AE, the Investigator should consult with the Sponsor to consider discontinuing IP permanently.

Discontinuation of Investigational Product

Subjects who permanently discontinued treatment with IP for any reason and who have not reached an endpoint of composite all-cause allograft loss or irreversible loss of allograft function, defined as:

- eGFR < 15 mL/min/1.73 m^2*
- return to dialysis*
- allograft nephrectomy
- retransplantation
- death from any cause, or
- a sustained (≥ 60 days) 40% decline in eGFR from Baseline,

will continue in the study as described in Section 9.2.5.3.

(*total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days.)

If the eGFR < 15 mL/min/1.73 m^2 is the only component reached, the value must be sustained over at least 60 days and must be confirmed by a repeat measurement after ≥60 days from the date of the first measurement. The confirmatory measurement of eGFR < 15 mL/min/1.73 m^2 done at least 60 days from the initial measurement must be processed by the central laboratory.

If possible, the subject will return for an in-clinic EOT / Early withdrawal visit within 4-weeks of the last dose of IP. Following the EOT / Early withdrawal visit, subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. In addition, all subjects will be contacted by TC 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data.

Subjects who are pregnant will permanently discontinue treatment with IP and continue in the study as described in Section 9.2.5.3. Monitoring and reporting of pregnancies is described in Section 10.3.3.

5.6.1 Withholding or Discontinuation of Investigational Product Due to an Adverse Event

Subjects may have IP withheld or permanently discontinued due to the occurrence of an AE. If a subject is discontinued from receiving double-blind medication due to an AE, the event should be followed by the Investigator through regular contact with the subject until resolution or stabilization has occurred or the subject is lost to follow-up. Every effort must be made to perform protocol specified safety follow-up procedures (see Section 10.3).

Subjects who permanently discontinued IP treatment due to an AE, and who have not reached an endpoint of composite all-cause allograft loss or death will continue in the study as described in Section 9.2.5.3.

5.6.2 Withholding or Discontinuation of Investigational Product Due to Abnormal LFTs

The guidelines for dose modification, withholding, or discontinuing IP due to abnormal LFTs are described in Table 5.

Subjects who permanently discontinued IP treatment due to abnormal LFTs, and who have not reached a composite endpoint of all-cause allograft loss or death will continue in the study as described in Section 9.2.5.3.

5.6.3 Withholding or Discontinuation of Investigational Product Due to Neutropenia and / or Thrombocytopenia

The guidelines for dose modification, withholding, or discontinuing IP due to neutropenia and / or thrombocytopenia are described in Table 5.

Subjects who permanently discontinued IP treatment due to neutropenia and / or thrombocytopenia, and who have not reached a composite endpoint of all-cause allograft loss or death will continue in the study as described in Section 9.2.5.3.

5.6.4 Discontinuation of Investigational Product Due to BKV, CMV, or EBV Viral Infection

The guidelines for dose modification, withholding, or discontinuing IP due to BKV, CMV, or EBV viral infection are described in Table 6. Subjects who are discontinued from IP will be treated as deemed appropriate by the Investigator.

Subjects who permanently discontinued IP treatment due to BKV, CMV, or EBV viral infection, and who have not reached a composite endpoint of all-cause allograft loss or death will continue in the study as described in Section 9.2.5.3.

6. Randomization, Blinding and Unblinding Procedures

6.1 Randomization

All enrolled subjects will be assigned a unique subject number, and the Investigator will maintain a list of subject numbers and subject names.

Approximately 350 subjects will be randomized (via an IRT) 1:1 into the 2 treatment arms using a stratified block randomization scheme: 175 subjects in the clazakizumab group and 175 subjects in the placebo group. Instructions for the IRT will be provided in a separate manual.

Stratification factors will include Baseline eGFR (25 to 45 mL/min/1.73 m^2 or > 45 mL/min/1.73 m^2; Baseline eGFR is defined as an average of 2 pre-treatment measurements up to 8 weeks apart); Baseline proteinuria (UACR < 300 mg/g [< 30 mg/mmol] or UACR ≥ 300 mg/g [≥ 30 mg/mmol]); treatment for early (within 6 months of transplant) ABMR rejection episodes (yes / no); and treatment for late (greater than 6 months post-transplant) ABMR rejection episodes (yes / no).

6.2 Blinding

This study is double-blind and therefore neither the Investigator, the subject, the Sponsor and its representatives (eg, Contract Research Organization [CRO], health care provider), nor other designated study site personnel involved in running of the study will be aware of the identification of the IP administered to each subject. To maintain blinding, interim analyses (see Section 12.11) will be conducted by the DSMB. Detailed procedures for maintaining the blind are specified in the DSMB charter and / or Data Access Plan.

Given that clazakizumab and placebo are packaged differently, IP will be prepared and dispensed by an unblinded pharmacist / qualified personnel at each investigational site. To maintain blinding during the study, the pharmacist / designated staff will dispense either clazakizumab or placebo into identical syringes, according to each subject's randomized treatment allocation, and all subjects will receive each dose of IP (clazakizumab or placebo) as a SC injection (see Section 7.2 and the IMP Manual).

The pharmacist / designated staff will ensure that blinded personnel will not have access to drug supply records.

6.3 Unblinding

In the event that an AE occurs for which knowledge of the identity of the IP administered is necessary to manage the subject's condition and / or for regulatory reporting of a suspected unexpected serious adverse reaction (SUSAR), the blinding code for that subject may be broken by the Sponsor's Global Clinical Safety and Pharmacovigilance (GCSP) personnel not directly involved with the study. The blinding code is obtained via IRT and is provided to the Investigator by the GCSP personnel not directly involved with the study. The GCSP physician and other personnel involved in the study remain blinded.

Emergency unblinding should only be considered if the safety of the subject is at risk and planned interventions depend on the knowledge of the administered drug (clazakizumab or placebo). If the safety of the subject is not at risk and unblinding is deemed necessary by the Investigator, the Investigator should make a reasonable attempt to contact the Medical Monitor to discuss a potential unblinding. Only after a reasonable, but unsuccessful attempt has been made to consult with the Medical Monitor, the Investigator can unblind the subject's treatment allocation using the IRT. The Investigator must note the date, time, and reason for unblinding. The subject's treatment allocation should not be recorded in the subject's source documents. The Investigator should also subsequently inform the Medical Monitor that the subject was unblinded. However, the subject's treatment allocation should not under any

circumstances be revealed to the study team (Sponsor and their representatives). Details of unblinded treatment assignments should also not be shared with the Study Monitor, site personnel, or Sponsor team or their representatives (CRO) unless necessary for emergency care.

7. Study Treatments

7.1 Dosage Forms / Formulation

All IPs used in this study have been manufactured in accordance with current Good Manufacturing Practice.

7.1.1 Clazakizumab – Investigational Treatment

Clazakizumab will be provided to study sites by CSLB.

Generic name:	Clazakizumab
Active ingredient:	Genetically engineered humanized anti-IL-6 mAb
Strength:	12.5 mg/mL
Excipients:	L-histidine, L-histidine monohydrochloride, sorbitol, polysorbate-80, and water for injection
Dosage form:	Single-dose vials (12.5 mg/mL) for injection
Drug Product:	Clear to slightly opalescent, colorless to yellow colored solution (12.5 mg/mL vial)
Manufacturer:	Patheon, Greenville, NC

Storage: Clazakizumab must be stored according to the labeled conditions.

7.1.2 Placebo Control

The placebo will be sourced locally at each study center from commercially available saline.

Generic name:	NaCl (normal saline)
Active ingredient:	NaCl
Strength:	0.9% w/v NaCl as a sterile solution
Excipients:	None
Storage:	Per product labeling

7.1.3 Pneumocystis Jiroveci Pneumonia Prophylaxis

All subjects will be required to take prophylactic treatment for PJP; these drugs will be prescribed and supplied by the investigational sites. For the first year of the study (ie, from

Screening up to and including Week 52), PJP prophylaxis should be administered per the dosing guidelines in Section 7.1.3.1 and Section 7.1.3.2. For the remainder of the study (ie, after Week 52), PJP prophylaxis should be continued at the discretion of the Investigator.

7.1.3.1 Trimethoprim / Sulfamethoxazole

Year 1 (Screening to Week 52 Inclusive)

Oral trimethoprim / sulfamethoxazole:

Single-strength pill (80 mg as trimethoprim) daily, or
Double-strength pill (160 mg as trimethoprim) 3 times per week.

It is recommended that treatment with trimethoprim / sulfamethoxazole should be started approximately 1 week before the Day 1 Baseline Visit (Visit 2) (for subjects not already taking trimethoprim / sulfamethoxazole or other suitable Investigator-approved PJP prophylactic therapy prior to entry in the study) or 1 week before Screening if already taking it.

In the event of acute kidney injury (AKI)(eg, interstitial nephritis) considered related to trimethoprim / sulfamethoxazole, prophylactic treatment with this drug should be discontinued, and the subject should be started on another antibiotic therapy for PJP prophylaxis (see Section 7.1.3.2). In the event of other serious adverse reactions, the Medical Monitor should be consulted with respect to discontinuing prophylactic treatment or switching to another prophylactic treatment.

Year 2 to the Safety Follow-up Visit

For the remainder of the study (ie, after Week 52), PJP prophylaxis should be continued at the discretion of the Investigator.

7.1.3.2 Other Antibiotics for Pneumocystis Jiroveci Pneumonia Prophylaxis

Year 1 (Screening to Week 52 Inclusive)

Subjects who are already receiving PJP prophylactic therapy (other than trimethoprim / sulfamethoxazole) at Screening, may remain on their current therapy at the discretion of the Investigator and not start trimethoprim / sulfamethoxazole. If the Investigator does not consider a subject's current prophylactic therapy to be appropriate, trimethoprim / sulfamethoxazole should be started approximately 1 week before the Day 1 Baseline Visit (Visit 2) (see dosing guidelines in Section 7.1.3.1). Subjects who are intolerant to

trimethoprim / sulfamethoxazole and not already receiving a suitable Investigator-approved alternative therapy should be started on atovaquone (mepron), inhaled pentamidine, or oral dapsone, for approximately 1 week before the Day 1 Baseline Visit (Visit 2) based on consultation with the Medical Monitor.

Year 2 to the Safety Follow-up Visit

For the remainder of the study (ie, after Week 52), PJP prophylaxis should be continued at the discretion of the Investigator.

7.2 Dosage and Administration of Investigational Product – Clazakizumab or Placebo

All IP administration will be performed by trained, qualified staff. Clazakizumab will be administered at a target dose of 12.5 mg Q4W by SC injection with the possibility of a reduced dose of 6.25 mg Q4W by SC injection to support potential dose reductions directed by protocol-defined safety parameters (see Section 7.5).

Clazakizumab or placebo will be administered Q4W by SC injection. Each 12.5 mg dose will be administered as a 1 mL injection of clazakizumab (12.5 mg/mL) or placebo by blinded qualified study personnel at each site. Each 6.25 mg dose will be administered as a 0.5 mL injection of clazakizumab (12.5 mg/mL) or placebo by blinded qualified study personnel at each site. All IP administrations will be documented in the subject's source documents and in the eCRF.

For additional information on the preparation and dispensation of IP, please refer to the IMP Manual.

7.3 Packaging and Labeling

Clazakizumab will be supplied as single-dose vials. Vials are 2 mL flint glass, containing clazakizumab (12.5 mg/mL) to deliver 1 mL (12.5 mg). Vials of clazakizumab will be labeled with an Annex 13 compliant label.

7.4 Site Supply, Storage, and Accountability

7.4.1 Site Supply

Once a subject is screened, the site will be supplied with an initial stock of clazakizumab. Placebo (normal saline) will be sourced as described in the Pharmacy / IMP Manual. An unblinded pharmacist / qualified personnel will prepare and dispense IP in filled, identical

syringes for injection (see Section 7.2). IP will be administered at the clinic by the Investigator / designee.

The need for drug resupply will be assessed on a regular basis considering the number of subjects enrolled and the number of subjects in Screening at the site. Resupply is triggered automatically by an IRT system based on site /subject needs.

7.4.2 Storage

Clazakizumab (and placebo) should be stored at conditions specified in the product labeling.

For storage of filled syringes, see the IMP Manual.

7.4.3 Accountability

The Investigator at each site is ultimately responsible for accountability of IP supplies (including prophylactic antibiotics where applicable). The Investigator / designee will ensure that an accurate and current accounting of the dispensing of IP for each subject is maintained on an ongoing basis by the study site unblinded pharmacist / designee (see Section 7.4.1). All data regarding the IP (eg, vial numbers) must be recorded on the eCRF by the unblinded pharmacist / designee and on any other relevant forms provided. The Investigator is ultimately responsible for ensuring that only study subject receive IP.

Further details regarding IP accountability and the drug accountability log will be provided in the Pharmacy / IMP Manual.

7.4.4 Destruction of Investigational Product

For this study, IP such as partially used IP vials and syringes may be destroyed on-site.

Any unused IP vials can only be destroyed only after being inspected and reconciled by the responsible unblinded Study Monitor, after approval by the Sponsor.

On-site destruction is allowed. If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of IP.

It is the Investigator’s responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are maintained.

Further details describing the procedures for destruction of unused materials will be provided in the Pharmacy Manual.

7.5 Guidelines for Dose Modification, Withholding or Discontinuation of Investigational Product and / or Modification of Background Immunosuppression

During the study, subjects will be monitored for abnormal LFTs, neutrophil and platelet counts, and viral infection with BKV, CMV and EBV as detailed in the SOE. Based on the results of these assessments, the dose of IP may be reduced to 6.25 mg SC Q4W (temporarily or permanently), temporarily withheld, or permanently discontinued as detailed in Sections 7.5.1 and 7.5.2. Once the AE has resolved, IP may be restarted at the reduced dose or at the target dose. Decisions regarding dose modification, withholding, discontinuation, or restarting of IP should be made in consultation with the Medical Monitor (as per the dose modification guidance provided below). Background immunosuppression may also be reduced.

During the study, subjects will also be monitored for hypogammaglobulinemia (IgG < 400 mg/dL). Based on IgG levels, background immunosuppression may be reduced or discontinued, and subjects may be treated with IVIG (see Section 7.5.3). Decisions regarding dose modification / treatment should be made in consultation with the Medical Monitor.

In general, the approach to IP dose modification, withholding, discontinuation, or restarting described for abnormal LFTs (Table 5) should be followed at the discretion of the Investigator for any laboratory abnormality depending on the CTCAE severity (CTCAE Grade 1 [mild], Grade 2 [moderate], Grade 3 [severe or medically significant]) and corrective actions taken. In the case of neutropenia or thrombocytopenia, guidelines for modification of mycophenolate mofetil (MMF) / mycophenolic acid (MPA) / azathioprine (AZA) are also provided in Table 5.

Similarly, the approach to IP dose modification, discontinuation, withholding or restarting described for BKV, CMV, and EBV infection (Table 6) should be followed for any other clinically significant infection. IP should be withheld, or dose reduced to 6.25 mg SC Q4W, and the subject should be managed as per clinical practice with respect to background immunosuppressants. Once the infection has been treated and resolved, IP can be restarted at the reduced dose or dose increased back to 12.5 mg SC Q4W at the discretion of the Investigator. Guidelines for modification of background immunosuppression are also provided in Table 6.

If IP is withheld for 3 consecutive doses because of an AE, the Investigator should consult with the Medical Monitor to consider discontinuing IP permanently.

Subjects who permanently discontinued treatment with IP because of an AE, and who have not reached a non-fatal composite endpoint of all-cause allograft loss or irreversible loss of allograft function will continue in the study and undergo EOT assessments within 4 weeks of receiving the last dose of IP. Subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. In addition, all subjects will be contacted by telephone call 1, 2, and 4 months after last dose of IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data (Section 9.2.5.3).

Subjects who permanently discontinued IP treatment due to loss of their allograft will undergo EOT / Early Withdrawal assessments and be contacted monthly for post-treatment follow-up for 5 months after their last dose of IP. An in-clinic SFV will be performed after the 5-month safety follow-up period (see Section 9.2.5.2).

7.5.1 Guidelines for Dose Modification, Withholding or Discontinuation of Investigational Product and / or Modification of Background Immunosuppression Based on Abnormal LFTs, Neutropenia, or Thrombocytopenia

During the study, LFT abnormalities will be monitored and neutropenia and thrombocytopenia will be evaluated at Screening and every 4 to 8 weeks in Year 1, and Q8W weeks after Year 1 as detailed in the SOE. Depending on CTCAE Version 5.0 severity grading, IP dose reduction (to 6.25 mg SC Q4W), withholding or discontinuation will be permitted in the event of abnormal LFTs (ie, AST / ALT), neutrophil, or platelet counts as per Table 5. IP should be temporarily withheld or discontinued for any LFT abnormalities, neutrophil or platelet counts that meet CTCAE Grade ≥ 3 (see also Sections 5.6.2 and 5.6.3, respectively). Once the AE resolves, IP may be restarted (at reduced dose or target dose) if clinically appropriate. Table 5 provides further guidelines for dose adjustment of IP and / or background immunosuppression according to CTCAE severity grade. Decisions regarding dose modification, withholding, discontinuation, or restarting of IP should be made in consultation with the Medical Monitor.

Table 5 Guidelines for Dose Modification, Withholding or Discontinuation of Investigational Product and / or Modification of Background Immunosuppression Based on Abnormal LFTs, Neutropenia, or Thrombocytopenia

Parameter	Guidelines for Modification of Dose of Investigational Product and / or Background Immunosuppression
LFTs (AST / ALT)	
> ULN to 3.0 x ULN (CTCAE Grade 1)	• No change to IP dose.
> 3.0 to 5.0 x ULN (CTCAE Grade 2)	• In addition, if total bilirubin is ≥ 2.0 x ULN (or INR > 1.5), withhold or discontinue IP and contact Medical Monitor. • If total bilirubin is < 2.0 x ULN, reduce dose of IP to 6.25 mg SC Q4W. Repeat LFT analysis every 2 to 4 weeks and consult Medical Monitor. • Increase dose of IP back up to 12.5 mg SC Q4W if circumstances allow or continue at 6.25 mg SC Q4W. • Perform investigations to exclude other causes of abnormal LFTs (eg, other hepatotoxic drugs, alcohol, viral infections, autoimmune hepatitis, hemochromatosis, etc).
> 5.0 x ULN (CTCAE Grade ≥ 3)	• Withhold or discontinue IP and contact Medical Monitor.
LFTs (Total bilirubin)	
> 3.0 x ULN	• Withhold or discontinue IP and contact Medical Monitor.
Neutrophils (cells per mm^3)	
< 2500 to 1500 (CTCAE Grade 1)	• Reduce dose of MMF / MPA / AZA by 50%. • No change to IP dose.
< 1500 to 1000 (CTCAE Grade 2)	• Reduce dose of MMF / MPA / AZA by 50%. • Reduce dose of IP to 6.25 mg SC Q4W. Repeat CBC every 2 to 4 weeks and consult Medical Monitor. • Increase dose of IP back up to 12.5 mg SC Q4W if circumstances allow or continue at 6.25 mg SC Q4W.
< 1000 (CTCAE Grade ≥ 3)	• Withhold or discontinue IP and contact Medical Monitor.
Platelets (cells per mm^3)	
< LLN to 75,000 (CTCAE Grade 1)	• Reduce dose of MMF / MPA / AZA by 50%. • No change to IP dose.

Parameter	Guidelines for Modification of Dose of Investigational Product and / or Background Immunosuppression
< 75,000 to 50,000 (CTCAE Grade 2)	• Reduce dose of MMF / MPA / AZA by 50%. • Reduce dose of IP to 6.25 mg SC Q4W. Repeat CBC every 2 to 4 weeks and consult Medical Monitor. • Increase dose of IP back up to 12.5 mg SC Q4W if circumstances allow or continue at 6.25 mg SC Q4W.
< 50,000 (CTCAE Grade ≥ 3)	• Withhold or discontinue IP and contact Medical Monitor.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AZA = azathioprine; CBC = complete blood count; CTCAE = Common Toxicity Criteria for Adverse Events; INR = International Normalized Ratio; IP = investigational product; LFT = liver function test; LLN = lower limit of normal; MMF = mycophenolate mofetil; MPA = mycophenolic acid; Q4W = once every 4 weeks; SC = subcutaneous; ULN = upper limit of normal.
Source: CTCAE, Version 5.0 [NCI, 2017].

In general, in cases where IP is reduced to 6.25 mg SC Q4W, it should be continued at the reduced dose for 1 or 2 doses and laboratory test monitoring performed before considering increasing IP dose back to 12.5 mg SC Q4W. In the case of resolved neutropenia or thrombocytopenia, increasing the IP dose back to 12.5 mg SC Q4W should be considered first before increasing MMF / MPA / AZA. If this is not possible, the subject should continue in the study at the reduced dose of IP.

Note: Given the potential for drug-drug interactions between clazakizumab and calcineurin inhibitors (CNIs) (see Section 8.3.1) routine monitoring of CNI levels will be conducted throughout the study per the SOE (see Table 1 and Table 2 [for subjects taking a concomitant CNI]).

7.5.2 Guidelines for Dose Modification, Withholding, or Discontinuation of Investigational Product and / or Modification of Background Immunosuppression Based on Results of Monitoring for BKV, CMV, and EBV Infection

During the study, monitoring for BKV, CMV, and EBV infection will be performed by plasma PCR test at Screening and every 4 to 24 weeks after Baseline as detailed in the SOE. If the DNA Viral PCR test result is positive (ie, exceeds the LLOQ) or viral load increases, IP dose reduction (to 6.25 mg SC Q4W), withholding, or discontinuation will be permitted as summarized in Table 6. IP should be permanently discontinued for serious BKV, CMV, or EBV infections according to the criteria defined in Table 6 and Section 5.6.4. Table 6 provides further guidelines for dose adjustment / withdrawal of IP and / or background immunosuppression according to the viral load as detected by the plasma PCR test. Decisions

regarding discontinuation or withholding of IP should be made in consultation with the Medical Monitor.

Table 6 Guidelines for Dose Modification, Withholding or Discontinuation of Investigational Product and / or Modification of Background Immunosuppression Based on Results of Monitoring for BKV, CMV, and EBV Infection

Parameter			Modification of Dose of Investigational Product and / or Background Immunosuppression
BKV[(a)]			
> LLOQ to < 320 IU/mL	> LLOQ to < 2.51 log IU/mL	> LLOQ to < 1000 copies/ mL	• Reduce dose of MMF / MPA / AZA by 50% or reduce CNI target trough levels (ie, cyclosporine: 25 to 75 ng/mL; tacrolimus: 4 to 6 ng/mL). • No change to IP dose. • Repeat PCR test every 2 weeks and contact Medical Monitor.
≥ 320 to < 320 0 IU/mL	≥ 2.51 to < 3.51 log IU/mL	≥ 1000 to < 10,000 copies/ mL	• Reduce dose of MMF / MPA / AZA by 50% and / or reduce CNI target trough levels (ie, cyclosporine: 25 to 75 ng/mL; tacrolimus: 4 to 6 ng/mL). • Reduce IP to 6.25 mg SC Q4W or consider withholding or discontinuing IP depending on severity of infection. • Repeat PCR test every 2 weeks and contact Medical Monitor. • Increase IP dose back up to 12.5 mg SC Q4W if circumstances allow or continue at 6.25 mg SC Q4W. Or, if IP was temporarily withheld, restart at 6.25 mg SC Q4W if circumstances allow. Repeat PCR at discretion of Investigator.
Biopsy-proven BKV nephropathy or:			• Discontinue IP and contact Medical Monitor. (Adjustment of MMF / MPA / AZA dose and CNI levels at Investigator's discretion.)
≥ 3200 IU/mL	≥ 3.51 log IU/mL	≥ 10,000 copies/mL	
CMV[(b)]			
> LLOQ to < 1000 IU/mL	> LLOQ to < 3.0 log IU/mL	> LLOQ to < 640 copies/ mL	• No change to IP dose. • Repeat PCR test weekly and contact Medical Monitor.

Parameter			Modification of Dose of Investigational Product and / or Background Immunosuppression
≥ 1000 to < 5000 IU/mL	≥ 3.0 to < 3.70 log IU/mL	≥ 640 to < 3200 copies/ mL	• Treat with oral valganciclovir or IV ganciclovir. • Repeat PCR test weekly and contact Medical Monitor.
≥ 5000 IU/mL	≥ 3.70 log IU/mL	≥ 3200 copies/ mL	• Reduce dose of MMF / MPA / AZA by 50% and / or reduce CNI target trough levels (ie, cyclosporine: 25 to 75 ng/mL; tacrolimus: 4 to 6 ng/mL). • Treat with oral valganciclovir or IV ganciclovir. • Repeat PCR test weekly and contact Medical Monitor. • Reduce IP to 6.25 mg SC Q4W or consider withholding or discontinuing IP depending on severity of infection. • Increase IP dose back up to 12.5 mg SC Q4W if circumstances allow, or continue at 6.25 mg SC Q4W. Or, if IP was temporarily withheld, restart at 6.25 mg SC Q4W if circumstances allow. Repeat PCR at discretion of Investigator.
CMV end-organ disease (eg, hepatitis, colitis, pneumonitis, retinitis)			• Discontinue IP and contact Medical Monitor. (Adjustment of MMF / MPA / AZA dose and CNI levels at Investigator's discretion.)
EBV[e]			
> LLOQ to < 10,200 IU/mL	> LLOQ to < 4.01 log IU/mL	> LLOQ to < 5000 copies/ mL	• No change to IP dose. • Repeat PCR test every 2 weeks and contact Medical Monitor.
≥ 10,200 to < 20,400 IU/mL	≥ 4.01 to < 4.31 log IU/mL	≥ 5000 to < 10,000 copies/ mL	• Reduce dose of MMF / MPA / AZA by 50% and / or reduce CNI target trough levels (ie, cyclosporine: 25 to 75 ng/mL; tacrolimus: 4 to 6 ng/mL). • Repeat PCR test every 2 weeks and contact Medical Monitor.

Parameter	Modification of Dose of Investigational Product and / or Background Immunosuppression
Post-transplant lymphoproliferative disorder or primary EBV infection in seronegative recipient or: ≥ 20,400 IU/mL ≥ 4.31 log IU/mL ≥ 10,000 copies/mL	• Discontinue IP and contact Medical Monitor. (Adjustment of MMF / MPA / AZA dose and CNI levels at Investigator's discretion.)

AZA = azathioprine; BKV = polyoma BK virus; CMV = cytomegalovirus; CNI = calcineurin inhibitor; EBV = Epstein-Barr virus; IP = investigational product; IU = International Units; IV = intravenous; LLOQ = lower limit of quantification; MMF = mycophenolate mofetil; MPA = mycophenolic acid; PCR = polymerase chain reaction; Q4W = once every 4 weeks; SC = subcutaneous
Notes:
[a] LLOQ for BKV: 50.12 IU/mL (1.70 log IU/mL; 156 copies/mL)
[b] LLOQ for CMV: 371.54 IU/mL (2.57 log IU/mL; 238 copies/mL)
[c] LLOQ for EBV: 50.12 IU/mL (1.70 log IU/mL; 24.6 copies/mL)

In general, in cases where IP is reduced to 6.25 mg SC Q4W, it should be continued at the reduced dose for 1 or 2 doses and plasma PCR test monitoring performed before considering increasing IP dose back to 12.5 mg SC Q4W. Restoring the investigational dose back to 12.5 mg SC Q4W should be considered first before restarting / increasing MMF / MPA / AZA or increasing CNI levels. If this is not possible, the subject should continue in the study at the reduced dose.

Note: Given the potential for drug-drug interactions between clazakizumab and CNIs (see Section 8.3.1), routine monitoring of CNI levels will be conducted throughout the study per the SOE (see Table 1 and Table 2 [for subjects taking a concomitant CNI]).

7.5.3 Guidelines for Modification of Dose of Background Immunosuppression Based on Results of Monitoring for Hypogammaglobulinemia

During the study, IgG levels will be monitored at Screening and every 12 weeks after Baseline in Year 1 and every 16 weeks in Year 2 through SFV as detailed in the SOE. In the case of severe hypogammaglobulinemia (IgG < 400 mg/dL), reduction of background immunosuppression and treatment with IVIG will be permitted as detailed in Table 7. Pharmacokinetic samples for the assessment of clazakizumab will be collected for subjects that receive IVIG as defined in Table 9. Decisions regarding treatment with IVIG should be made in consultation with the Medical Monitor.

Table 7 Guidelines for Modification of Dose of Background Immunosuppression Based on Low IgG Levels

Parameter	Modification of Dose of Background Immunosuppression
IgG (mg/dL)	
≥ 400	• No change to background immunosuppression. • No change in dose of IP.
< 400	• Reduce dose of MMF / MPA by 50%. • No change in dose of IP. • After 4 weeks, if IgG < 400 mg/dL, continue with reduced dose of MMF / MPA and treat with IVIG, 0.5 g/kg monthly for 6 months, administered in between doses of IP (ie, 2 weeks postdose of IP is recommended). • After 6 months of IVIG treatment: o If IgG ≥ 400 mg/dL, continue with reduced MMF / MPA dose. If IgG levels remain ≥ 400 mg/dL after another 6 months post-IVIG treatment, MMF / MPA dose may be increased back to original dose. o If IgG < 400 mg/dL, consider stopping MMF / MPA and consult the Medical Monitor.

IgG = immunoglobulin G; IP = investigational product; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; MPA = mycophenolic acid

Note: Clazakizumab should be administered 2 weeks after IVIG due to potential binding of clazakizumab by IVIG. Subjects are not allowed to receive IVIG for any reason during the 3 month period before Screening. For treatment with IVIG, subjects may be called in for unscheduled visits between regularly scheduled dosing with IP according to the SOE.

7.6 Prohibited Therapy and Concomitant Treatments / Interventions

7.6.1 Prohibited Therapy and Medications

Treatments for ABMR (including CABMR) and TCMR are not allowed within 3 months prior to the start of Screening with the exception of steroids. If treatment for ABMR (including CABMR) or TCMR (other than steroids*) was given between 3 to 12 months of Screening, a repeat kidney biopsy and DSA analysis are required at least 6 weeks after the end of treatment to confirm continuing CABMR and presence of HLA DSA and to determine eligibility (see Section 5.2). * A maximum dose of 2g of methylprednisolone intravenously

(or dose equivalent of other steroids), followed by a taper to the original maintenance steroid dose is allowed.

mTOR inhibitors (everolimus, sirolimus) are not allowed within 4 weeks prior to the start of Screening or during the study. Subjects may discontinue mTOR inhibitors and switch to another suitable immunosuppressant and be treated for at least 4 weeks prior to Screening for eligibility.

Subjects already taking belatacept at Screening may continue to take belatacept for the duration of the study.

Administration of live vaccines (eg, measles, mumps, and rubella; varicella zoster) is prohibited within the 6 weeks prior to the start of Screening and during the study. It is recommended that all subjects be brought up to date with all immunizations in agreement with current immunization guidelines within 6 weeks prior to the start of Screening. During the 5-month safety follow-up period following the last dose of IP, live vaccines, and any additional immunosuppressive therapies should be administered only after careful consideration of the risk / benefit profile by the health care provider.

In addition, the following are prohibited during the study:

- Anti-IL-6 / IL-6R mAbs (both approved and investigational).
- Belatacept, unless subject is already taking belatacept at the start of Screening.
- Eculizumab.
- IVIG and PLEX:
  - **Screening**: IVIG and PLEX are prohibited for any reason for the 3-month period prior to Screening.
  - **During the study**[1]**:** IVIG and PLEX may be administered only to subjects who 1) have hypogammaglobulinemia at any point during the study, 2) meet the 40% decline in eGFR (from Baseline) endpoint and who have received > 12 months of IP (see Section 7.5.3).
    - Double-blind medication and IVIG should be administered 2 weeks apart due to potential binding of IVIG to clazakizumab. For treatment with IVIG, subjects may be called in for unscheduled visits between regularly scheduled dosing with IP according to the SOE.
    - DSA testing, per the SOE should occur ≥ 2 weeks after administration of IVIG.

  - Pharmacokinetic samples for the assessment of clazakizumab will be collected for subjects that receive IVIG as defined in Table 9.

- Proteasome inhibitors (eg, bortezomib).
- Rituximab.
- T cell depleting agents (eg, alemtuzumab, anti-thymocyte globulin [except for acute TCMR]).
- Other IPs / treatments.

[1] In a specific clinical setting only (ie, worsening DSA and / or worsening proteinuria, AND pathology showing stable to worsening cg score or other measure[s] of chronic pathology on recent / updated biopsy, accompanied by a worsening measure[s] of activity [eg, ptc, g, C4d]), consideration for use of this medications must be discussed with the Medical Monitor prior to its use.

7.6.2 Allowed Concomitant Medications / Interventions

The following concomitant medications are permitted during the study:

- Antidiabetic agents (eg SGLT2 inhibitors).
- Anti-hypertensive agents (eg, ACEIs, ARBs).
  - ACEIs and ARBs should be started, and dose should be stable for at least 2 months prior to Screening Visit and not planned to be increased.
- Background immunosuppressants: Subjects are expected to be on background immunosuppression per standard of care. Recommended dosing / target levels for AZA, CNIs, MMF / MPA are:
  - AZA
    - Recommended AZA dose: 1.0 to 2.0 mg/kg/day.

Note: In case of neutropenia / thrombocytopenia or viral infection, the dose of AZA may be reduced as indicated in Table 5 and Table 6, respectively.

- CNIs: Investigators should attempt to achieve recommended CNI target trough levels within the Screening Period and maintain these levels throughout the study
  - Recommended target tacrolimus plasma trough levels: 5 to 8 ng/mL.
  - Recommended target cyclosporine plasma trough levels: 50 to 150 ng/mL.

Note: In case of viral infection, the CNI target trough level may be modified as indicated in Table 6. Given the potential for drug-drug interactions between clazakizumab and CNIs, CNIs will be monitored every 2 weeks following a change in CNI dose until target trough levels are achieved (see Section 8.3.1).

- MMF / MPA (or equivalent after approval by the Medical Monitor).
  - Recommended MMF dose: 1.0 to 2.0 g/day.
  - Recommended MPA dose: 720 to 1440 mg/day.

Note: In case of neutropenia / thrombocytopenia, viral infection, or severe hypogammaglobulinemia, the dose of MMF / MPA may be reduced as indicated in, Table 6 and Table 7, respectively.

Note: The next administration of IP and any DSA testing as per the SOE should occur ≥ 2 weeks after lymphocyte immune globulin / anti-thymocyte globulin therapy.

- Low dose corticosteroids (prednisone / prednisolone ≤ 10 mg/day).
- Treatment for acute TCMR allowed: pulse steroid (eg, IV methylprednisone 1000 mg, or oral prednisone 200 mg/day [or equivalent] and taper to Baseline level over 2 weeks).
- Lymphocyte immune globulin / anti-thymocyte globulin therapy is allowed for TCMR Banff ≥ IIa, V1 lesion.
- Treatment with oral valganciclovir or IV ganciclovir is permitted for CMV infection as described in Section 7.5.2.
- Trimethoprim / sulfamethoxazole or inhaled pentamidine or oral dapsone (required – see Section 7.6.3).

Subjects already taking belatacept at Screening may continue to take belatacept for the duration of the study but otherwise, subjects may not begin treatment with belatacept (or switch from a CNI) during the study (see Section 7.6.1).

While the administration of live (attenuated) vaccines should be avoided during the study (see Section 7.6.1), inactivated (killed or toxin) vaccines, subunit / conjugate vaccines, or vaccines based on novel, non-live virus technology (messenger RNA [mRNA] and protein subunit) such as the COVID-19 vaccine, are acceptable and should be administered based on local practice and treatment recommendations. Further novel vaccines if developed and approved for use (eg, vector vaccines) should be discussed with the Medical Monitor and Sponsor.

Additional treatments may be used as medically indicated, according to the Investigator's medical judgment. In general, the use of herbal and homeopathic medicines (eg, St. John's Wort, echinacea, goldenseal, Schisandra sphenanthera extracts) is strongly discouraged.

Any concomitant treatment given for any reason during the course of the study must be recorded in the eCRF and in the subject's medical records, including dosage, start and stop dates, and reason for use.

Similar to Actemra / RoActemra [Actemra® Prescribing Information (USA), 2017; Actemra® Product Monograph (Canada), 2018; RoActemra® Summary of Product Characteristics (EU), 2018], a reduction in systemic exposure to clazakizumab when given in combination with CYP P450 substrates, cannot be excluded (see Section 8.3.1).

7.6.3 Required Background (Prophylactic) Therapy

All subjects will be required to take prophylactic treatment for PJP; these drugs will be prescribed and supplied by the investigational sites. For the first year of the study (ie, from Screening up to and including Week 52), PJP prophylaxis should be administered per the dosing guidelines in Section 7.1.3. For the remainder of the study (ie, after Week 52), PJP prophylaxis should be continued at the discretion of the Investigator.

If the subject is already taking trimethoprim / sulfamethoxazole prior to entry in the study, the dose should be stable for at least 1 week before the Screening Visit. If a subject is not on trimethoprim / sulfamethoxazole prior to entry in the study (and is not already receiving a suitable alternative therapy approved by the Investigator), it is recommended that treatment with trimethoprim / sulfamethoxazole should be started approximately 1 week before the Day 1 Baseline Visit (Visit 2).

If the subject is already receiving another suitable Investigator-approved therapy for PJP prophylaxis (see Section 7.1.3.2), the subject should remain on that therapy and not start trimethoprim / sulfamethoxazole. Subjects who are intolerant to trimethoprim / sulfamethoxazole and not already receiving a suitable Investigator-approved suitable alternative therapy should be started on atovaquone (mepron), inhaled pentamidine or oral dapsone for approximately 1 week before the Day 1 Baseline Visit (Visit 2) based on consultation with the Medical Monitor.

8. Risks / Precautions

8.1 Identified Risks

The safety profile of clazakizumab based on previous clinical studies is consistent with its anti-IL-6 blocking activity. Identified risks associated with clazakizumab administration include the following: infections, LFT abnormalities, changes in hematology parameters (ie, neutropenia and thrombocytopenia), dyslipidemia (ie, hypercholesterolemia and hypertriglyceridemia), GI perforations, and injection site reactions [see the CSL300 Investigator's Brochure].

8.1.1 Infections

IL-6 is important in innate and adaptive immune responses during infections, and IL-6 blockade can potentially promote infections.

In the clinical development program to date, the overall risk of infection with clazakizumab is comparable to other disease-modifying antirheumatic drugs (DMARDs) such as MTX or adalimumab, even when MTX and other DMARDs and oral corticosteroids have been used concomitantly. For further details regarding the identified risk of infection with clazakizumab, please consult the CSL300 Investigator's Brochure.

As clazakizumab could reduce immune response to infections, clazakizumab should not be administered to subjects with systemic active bacterial, viral, or fungal infections, or subjects who meet certain laboratory criteria that could predispose subjects to infections (eg, low absolute neutrophil count).

Prior studies have shown that even at low doses, clazakizumab can suppress CRP for several weeks after the last dose, which could potentially mask infections. Therefore, Investigators should be vigilant for any signs or symptoms of infection even after IP discontinuation, according to protocol instructions.

Infections should be monitored and treated according to standard of care; for serious and opportunistic infections, Investigators should consider modifying the dose of IP, withholding or discontinuing treatment with IP and / or reducing background immunosuppression. Decisions regarding dose modification, withholding, or discontinuation, of IP should be made in consultation with the Medical Monitor.

8.1.1.1 Viral Monitoring for BKV, CMV, and EBV Infection

During the trial, routine monitoring for BKV, CMV, and EBV infection will be performed by plasma PCR test at Screening and every 4 to 24 weeks thereafter as detailed in the SOE (see Table 1 and Table 2). In the event of positive results, recommendations for modification of the dose of IP and / or background immunosuppression and criteria for recommended withholding or discontinuation of IP are provided in Section 7.5.2. Decisions regarding dose modification, withholding, discontinuation, or restarting of IP should be made in consultation with the Medical Monitor.

These guidelines should be followed for any other clinically significant infection.

8.1.1.2 Viral Monitoring for COVID-19 Infection

Subjects with an active COVID-19 infection at Screening are not eligible for inclusion in the study (see Exclusion Criterion 34.A9). No routine COVID-19 rapid antigen test or PCR testing is required during the Treatment Period unless clinically indicated. If a subject tests positive for COVID-19 during the Treatment Period, background immunosuppressive medications should be managed per local medical practice. The IP may be continued, however the decision regarding discontinuation and restarting of IP should be made in consultation with the Medical Monitor.

8.1.2 Liver Function Test Abnormalities

Treatment with clazakizumab may infrequently be associated with elevated transaminases. In the clinical development program to date, increases in LFTs were mostly mild to moderate (CTCAE Grade 1 or 2) in severity, and clinically significant increases (Grade 3 and above) occurred only in a few patients. These clinically significant increases were invariably reported in subjects who had other predisposing factors which may have contributed to the LFT abnormalities. No cases of Hy's Law were observed and the abnormalities in LFTs resolved without clinical sequelae.

In studies in advanced cancer, where clazakizumab was administered (without MTX) at 320 mg IV, no clinically significant effects were seen on LFTs.

Subjects with evidence of significant liver disease and significant alcohol or illegal drug use are excluded from studies with clazakizumab.

Liver function tests and hepatobiliary AEs should be closely monitored.

During the trial, routine monitoring of LFTs will be performed at Screening and every 4 to 8 weeks thereafter as detailed in the SOE (see Table 1 and Table 2). In the case of mild to moderate LFT abnormalities, the dose of clazakizumab may be modified, and in the case of severe LFT abnormalities (CTCAE Grade ≥ 3), treatment with clazakizumab should be withheld or discontinued (see Table 5). Decisions regarding dose modification, withholding, discontinuation, or restarting of IP should be made in consultation with the Medical Monitor.

To ensure subject safety, the most recent LFTs will be reviewed prior to dosing (see Section 9.2.2).

8.1.3 Hematology Parameters

Treatment with clazakizumab is associated with decreased numbers of platelets and neutrophils. In the clinical development program to date, reductions of platelets and neutrophils were mostly mild or moderate and without clinical consequences.

Platelets and neutrophils should be carefully monitored. During the trial, a CBC will be evaluated at Screening and every 4 to 8 weeks thereafter as detailed in the SOE (see Table 1 and Table 2). In the case of mild to moderate neutropenia or thrombocytopenia, the dose of clazakizumab and / or background immunosuppression may be modified, and in the case of severe neutropenia or thrombocytopenia (CTCAE Grade ≥ 3), treatment with clazakizumab should be withheld or discontinued (see Table 5). Decisions regarding dose modification, withholding, discontinuation, or restarting of IP should be made in consultation with the Medical Monitor.

To ensure subject safety, the most recent neutrophil and platelet results will be reviewed prior to dosing (see Section 9.2.2).

8.1.4 Dyslipidemia

Treatment with clazakizumab may be associated with dyslipidemia. In the clinical development program to date, modest increases in total cholesterol and triglyceride levels were observed. The increases tended to occur early after the first drug administration and remained relatively stable thereafter. The clinical implication of these elevated lipids is unclear.

Routine monitoring of lipid levels should be performed for subjects being treated with clazakizumab. During the trial, cholesterol and triglycerides will be assessed at Day 1 Baseline Visit (Visit 2) and every 4 to 8 weeks thereafter as detailed in the SOE (see Table 1 and Table 2).

8.1.5 Gastrointestinal Perforation

Treatment with clazakizumab may be associated with gastrointestinal perforation.

Subjects with a history of GI perforation; diverticular disease defined as clinically significant diverticulosis (except if disease has been fully excised and subject has recovered from surgery) or diverticulitis (except if disease has been fully excised and subject has recovered from surgery); or inflammatory bowel disease (except fully excised ulcerative colitis and subject has recovered from surgery) should not be treated with clazakizumab and are excluded from the study (Section 5.3). For further details regarding the identified risk of GI perforation with clazakizumab, please consult the CSL300 Investigator's Brochure.

8.1.6 Injection Site Reactions

Injection site reactions have been reported with SC administration, and most frequently reported as erythema and rash. Reactions have been mild or moderate and have resolved without treatment.

8.2 Potential Risks

Potential risks with clazakizumab treatment have been identified based on known risks associated with TCZ, sarilumab, prolonged immunosuppressive therapy, and other biologics used in the treatment of RA.

8.2.1 Demyelination

Demyelinating events were observed in TCZ trials. It is unclear whether TCZ administration was associated with such events. In the clinical program to date, 1 demyelinating event (demyelinating polyneuropathy) considered possibly related to treatment with clazakizumab was reported in 1 subject in a study in RA.

8.2.2 Malignancies

Malignancies are known risks associated with prolonged immunosuppression. Malignancies are identified as a potential risk for therapies that modulate the immune system and should be monitored in this context during the clazakizumab trials. Malignancies have been observed in clinical trials with other IL-6 antagonists [Actemra® Prescribing Information (USA), 2017; Kevzara® Prescribing Information (USA), 2017; Actemra® Product Monograph (Canada), 2018; RoActemra® Summary of Product Characteristics (EU), 2018].

In the clinical program to date, malignancies considered possibly related to treatment with clazakizumab were reported in 4 subjects in a study in RA: breast cancer, squamous cell carcinoma of the skin, invasive ductal breast carcinoma, and gastric cancer.

8.2.3 Immunogenicity

As a mAb, the development of anti-drug antibodies (ADAs) is a potential risk. Such antibodies could theoretically lead to reduced efficacy or have safety consequences. To date, ADAs have not been detected in healthy volunteers treated with clazakizumab. ADAs were detected in some subjects in studies of RA and PsA.

Anti-clazakizumab antibodies will be monitored during the course of the study as detailed in the SOE (see Table 1 and Table 2).

8.2.4 Infusion Related (Allergic) Reactions

To date, no infusion reactions have been associated with clazakizumab administered by IV infusion.

As with any protein therapeutic, there is a risk of a serious allergic reaction. Clazakizumab should not be administered to subjects who have had any previous allergic reactions to mAbs. Allergic reactions should be treated with standard of care. Subjects who have developed significant allergic reaction to study drugs should not be rechallenged.

8.3 Additional Warnings and Precautions

8.3.1 Drug Interactions

No formal clinical drug interaction studies of clazakizumab have been performed.

As a mAb, direct PK interactions with other drugs are not anticipated. However, in vitro studies showed that clazakizumab has a similar effect to TCZ in reversing the IL-6 effect on the down-regulation of mRNA levels of multiple CYP enzymes [CSL300 Investigator's Brochure]. Therefore, treatment with clazakizumab may restore CYP enzyme-mediated drug clearance, resulting in a potential lowering of systemic exposure of drugs metabolized by CYP enzymes, as has been observed with TCZ (see Actemra / RoActemra prescribing information [Actemra® Prescribing Information (USA), 2017; Actemra® Product Monograph (Canada), 2018; RoActemra® Summary of Product Characteristics (EU), 2018]).

This effect may be particularly important for CYP enzyme substrate drugs that have a narrow therapeutic index where the dose is individually adjusted. In the labeling of TCZ and

sarilumab, 2 approved anti-IL-6R mAbs, it is recommended that, upon initiation or discontinuation of these mAbs, therapeutic monitoring of effect (eg, warfarin) or drug concentration (eg, theophylline, cyclosporine) be performed and the individual dose of the CYP enzyme substrate drugs be adjusted as needed [Actemra® Prescribing Information (USA), 2017; Kevzara® Prescribing Information (USA), 2017; Actemra® Product Monograph (Canada), 2018; RoActemra® Summary of Product Characteristics (EU), 2018]. Similarly, caution should be exercised when coadministering clazakizumab with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (eg, hormonal contraceptives, 3-hydroxy-3-methyl-glutaryl-co-enzyme A reductase inhibitors).

Note: Given the potential for drug-drug interactions between clazakizumab and CNIs, CNI trough levels will be monitored at Year 1: Visits 2 (Baseline) through 6, 8, 10, 12, 14, and 16; Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit (for subjects taking a concomitant CNI). At these visits, treatment with CNIs is to be withheld until after sample collection for determination of CNI levels. CNIs will also be monitored every 2 weeks following a change in CNI dose, withholding, discontinuation, or restarting of IP, until target CNI trough levels are achieved.

After Year 1, CNI levels may be checked per local practice through local laboratories, including being a part of evaluating any significant changes in creatinine. Locally drawn CNI levels may qualify for monitoring if drawn within the specified interval of ± 2 weeks. Routine monitoring of CNI levels are summarized as per the SOE (see Table 1 and Table 2).

With prior alignment and permission from CSLB, CNI monitoring may be conducted locally during Year 1. If monitored locally during Year 1,CNI monitoring should be conducted at the same laboratory throughout the study, ie beginning from and including the Baseline CNI level. Also, if CNI monitoring is conducted locally in Year 1, a sample should be drawn and submitted to the central laboratory each time CNI levels are assessed as per the schedule described in the SOE (see Table 1 and Table 2).

8.3.2 Overdose

There are no specific antidotes or measures to take in the event of an overdose of clazakizumab injection. Subjects should be treated with the appropriate supportive care.

8.3.3 Women of Childbearing Potential

A WOCBP, ie fertile, following menarche and until becoming post-menopausal unless permanently sterile, as defined in the European “Heads of Medicines Agencies” 2014 CTFG document “Recommendations related to contraception and pregnancy testing in clinical

trials". Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

There are no adequate well-controlled studies in pregnant or lactating women. In nonclinical studies, an increase in the number of monkeys with retention of the placenta at parturition was observed at clazakizumab doses corresponding to 34 and 340 times the planned human dose of 12.5 mg Q4W in this study. These doses are expected to generate exposures approximately 48 and 480 times higher, respectively, than the human doses of 12.5 mg SC injection, Q4W. In 3 of the 5 monkeys with retained placentas, the resulting excessive uterine hemorrhage led to moribund status in the mothers.

There have been pregnancy cases in clinical trials. For the latest information, please refer to the CSL300 Investigator's Brochure.

All subjects of childbearing potential being treated with clazakizumab (and their partners) must be informed of this risk, and use adequate contraception, as defined in the study protocol (see Section 5.4). Administration of clazakizumab may decrease the efficacy of hormonal contraceptive methods; therefore, a WOCBP subject using a hormonal contraceptive method must also supplement with a barrier method of contraception (preferably male condom) (see Section 5.4).

Under no circumstances shall clazakizumab be administered to women known to be pregnant or lactating. Women who have a confirmed positive pregnancy test during the study will be permanently discontinued from IP but continue in the study as described in Section 9.2.5.3. All pregnancies must be reported to CSLB and the CRO within 24 hours of awareness and in accordance with reporting procedures (see Section 10.3.3).

For further details, see the CSL300 Investigator's Brochure.

9. Study Procedures

9.1 Description of Study Assessments

9.1.1 Clinical Laboratory Assessments

All samples will be analyzed at the central laboratory using standard validated methods (see the Laboratory Manual for contact details). Local laboratories may be utilized for unscheduled safety analyses between visits and where applicable; results must be recorded on the eCRF.

Samples for the following efficacy and safety assessments will be collected in accordance with the SOE in Table 1 (Year 1) and Table 2 (Year 2 to SFV / CTEV). All blood and urine samples should be collected prior to dosing at the clinic visit. A summary of all laboratory assessments is provided in Table 8.

Table 8 Summary of Laboratory Assessments

Test Type	Test Parameters	Collection
Clinical Chemistry (serum)	• BUN or Urea • Chloride • CO_2 • Creatinine • LFTs (AST, ALT, alkaline phosphatase, GGT, total bilirubin, direct bilirubin, INR) • hsCRP • Potassium • Sodium	Year 1: Visits 1 (Screening), 2, 4, 5, 6, 8, 10, 12, 14, and 16. Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit / SFV / Q6M (for subjects who discontinued IP) / CTEV.
	• Fasting glucose[a]	Year 1: Visits 2, 4, 5, 6, 8, 10, 12, 14, and 16. Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit / SFV / Q6M (for subjects who discontinued IP) / CTEV.
Lipids (serum)[a]	• Cholesterol (total, HDL, and LDL), fasting • Triglycerides, fasting	Year 1: Visits 2, 4, 5, 6, 8, 10, 12, 14, and 16. Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit / SFV / Q6M (for subjects who discontinued IP) / CTEV.

Hematology	• CBC
	  ○ Hb
	  ○ Hematocrit
	  ○ Red blood cell count
	  ○ White blood cell count
		Year 1: Visits 1 (Screening), 2, 4, 5, 6, 8, 10, 12, 14, and 16.
		Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit / SFV / Q6M (for subjects who discontinued IP) / CTEV.

Test Type	Test Parameters	Collection
	○ White blood cell differential (absolute and %) ○ Platelet count	
Serology	• HIV • HBsAg	At Visit 1 (Screening) (unless known seropositive history).
Viral monitoring (plasma PCR) (see Section 9.1.1.1)	• Hepatitis C RNA	At Visit 1 (Screening).
	• COVID-19 RNA	At Visit 1 (Screening)[(b)].
	• BKV, CMV, EBV, DNA Viral PCR monitoring	Year 1: Visits 1 (Screening), 4, 5, 6, 8, 10, 12, 14, and 16. Year 2 through EOT/ Early Withdrawal Visit (approximately every sixth visit [Q24W]): Visits 22, 28, 34, 40, 46, 52, 58, 64, 68, 74, 80, 86, 92, and EOT / Early Withdrawal / CTEV.
Urinalysis	• Dipstick chemical profile with optional microscopic profile if dipstick is abnormal	At Visit 1 (Screening).
	• UACR spot urine test	At Visits 1 (Screening), 6, 9, and 15. Year 2 through EOT / Early Withdrawal Visit (approximately every sixth visit [Q24W]): Visits 20, 26, 32, 38, 44, 50, 56, 62, 68, 72, 78, 84, 90, and EOT / Early Withdrawal / SFV / Q6M (for subjects who discontinued IP) / CTEV.
Pregnancy test	• POCT urine pregnancy test for WOCBP (any positive results will be confirmed by a serum test at the central laboratory)[(c)]	At all visits except Visit 3 (Visits 1, 2, and 4 through-EOT) / SFV / CTEV.
Special tests	• IgG (see Section 9.1.1.2)	Year 1: Visits 1 (Screening), 6, 9, 12, and 15. Year 2 through EOT: every fourth visit (Q16W) starting with Visit 18 through the EOT / Early Withdrawal Visit / CTEV.
	• eGFR (MDRD4) (see Section 9.1.1.3)	Year 1: all visits except Visit 3. Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit / SFV / Q6M (for subjects who discontinued IP) / CTEV.
	• DSA MFI scores (for anti-HLA antibodies) (see Section 9.1.1.4)	Year 1: Visits 1 (Screening)[(d)], 2, 9, and 16. Year 2 through EOT: Visits 28, 42, 54, 68, 80, 94, and the EOT / Early Withdrawal Visit / SFV / Q12M (for subjects who discontinued IP) / CTEV.
	• DSA titers (for anti-HLA antibodies) (see Section 9.1.1.4)	Year 1: Visits 2 (Baseline), 16 and the EOT / Early Withdrawal Visit.

Test Type	Test Parameters	Collection
	• Plasma IL-6 (total and free)[(e)] (see Section 9.1.1.6)	Year 1: Visits 2 (Baseline), 6, 9, and 15. Year 2 through EOT / Early Withdrawal Visit (approximately every sixth visit [Q24W]): Visits 20, 26, 32, 38, 44, 50, 56, 62, 68, 72, 78, 84, 90, and EOT / Early Withdrawal / SFV / CTEV.
	• Serum clazakizumab [(e,f)] (see Section 9.1.1.7)	Year 1: Visits 2 (Baseline), 6, 9, and 15. Year 2 through SFV: (approximately every sixth visit [Q24W]): Visits 20, 26, 32, 38, 44, 50, 56, 62, 68, 72, 78, 84, 90, and EOT / Early Withdrawal, and SFV / CTEV.
	• Immunogenicity (ADA) (see Section 9.1.1.8)	Year 1: Visits 2 (Baseline), 6, 9, and 15. Year 2 through SFV (approximately every sixth visit [Q24W]): Visits 20, 26, 32, 38, 44, 50, 56, 62, 68, 72, 78, 84, 90, and EOT / Early Withdrawal, and SFV / CTEV.
	• MPA levels (see Section 9.1.1.9)	At Visit 2 (Baseline), as clinically indicated during the Treatment Period, and EOT / Early Withdrawal Visit / CTEV.
	• CNI levels (see Section 9.1.1.10)	Year 1: Visits 2 through 6, 8, 10, 12, 14, and 16. Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit / CTEV.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BKV = polyoma BK virus; BUN = blood urea nitrogen; CBC = complete blood count; CMV = cytomegalovirus; CNI = calcineurin inhibitor; CTEV = common treatment end visit; DSA = donor-specific antibodies; EBV = Epstein-Barr virus; eGFR = estimated glomerular filtration rate; EOT = end of treatment; GGT = Gamma-glutamyl transferase; Hb = hemoglobin; HBsAg = hepatitis B surface antigen; HDL = high density lipoprotein; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; hsCRP = high-sensitivity C-reactive protein; IgG = immunoglobulin G; IL-6 = interleukin 6; INR = international normalized ratio; IP = investigational product; LDL = low density lipoprotein; MDRD4 = Modification of Diet in Renal Disease-4; MFF = mycophenolate mofetil; MFI = mean fluorescence intensity; MPA = mycophenolic acid; PCR = polymerase chain reaction; POCT = point of care test; SFV = safety follow-up visit; Q6M = every 6 months; UACR = urine albumin creatinine ratio; WOCBP = women of childbearing potential.

Notes:

[a] At least 10 hours of fasting is required for determination of fasting glucose and for lipids / triglycerides. If the subject failed to fast, samples should still be collected and processed with failure to fast recorded on the laboratory requisition and as a protocol deviation. (Glucose and lipids / triglycerides will not be assessed at Visit 1.)

[b] Subjects must have a negative rapid antigen test or PCR test result during the Screening Period as near to Day 1 (Baseline Visit [Visit 2]) as possible. Subjects must be without symptoms attributable to COVID-19 for at least 1 month prior to the start of Screening. Additional testing during the trial may be performed at the discretion of the Investigator if clinically indicated.

[c] POCT urinary pregnancy test prior to every dose of IP. For subjects who permanently discontinued investigational treatment with clazakizumab / placebo, this assessment will be conducted for an additional 5 months following the last dose of IP.

[d] At Screening, local laboratory DSA results will be reviewed by the central HLA reviewer to confirm eligibility for entry into the study. If the presence of HLA DSA is confirmed within 6 months prior to the start of Screening, the test does not need to be repeated for eligibility.

[e] Additional blood samples may be taken for those participating in the PK / PD Substudy (see Table 3).

[f] Additional blood samples will be taken for those subjects that receive IVIG treatment (see Table 9).

9.1.1.1 Viral Monitoring (Plasma PCR)

Viral monitoring will be performed using plasma PCR. Further details are provided in the Laboratory Manual.

HCV infection will be tested at Visit 1 (Screening) by PCR detection of viral RNA.

Subjects not known to have been previously infected with COVID-19 must have a negative rapid antigen test or PCR test result during the Screening Period as near to the Day 1 Baseline Visit (Visit 2) as possible.

BKV, CMV and EBV will be monitored throughout the study by Viral PCR detection of DNA at Year 1: Visits 1 (Screening), 4, 5, 6, 8, 10, 12, 14, and 16; Year 2 through EOT/ Early Withdrawal Visit (approximately every sixth visit [Q24W]): Visits 22, 28, 34, 40, 46, 52, 58, 64, 68, 74, 80, 86, 92, and EOT / Early Withdrawal / CTEV.

Note: PCR testing for BKV, CMV, EBV, and HCV will be conducted at the central laboratory.

9.1.1.2 Monitoring for Hypogammaglobulinemia (IgG)

Monitoring for hypogammaglobulinemia will be performed by measuring IgG levels at the central laboratory. Further details are provided in the Laboratory Manual.

- IgG levels will be determined at Year 1: Visits 1 (Screening), 6, 9, 12, and 15. Year 2 through EOT: every fourth visit (Q16W) starting with Visit 18 through the EOT / Early Withdrawal Visit / CTEV.

9.1.1.3 eGFR

Estimated glomerular filtration rate will be determined using the MDRD4 equation [Levey et al, 2006]:

$$eGFR = 175 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female; } 1 \text{ otherwise}) \times (1.212 \text{ if black; } 1 \text{ otherwise})$$

The eGFR will be determined by the central laboratory at all visits except Visit 3 (Year 1); Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit SFV / Q6M (for subjects who discontinued IP) / CTEV.

eGFR should be assessed by the central lab for subjects who permanently discontinued treatment with IP and continues to attend in-clinic study visit. This may be complemented by additional eGFR results that are obtained between in-clinic visits and may be taken by a local laboratory.

9.1.1.4 DSA Titers and MFI Scores

DSA for HLA (Class I and Class II) will be determined using single-antigen bead-based assays at the central laboratory. Further details are provided in the Laboratory Manual.

- DSA for MFI scores will be determined at Year 1: Visits 1 (Screening), 2 (Baseline), 9, and 16; Year 2 through EOT: Visits 28, 42, 54, 68, 80, 94 and the EOT / Early Withdrawal Visit / SFV / Q12M (for subjects who discontinued IP) / CTEV.
- DSA for titers will be determined at Year 1: Visits 2 (Baseline),16, and the EOT / Early Withdrawal Visit.

At Screening, local laboratory DSA results will be reviewed by the central HLA reviewer to confirm eligibility for entry into the study. If the presence of HLA DSA is confirmed within 6 months prior to the start of Screening, the test does not need to be repeated for eligibility. If the central HLA reviewer disagrees with the local laboratory results, the Screening DSA test may be repeated once by the central laboratory and the repeated results must be reviewed by the central HLA reviewer to confirm DSA eligibility criteria. To be considered for determination of study eligibility, the DSA analysis must be performed and should occur at least 6 weeks after the end of any prior treatment for ABMR (including CABMR) or TCMR, in order to show continuing CABMR. In addition, treatments for ABMR or TCMR are not allowed within 3 months prior to the start of Screening with the exception of steroids.

In cases where local DSA testing is unavailable at the site, Screening DSA analysis will be conducted by the central laboratory and reviewed by the central HLA reviewer to confirm eligibility.

9.1.1.5 Plasma hsCRP

Plasma hsCRP levels will be measured using a validated assay by a central laboratory. Further details are provided in the Laboratory Manual.

Plasma hsCRP levels will be measured at Year 1: Visits 1 (Screening) 2, 4, 5, 6, 8, 10, 12, 14, and 16. Year 2 through EOT: every second visit (Q8W) starting with Visit 18 through the EOT / Early Withdrawal Visit / SFV / every 6 months (Q6M) (for subjects who discontinued IP) / CTEV.

For those participating in the PK / PD Substudy, plasma hsCRP will also be measured before dosing on Day 8 (168 h), Visit 4 (before dosing), Visit 9 (Week 24 [before dosing], 72 h and 120 h after Visit 9 IP injection]), Week 25 (168 h after Visit 9 IP injection), Week 26 (336 h after Visit 9 IP injection), Week 27 (504 h after Visit 9 IP injection) as per Table 3. These

measurements are in addition to those taken as part of the main study. Note: Assessment of hsCRP levels is not required if the subject has been permanently discontinued from treatment with IP.

9.1.1.6 Plasma IL-6

Total IL-6 (ligand bound / unbound to soluble IL-6R and bound / unbound to clazakizumab) and free IL-6 (ligand unbound to soluble IL-6R and unbound to clazakizumab) levels will be measured using a validated SIMOA® assay by a central laboratory. Further details are provided in the Laboratory Manual.

In the main study, plasma IL-6 levels (total and free) will be determined at Year 1: Visits 2 (Baseline), 6, 9, and 15; Year 2 through EOT / Early Withdrawal Visit (approximately every sixth visit [Q24W]): Visits 20, 26, 32, 38, 44, 50, 56, 62, 68, 72, 78, 84, 90, and EOT / Early Withdrawal / SFV / CTEV.

For those participating in the PK / PD Substudy, plasma IL-6 will also be measured at Week 1 (Day 8 [168 h]), Week 4 / Visit 4 (before dosing), Week 24 (Day 3 [72 h after Visit 9 IP injection], Day 5 [120 h after Visit 9 IP injection]), Week 25 (Day 7 [168 h after Visit 9 IP injection]), Week 26 (Day 14 [336 h after Visit 9 IP injection]), Week 27 (Day 21 [504 h after Visit 9 IP injection]) as per Table 3. These measurements are in addition to those taken as part of the main study. Note: Assessment of IL-6 levels is not required if the subject has been permanently discontinued from treatment with IP.

9.1.1.7 Serum Clazakizumab

A validated enzyme-linked immunosorbent assay method will be used to measure concentrations of clazakizumab in serum. Samples will be analyzed by the central laboratory. Pharmacokinetic samples are to be drawn prior to administration of IP. Those samples drawn for the PK / PD Substudy and for IVIG treatment are described below.

In the main study, serum clazakizumab concentrations will be determined at Year 1: Visits 2 (Baseline), 6, 9, and 15; Year 2 through SFV: (approximately every sixth visit [Q24W]): Visits 20, 26, 32, 38, 44, 50, 56, 62, 68, 72, 78, 84, 90, and the EOT / Early Withdrawal Visit, and the SFV / CTEV. Note: Assessment of clazakizumab levels is not required if the subject has been permanently discontinued from treatment with IP.

In a separate PK / PD Substudy, subjects that consented to additional blood draws, serum clazakizumab will be measured at Visit 2 (Baseline), Day 8 (168 h), Visit 4 /Week 4 (before dosing), Visit 9 (Week 24 [before clazakizumab dose, 72 h and 120 h after the Visit 9 IP

injection]), Week 25 (Day 7 [168 h after Visit 9 IP injection]), Week 26 (Day 14 [336 h after Visit 9 IP injection]), and Week 27 (Day 21 [504 h after Visit 9 IP injection]) as per Table 3. These measurements are in addition to those taken as part of the main study.

For all subjects that go on to receive IVIG, the following blood samples for measurement of clazakizumab concentration in serum will be taken as defined in Table 9.

Table 9 Pharmacokinetic Sample Collection for Subjects Receiving IVIG

Activity	Analyte	Sampling Timepoint	Timepoint Window Relative to IVIG Treatment	Notes
Blood Draw	Clazakizumab	Before dose of IVIG	Up to -2 weeks prior to IVIG dosing.	Optional if the subject has been on study for longer than 24 weeks. Blood draw can coincide with IP administration visit. Sample must be taken prior to administration of IVIG.
For Subjects Receiving Only One Dose of IVIG				
Blood Draw	Clazakizumab	2 weeks after the IVIG treatment	±2 days	Blood draw can coincide with the next visit for clazakizumab administration and should be drawn prior to administration of clazakizumab.
For Subjects Receiving Multiple Doses of IVIG				
Blood Draw	Clazakizumab	2 weeks after each IVIG treatment for the remainder of IVIG treatment	±2 days	Blood draw can coincide with the next visit for clazakizumab administration and should be drawn prior to administration of clazakizumab.

IP = investigational product; IVIG = intravenous immunoglobulin

9.1.1.8 Immunogenicity

A validated electrochemiluminescence immunoassay method will be used to measure titers of clazakizumab antibodies in serum. Samples will be analyzed by the central laboratory. Further details are provided in the Laboratory Manual.

Plasma anti-clazakizumab antibody levels will be measured at Year 1: Visits 2 (Day 1, Baseline), 6, 9, and 15; Year 2 through SFV: (approximately every sixth visit [Q24W]): Visits 20, 26, 32, 38, 44, 50, 56, 62, 68, 72, 78, 84, 90, and the EOT / Early Withdrawal Visit, and the SFV / CTEV.

Note: Assessment of anti-clazakizumab antibody levels is not required if the subject has been permanently discontinued from treatment with IP.

9.1.1.9 MPA Levels

MPA levels in serum / plasma will be measured by a validated quantitative liquid chromatography-tandem mass spectrometry (LC-MS / MS) method at a central laboratory. Further details are provided in the Laboratory Manual.

For subjects taking concomitant MMF / MPA, MPA levels will be measured at Visits 2 (Baseline), as clinically indicated per investigator discretion during the Treatment Period, and the EOT / Early Withdrawal Visit / CTEV. At these visits, treatment with MMF / MPA is to be withheld until after blood sample collection for determination of MPA levels.

9.1.1.10 CNI Levels

CNI (tacrolimus and cyclosporine) trough levels in serum / plasma will be measured by a validated quantitative LC-MS / MS method at a central laboratory. Further details are provided in the Laboratory Manual.

For subjects taking a concomitant CNI, CNI trough levels will be measured as described in the SOE (See Table 1 and Table 2). At these visits, treatment with CNIs is to be withheld until after sample collection for determination of CNI levels.

CNIs will also be monitored Q2W following a change in CNI dose, withholding, discontinuation, or restarting of IP, until target CNI trough levels are achieved (see Section 8.3.1).

After Year 1, CNI levels may be checked locally through local laboratories. CNI monitoring will be continued as described in the SOE, blood samples for CNI monitoring have to be drawn within the specified interval of ± 2 weeks from study drug administration. All CNI values from central and local laboratories are required to be entered into the subject eCRFs by the study team. It is the site's responsibility to determine if the measured levels are within the expected range and if any intervention needs to be taken. In case of any issue as described in Section 8.3.1, repeat levels should be determined and reported.

With prior alignment and permission from CSLB, CNI monitoring may be conducted locally during Year 1. If monitored locally during Year 1,CNI monitoring should be conducted at the same laboratory throughout the study, ie beginning from and including the Baseline CNI level. Also, if CNI monitoring is conducted locally in Year 1, a sample should be drawn and submitted to the central laboratory each time CNI levels are assessed as per the schedule described in the SOE (see See Table 1 and Table 2).

Note: Attendance at Visit 3 is required only if the subject is taking a CNI.

9.1.1.11 Biomarkers and Pharmacogenomics Research

Leftover blood samples for biomarker and pharmacogenomics research will be frozen and stored for future analysis. Possible evaluations may include analysis of biomarkers to further characterize disease manifestation of CABMR, PK / PD and potential safety signals. Samples will be stored up to 2 years after study completion. Additional details on storage are provided in the ICF.

9.1.2 Physical Examinations

At Visit 1 (Screening), a complete physical examination as per standard of care will be conducted by either the Investigator or a sub-Investigator who is a physician. An abbreviated physical examination will be conducted at Year 1: Visits 2 (Baseline), 4, 5, 6, 9, 12, 15: Year 2 through EOT: every fourth visit (Q16W) starting with Visit 18 through the EOT /Early With drawal visit; these limited examinations may be completed by other qualified staff.

Subject weight will be recorded at each physical examination. Height will be recorded at Visit 1 only.

Where possible, at each study site the same person should perform all physical examinations for a given subject, throughout the study.

9.1.3 Vital Signs

Vital signs will be measured at Year 1: Visits 1 (Screening), 2 (Baseline), 4, 5, 6, 9, 12, 15; Year 2 through EOT: every fourth visit (Q16W) starting with Visit 18 through the EOT / Early Withdrawal Visit.

All assessments will be taken after the subject has been at rest in a sitting position for 5 minutes. To avoid variability, the same method of obtaining body temperature should be used throughout the study.

The following vital signs will be measured:

- Blood pressure (systolic and diastolic)
- Heart rate
- Body temperature (°C or °F)
- Respirations

9.1.4 Standard 12-lead Electrocardiogram

The electrocardiogram (ECG) will be a standard 12-lead tracing performed at the investigational site, assessed by a qualified physician at the investigational site, and retained as a source document. Results including any abnormalities will be recorded in the eCRF. Electrocardiograms will be recorded digitally after the subject has been in a resting, supine position for at least 5 minutes. Significant abnormalities, including findings that may prompt discontinuation of IP should be discussed with the Medical Monitor.

Electrocardiograms will be performed at Year 1: Visits 1 (Screening), 6, 9, and 15; Year 2 through EOT: 28, 42, 54, 68, 80, 94, and the EOT / Early Withdrawal Visit / CTEV.

9.1.5 Tuberculosis Screening

Screening for active and latent TB is required to determine subject eligibility to enroll in this study. The following procedures are required:

- A complete physical examination and medical history to evaluate exposure to TB and whether subjects with a history of latent TB (without active TB) completed a documented course of prophylactic treatment.
- Chest X-ray.
- QuantiFERON-TB Gold interferon-γ release assay. (Note: local QuantiFERON-TB Gold testing is acceptable.)

If a positive result is obtained for the interferon-γ release assay, the test should not be repeated. For an indeterminate result, the assay may be repeated 1 time. If the second test is positive or indeterminate, the result should be considered positive for that subject. A third test may not be performed.

For eligibility in the study, subjects with a history of latent TB must not have a history of active TB and must have documented evidence of a documented course of prophylactic treatment.

Subjects who have newly diagnosed TB should have IP discontinued and managed according to the local standard of care.

Note: a subject being rescreened is not required to have a repeat chest X-ray for TB screening if the first Screening chest X-ray was normal and conducted within 6 months from the start date of rescreening.

9.1.6 Renal Biopsy

Biopsy-proven CABMR (according to Banff 2015 diagnostic criteria [Loupy et al, 2017]) within 12 months prior to the start of Screening is required for assessment of subject eligibility to enroll in this study. A repeat biopsy is to be performed if previous biopsy is not within 12 months prior to the start of Screening and no intervening treatments have been administered. The local pathologist's diagnosis must be reviewed by a central pathologist to confirm eligibility for entry into the study. To be considered for determination of study eligibility, the biopsy should be performed at least 6 weeks after the end of any prior treatment for ABMR (including CABMR) or TCMR, in order to show continuing CABMR. In addition, treatments for ABMR or TCMR are not allowed within 3 months prior to the start of Screening with the exception of steroids.

Repeat biopsies per-protocol will be performed at Visit 16 (Week 52 [window -2 to + 6 weeks]). Unscheduled biopsies may be performed at any time if clinically indicated and, after local review for diagnostic purposes, should be sent to the central pathologist for analysis. If a for-cause biopsy has been performed within 2 months of Week 52, a repeat biopsy at Week 52 is not required.

9.1.7 Health-Related Quality of Life

HRQoL will be assessed using the tools described below. The data will be collected electronically for the visits reflected in the SOE. Subjects in the trial will enter their data through the electronic clinical outcomes assessment (eCOA) solution (see Section 15.2.1). PRO assessments should be completed before other medical procedures and assessments are performed whenever possible.

HRQoL data will be collected electronically through the use of validated patient-reported outcome assessments twice a year for the first 2 years of the study and once a year in the last 3 years of the study at Visits 2, 9, 16, 23, 29, 42, 55, 68, 81, 94, at the EOT / Early Withdrawal Visit), the SFV / Q6M visit (for subjects who discontinued IP) / CTEV. Subjects who are randomized before the availability of the eCOA solution will not complete HRQoL questionnaires.

9.1.7.1 EQ-5D-5L

The EuroQol 5 dimensions questionnaire (EQ-5D)-5L is a generic quality of life assessment that 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 [Herdman et al, 2011;

Janssen et al, 2013]. It will be performed in countries where validated language versions of the questionnaires are available.

The EQ-5D-5L descriptive profile of health states consists of the following 5 domains: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Within each domain, there are a series of questions with 5 response levels: no problems, slight problems, moderate problems, severe problems, and extreme problems or unable to perform task depending on the concept measured. A unique health state is defined by combining 1 level from each of the 5 domains. Each health state is referred to in terms of a 5-digit code. The visual analogue scale records the subject's self-rated overall health on a vertical numerical scale where the endpoints are 'Best imaginable health state' (100) and 'Worst imaginable health state' (0).

9.1.7.2 Kidney Disease Quality of Life Questionnaire – 36

The Kidney Disease Quality of Life 36 (KDQoL-36) survey is a short form that includes the SF12 as a generic core plus the burden of kidney disease, symptoms / problems of kidney disease, and effects of kidney disease scales from the KDQoL-SF [Chong K. et al, 2018]. There is also a KDQoL-36 Summary Score (KSS) which is a composite of items from the KDQoL-36's kidney targeted scales and is useful when kidney targeted HRQoL needs to be summarized in a single score [Peipert et al, 2019].

9.1.7.3 Functional Assessment of Chronic Illness Therapy – Fatigue Scale

The FACIT Fatigue scale is a 13-item patient-reported measure of fatigue with a 7-day recall period. Items are scored on a 0 to 4 response scale with anchors ranging from "Not at all" to "Very Much So". To score the FACIT Fatigue, all items are summed to create a single fatigue scale with a range of 0 to 52 [Acaster et al, 2015].

9.2 Schedule of Events

For a detailed SOE (including all protocol-required assessments, visits, and visit windows) please refer to Table 1 (Year 1) and Table 2 (Year 2 to SFV).

9.2.1 Screening Visit (Assessment Visit 1)

The Screening Period starts on the date the first Screening assessment is completed after signing the ICF. The Screening Visit (Visit 1) will take place within 42 days prior to Visit 2 (Baseline, Day 1). Every effort should be made to perform all visit assessments on the same day. If necessary, it is acceptable to conduct assessments over multiple days and Investigators are encouraged to complete all assessments within 1 week. The initial Screening assessments

performed over this 42-day period will include provision of informed consent; review of inclusion / exclusion criteria; complete physical examination (including weight and height); vital signs measurements, including weight and height; medical history (including historical serology for viral infections [HIV, HBsAg, HCV, CMV, and EBV; and test for HIV and HBsAg if seronegative or unknown]); a urine pregnancy test (for WOCBP); TB screening (QuantiFERON-TB Gold and Chest X-ray); 12-lead ECG; blood and urine sample collection for central laboratory assessments per SOE, eGFR, IgG monitoring, DSA MFI scores (if not confirmed within 6 months prior to the start of Screening), Renal biopsy (if previous biopsy is not within 12 months) prior to the start of Screening, standard urinalysis dipstick; spot urine collection (for determination of UACR); serology for HIV and HBsAg if seronegative or history unknown; DNA Viral PCR monitoring for BKV, CMV, and EBV and for HCV RNA. A rapid antigen test or PCR test for COVID-19 RNA (if applicable per Exclusion Criterion 34.A9); AE monitoring, administration of prophylactic antibiotic (as per the SOE), and review of prior and concomitant medications and entry criteria. With Sponsor approval, individual screening laboratory assessments may be repeated as appropriate to confirm eligibility.

Baseline eGFR is defined as an average of 2 pre-treatment measurements up to 8 weeks apart.

Any AEs that occur during the Screening Period (after informed consent but before Day 1 Baseline Visit [Visit 2]) will be recorded as medical history. Note: Any AE that meets the definition of an SAE (see Section 10.1.3) must be immediately reported to CSLB (or its delegate [eg, CRO]) within 24 hours of site awareness (see Section 10.3.2).

Informed consent must be in place prior to washout of prohibited medications. If more than 30 days passes between signing informed consent and the Screening Visit, it must be re-signed and re-dated at Screening to reaffirm the subject's continued interest to participate in the study.

If a subject has not undergone a qualifying kidney biopsy within 12 months prior to the start of Screening, one can be performed after signing consent, provided no intervening treatments have been administered and the results can be obtained and reviewed prior to randomization.

The local pathologist's biopsy diagnosis must be reviewed by a central pathologist to confirm eligibility for entry into the study.

At Screening, local laboratory results for DSA will be reviewed by the central HLA reviewer to confirm DSA eligibility criteria. If the presence of HLA DSA is confirmed within 6 months prior to the start of Screening, the test does not need to be repeated for eligibility. If the central HLA reviewer disagrees with the local laboratory results, the central laboratory may repeat the Screening DSA test once; the repeat results must be reviewed by the central HLA reviewer to confirm DSA eligibility criteria.

In cases where local DSA testing is unavailable at the site, Screening DSA will be conducted by the central laboratory and reviewed by the central HLA reviewer to confirm eligibility.

A subject determined to be a screen failure for either clinical or administrative reasons may be rescreened twice. Note: a subject being rescreened is not required to have a repeat chest X-ray for TB screening if the first screening chest X-ray was without clinically relevant findings and conducted within 6 months from the start date of rescreening. In addition, laboratory assessments do not need to be repeated if the prior Screening laboratory assessments were deemed acceptable for entry into the study and were conducted within 3 months of the prior Screening date.

9.2.2 Treatment Procedures

Throughout the Treatment Period, subjects will return to the clinic Q4W for investigational treatment with clazakizumab / placebo until the subject permanently discontinues IP, withdraws from the study, experiences allograft loss, dies, or reaches the CTED, whichever occurs first. Per the SOE (see Table 1 and Table 2), dosing with IP is scheduled to occur on Day 1 Baseline (Visit 2) through the CTED.

Before dosing, the following assessments will be conducted at Day 1 Baseline (Visit 2) through the CTED:

- AEs and concomitant medications (will be collected and recorded prior to the conduct of any other study assessments).
- Urine pregnancy test for WOCBP.
- Blood collection for the central laboratory analysis of eGFR.
- Review of the most recent safety laboratory tests (clinical chemistry, CBC, lipid, and hsCRP) and BKV, CMV & EBV DNA Viral PCR monitoring) results from a prior visit (scheduled or otherwise) to confirm if the subject is eligible to receive IP according to the safety limits for these criteria or if the dose of IP should be modified, temporarily

withheld, permanently discontinued, or restarted and / or if modification of the dose of background immunosuppression is recommended (see Section 7.5).

- Every effort should be made to start treatment with prophylactic antibiotic for PJP approximately 1 week prior to starting IP.

Additional assessments will be conducted prior to dosing, as detailed in the SOE, and include the following:

- A check of all inclusion / exclusion criteria (Visit 2 [Baseline, Day 1] only).
- Randomization (Visit 2 [Day 1] only).
- Abbreviated physical examination (including vital signs).
- ECG.
- Blood and urine sample collection for additional central laboratory analyses as detailed in Table 8 and in the SOE. A minimum of 10 hours of fasting are required for determination of fasting glucose and lipids / triglycerides. At relevant visits per the SOE, MMF / MPA and CNIs are to be withheld until after collection of the blood sample for determination of MPA levels and CNI trough levels.
- Renal biopsy (Visit 16; may be performed at an earlier visit if clinically indicated).
- DSA MFI scores.
- DSA titers.
- IL-6 levels (total and free).
- HRQoL.

At Visit 3, the only assessment conducted will be blood sample collection for monitoring of CNI trough levels. Therefore, attendance at this visit is required only if the subject is taking a CNI. As noted above, CNIs are to be withheld until after collection of the blood sample for determination of CNI trough levels.

9.2.2.1 Optional Home Health Visits

At some sites, home / workplace visits may be offered as an option instead of in-clinic visits for certain visits during the treatment phase (Table 1, Table 2, and Appendix 2). Home / workplace visits will be conducted by a qualified home health service provider. This service may not be available for all subjects at all sites.

Prior to each home / workplace visit, the Investigator will review the most recent LFT and CBC analyses and viral monitoring results from a prior visit (scheduled or otherwise) to confirm if the subject is eligible to receive IP according to the safety limits for these criteria or if the dose of IP should be modified, temporarily withheld, permanently discontinued, or restarted, and / or if modification of the dose of background immunosuppression is recommended (see Section 7.5). Note: if a dose modification (including withdrawal, discontinuation, or restart) of the IP and / or background immunosuppression is required, the subject should be called for an in-clinic visit.

If the subject is confirmed as eligible to receive IP, the site pharmacy will be notified to dispense IP. IP will be sent by courier to the subject's home / workplace where it will be received by the home health service provider.

A home health service provider will travel to the subject's home / workplace and conduct the following assessments prior to dosing (if applicable):

- AEs and concomitant medications (will be collected and recorded prior to the conduct of any other study assessments).
- Pregnancy test for WOCBP.
- Blood collection for the central laboratory analysis of eGFR and blood collection for PK / PD Substudy sample analysis.

Additional assessments will be conducted before dosing every 4 to 24 weeks, as detailed in the SOE, and include the following:

- Abbreviated physical examination (including vital signs).
- ECG (every 52 weeks).
- Blood and urine sample collection for additional central laboratory analyses as detailed in Table 8 and in the SOE. A minimum of 10 hours of fasting are required for determination of fasting glucose and lipids / triglycerides. At relevant visits per the SOE, MMF / MPA and CNIs are to be withheld until after collection of the blood sample for determination of MPA levels and CNI trough levels.

Following all assessments, the home health service provider will administer the IP as applicable.

The schedule of mandatory in-clinic visits is summarized in Table 10. Note: an in-clinic visit is required if a subject meets the primary efficacy endpoint (composite all-cause allograft loss). Furthermore, at the discretion of the Investigator, a subject may be required to attend additional in-clinic visits if clinically indicated (eg, because of an AE).

Table 10 Schedule of Mandatory In-Clinic Visits

Visit Number (Visit Day / Week)	Mandatory In-Clinic Visit
Visit 1 (Screening)	✓
Visit 2 (Day 1)	✓
Visit 4 (Week 4)	✓
Visit 6 (Week 12)	✓
Visit 9 (Week 24)	✓
Visit 15 (Week 48)	✓
Visit 16 (Week 52)	✓
Visit 22 (Week 76)	✓
Visit 28 (Week 100)	✓
Visit 34 (Week 124)	✓
Visit 40 (Week 148)	✓
Visit 46 (Week 172)	✓
Visit 52 (Week 196)	✓
Visit 58 (Week 220)	✓
Visit 64 (Week 244)	✓
Visit 70 (Week 268)	✓
Visit 76 (Week 292)	✓
Visit 82 (Week 316)	✓
Visit 88 (Week 340)	✓
Visit 94 (Week 364)	✓
EOT / Early Withdrawal	✓
SFV	✓
Q6M after permanent DC of IP	✓
CTEV	✓

CTEV = common treatment end visit; EOT = End of Treatment; Q6M = every 6 months; SFV = safety follow-up visit;
Note: An in-clinic visit is required if a subject meets the primary efficacy endpoint (composite all-cause allograft loss); and, at the discretion of the Investigator, if clinically indicated (eg, because of an AE).

All other visits can be home / workplace visits unless the subject is required to be seen at an in-clinic visit at the discretion of the Investigator (eg, even if a visit was previously planned to take place at home or workplace).

9.2.3 Modifications to the Visit Schedule Due to Extraordinary Circumstances

Visits 3 through 94 / EOT as described in Section 9.2 of the protocol, may be conducted as remote visits during extraordinary circumstances, with permission from the Investigator.
Note: Remote visits will be allowed only where home health service providers are available and are allowed by local regulation. Table 11 summarizes the site visits allowed to be completed as remote visits.

Table 11 Schedule of "Mandatory In-clinic" Visits that may be Completed as Remote Visits During Extraordinary Circumstances

Visit Number (Visit Day / Week)	Assessments Not Available During Remote Visits	
	All Regions	Outside North America
Visit 4 (Week 4)	–	APE
Visit 6 (Week 12)	ADA, Clazakizumab, ECG	APE
Visit 9 (Week 24)	ADA, Clazakizumab, ECG	APE
Visit 15 (Week 48)	ADA, Clazakizumab, ECG	APE
Visit 22 (Week 76)	ADA, Clazakizumab	APE
Visit 28 (Week 100)	ADA, Clazakizumab, ECG	APE
Visit 34 (Week 124)	ADA, Clazakizumab	APE
Visit 40 (Week 148)	ADA, Clazakizumab	APE
Visit 46 (Week 172)	ADA, Clazakizumab	APE
Visit 52 (Week 196)	ADA, Clazakizumab	APE
Visit 58 (Week 220)	ADA, Clazakizumab	APE
Visit 64 (Week 244)	ADA, Clazakizumab	APE
Visit 70 (Week 268)	ADA, Clazakizumab	APE
Visit 76 (Week 292)	ADA, Clazakizumab	APE
Visit 82 (Week 316)	ADA, Clazakizumab	APE
Visit 88 (Week 340)	ADA, Clazakizumab	APE
Visit 94 (Week 364)	ADA, Clazakizumab	APE

ADA = anti-drug antibody; APE = abbreviated physical examination (including vital signs); ECG = electrocardiogram.
Note: An in-clinic visit must be completed if a subject meets the primary efficacy endpoint (composite all-cause allograft loss).

All scheduled study procedures and assessments should be completed at any remote visit except for the following:

- All regions:
  - Anti-clazakizumab antibody (ADA).
  - Clazakizumab drug level, ECG, renal biopsy.

- Outside North America:
  - Abbreviated physical examination (including vital signs).

The following site visits are **not** permitted to be completed remotely:

- Visit 1 (Screening).
- Visit 2 (Day 1, Baseline).
- Visit 16 (Week 52).
- EOT / Early Withdrawal Visit.
- CTED Visit.

9.2.4 End of Treatment (or Early Treatment Withdrawal) Procedures

When a subject completes the study (ie, reaches any of the non-fatal composite all-cause allograft loss endpoints, or if the subject is withdrawn early, or if the CTED is reached), all assessments for EOT / Early Withdrawal will be completed per the SOE. For further information on withdrawal procedures and criteria, see Section 5.5.

Assessments at EOT / Early Withdrawal will include the following:

- AEs and concomitant medications (recorded prior to the conduct of other study assessments).
- Abbreviated physical examination (including vital signs) and ECG.
- Pregnancy test for WOCBP.
- Blood and urine sample collection for central laboratory analyses (safety laboratory tests [clinical chemistry, CBC, lipids, hsCRP], BKV, CMV, and EBV DNA Viral PCR monitoring, IgG monitoring, DSA MFI scores, DSA titers, eGFR, UACR, IL-6 levels [total and free]). A minimum of 10 hours of fasting is required for determination of fasting glucose and lipids / triglycerides. MMF / MPA and CNIs are to be withheld until after collection of the blood sample for determination of MPA levels and CNI trough levels.
- Clazakizumab drug levels and anti-clazakizumab antibodies.
- Renal biopsy (if the subject withdrawal on or after Visit 6 [Week 12] and prior to Visit 16 [Week 52], and the subject has not had a biopsy within this period).
- HRQoL including the EQ-5D-5L, KDQoL-36, and the FACIT Fatigue Scale.

Subjects who permanently discontinued investigational treatment with clazakizumab / placebo, and who have not reached a composite endpoint of all-cause allograft loss will continue in the study as described in Section 9.2.5.3. Following the in-clinic EOT / Early Withdrawal Visit within 4 weeks of receiving the last dose of IP, all subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. In addition, all subjects will be contacted by telephone call 1, 2, and 4 months after last dose of IP for monitoring for new AEs, SAEs, or pregnancies.Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data. If a subject is unable to return for 6-monthly follow-up visits, he / she will be asked to agree to be contacted at CTED to collect allograft and survival status.

Depending on the timing of early treatment discontinuation, this follow-up may consist of assessments conducted at regularly scheduled visits per-protocol and / or monthly follow-up TCs as needed and the SFV to complete 5 months of safety monitoring following their last dose of IP. Subjects who permanently discontinued treatment with IP ≥ 5 months before their EOT Visit (and complete the remainder of the study visits) will not require any follow-up TCs.

Only if a subject is **unable** / **unwilling** to continue in the study will he / she be withdrawn from the study. Every effort should be made before the subjects withdraws from the study, either voluntarily or at the Investigator's discretion, to undergo EOT assessments and safety follow-up as it is in the best interest of the subject. If possible, the subject will return for an in-clinic EOT / Early withdrawal visit within 4-weeks of the subject's last dose of IP. If the subject agrees to the safety follow-up following the EOT/ Early withdrawal visit, the subject will be asked to return for 2 in-clinical Safety Follow-up Visits, 3 and 5 months after the last dose of IP. Subjects may be called in for a clinic visit during the 5-month Follow-up period at the discretion of the investigator (see Section 5.5). Subjects who withdraw consent from further participation from all aspects of study participation will not undergo further assessments.

9.2.5 Study Procedures Based Upon Subject Disposition

Every effort should be made to retain subjects in the study and ensure attendance to the scheduled study visits up to the CTED, including those required after early discontinuation of IP. Detailed procedures for subjects who reach any of the non-fatal composite all-cause allograft loss or irreversible loss of allograft function endpoints, discontinue IP, withdraw from study, or are still on treatment until the CTED are outlined below.

9.2.5.1 Subjects Who Reach the Endpoint of "Sustained 40% Decline in eGFR from Baseline"

Subjects who reach the endpoint of sustained 40% decline in eGFR from Baseline (but did not reach a non-fatal endpoint components of allograft failure) will continue to receive double-blind medication until they reach any of the other primary endpoints of allograft loss. The subject will remain in the study attending all regular clinic visits and undergoing all assessments per the SOE. IVIG and PLEX may be administered at the discretion of the PI to these subjects if they have completed the Week 52 visit. Double-blind medication and IVIG should be administered 2 weeks apart due to potential binding of IVIG to clazakizumab. For treatment with IVIG, subjects may be called in for unscheduled visits between regularly scheduled dosing with IP according to the SOE.

9.2.5.2 Subjects Who Met Any of the Other Composite Non-fatal All-cause Allograft Loss Endpoints

Subjects will return for an in-clinic visit to undergo all assessments per the EOT / Early Withdrawal Visit schedule (Table 1 or Table 2). Following the EOT / Early Withdrawal Visit, all subjects will be contacted monthly by TC for 5 months after the last dose of IP for monitoring of new AEs, SAEs, or pregnancies. Subjects may be called in for a clinic visit during the 5-month Follow-up period at the discretion of the Investigator.

An in-clinic SFV will be performed after the 5-month Follow-up period. Assessments performed at the SFV are as follows:

- Pregnancy test (for WOCBP), safety laboratory tests (clinical chemistry, CBC, lipids, hs-CRP), DSA MFI scores, eGFR, UACR, and IL-6 levels (total and free).
- AEs and concomitant medications (recorded prior to the conduct of other study assessments).
- Blood sample collection for clazakizumab serum levels and for anti-clazakizumab antibodies.

9.2.5.3 Subjects Who Permanently Discontinued Investigational Product

The reason for IP discontinuation should be documented at the time of discontinuation.

Subjects who discontinue IP for any reason will remain in the study and be followed for composite all-cause allograft loss and irreversible loss of allograft function events, or until the CTED is reached, whichever occurs first.

Subjects who subsequently reach the endpoint of sustained (≥ 60 days) 40% decline in eGFR from Baseline will continue to remain in the study and will be followed for all-cause allograft loss events, or until subject withdraws from the study, or until the CTED is reached, whichever occurs first.

If possible, the subject should return for an in-clinic visit within 4-weeks of the last dose of IP for an EOT / Early Withdrawal Visit to undergo all assessments per Table 1 or Table 2. Following the EOT / Early Withdrawal Visit, all subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. In addition, all subjects will be contacted by TC 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data. If a subject is unable to return for 6-monthly follow-up visits, he / she will be asked to agree to be contacted at CTED to collect allograft and survival status.

- Note: Subjects who permanently discontinue treatment with IP ≥ 5 months before their EOT visit (and complete the remainder of the study visits) will not require any follow-up TCs.

An in-clinic SFV should be performed after the 5-month Follow-up period. Assessments performed at the SFV are as follows:

- Pregnancy test (for WOCBP), safety laboratory tests (clinical chemistry, CBC, lipids, hs-CRP), DSA MFI scores, eGFR, UACR, and IL-6 levels (total and free).
- AEs and concomitant medications (recorded prior to the conduct of other study assessments).
- Blood sample collection for clazakizumab serum levels and for anti-clazakizumab antibodies.

9.2.5.4 Subjects Who Withdraw from the Study (ie, Withdrawal of Consent from Further Participation in the Study, Including any Contact by Study Site Personnel)

The reason should be documented at the time of withdrawal.

Every effort should be made before the subjects withdraws from the study, either voluntarily or at the Investigator's discretion, to undergo EOT assessments and safety follow-up as it is in the best interest of the subject. If possible, the subject will return for an in-clinic EOT / Early withdrawal visit within 4-weeks of the subject's last dose of IP (Table 1 or Table 2).

If the subject agrees to the safety follow-up following the EOT/ Early withdrawal visit, all subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. In addition, all subjects will be contacted by TC 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies.

An in-clinic SFV should be performed after the 5-month Follow-up period. Assessments performed at the SFV are as follows:

- Pregnancy test (for WOCBP), safety laboratory tests (clinical chemistry, CBC, lipids, hs-CRP), DSA MFI scores, eGFR, UACR, and IL-6 levels (total and free).
- AEs and concomitant medications (recorded prior to the conduct of other study assessments).
- Blood sample collection for clazakizumab serum levels and for anti-clazakizumab antibodies.

If a subject refuses an EOT / Early withdrawal visit, safety follow-up TCs, and /or SFV, the reason for refusal should be fully documented in the subject's source document and recorded in the electronic case report form (eCRF).

9.2.5.5 Subjects Who are Still on Study When the Common Treatment End Date is Reached

Once the CTED is reached, the study will be closed. As per Section 4.4, clazakizumab will be offered to all study subjects at the discretion of the treating physician after the completion of the study.

Subjects who are still receiving IP, subjects in the 5-month safety follow-up period, and subjects who are being followed Q6M will return for an in-clinic CTEV. Subjects who are being followed for allograft and survival status will be contacted by telephone. The CTEV should occur within 4 weeks of the CTED being reached in order to complete the SOE assessments as described in Table 1 and Table 2.

Assessments performed at the CTE Visit are as follows:

- AEs and concomitant medications (recorded prior to the conduct of other study assessments).
- Abbreviated physical examination (including vital signs) and ECG.
- Pregnancy test for WOCBP.

- Blood and urine sample collection for central laboratory analyses (safety laboratory tests [clinical chemistry, CBC, lipids, hsCRP], BKV, CMV, and EBV DNA Viral PCR monitoring, IgG monitoring, DSA MFI scores, eGFR, UACR, IL-6 levels [total and free]). A minimum of 10 hours of fasting is required for determination of fasting glucose and lipids / triglycerides. MMF / MPA and CNIs are to be withheld until after collection of the blood sample for determination of MPA levels and CNI trough levels.
- Clazakizumab drug levels and anti-clazakizumab antibodies.
- HRQoL including the EQ-5D-5L, KDQoL-36, and the FACIT Fatigue Scale.

After the CTEV, any SAE, adverse event of special interest (AESI), AE assessed as related to IP, or pregnancy discovered by the Investigator for 5 months after each individual subject's last dose of IP is to be reported on the SAE Data Collection form (paper) to CSLB GCSP and will be documented in the CSLB safety database only.

9.2.6 Unscheduled Visits

Unscheduled visits may be performed during the study for safety reasons. Only the data relevant to the purpose of the visit will be collected in the source documents and eCRF.

Subjects who permanently discontinued treatment with IP may be called into the clinic for an unscheduled visit at the discretion of the Investigator. Subjects who permanently discontinued investigational treatment with clazakizumab / placebo and who have not reached an endpoint of composite all-cause allograft loss or death, will remain in the study and will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after last dose of IP. Thereafter, the subject will be asked to return in 6-month intervals until CTED is reached to collect renal function and allograft status data as described in Section 9.2.5.3.

10. Evaluation, Recording and Reporting of Adverse Events, Serious Adverse Events, and Special Situations

10.1 Definitions

10.1.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered IP and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of IP, whether considered related to the IP or not.

A treatment-emergent AE (TEAE) is defined as any AE after exposure to IP or any AE present prior to exposure that worsens in either intensity or frequency following the first administration of the IP.

10.1.2 Definition of Adverse Drug Reaction

In the pre-approval clinical experience with a new IP or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to an IP related to any dose should be considered ADRs. The phrase "responses to an IP" means that a causal relationship between an IP and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out. For instructions regarding determination of causality, see Section 10.2.2.

10.1.3 Definition of Serious Adverse Event

An SAE is defined as any AE or suspected adverse reaction that, in the view of either the Investigator or Sponsor, results in any of the following outcomes:

- Death.
- A life-threatening AE. (Note: the term life-threatening in definition of an SAE refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.)
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly / birth defect.
- Important medical events (see below).

Important medical events that may not be life-threatening, nor require hospitalization, nor result in death may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following hospitalizations are not considered SAEs in this study:

- A visit / admission to the emergency room and / or any other hospital department for < 24 hours (unless considered an important medical or life-threatening event).
- Elective surgery planned prior to signing informed consent for this study.
- Admissions as per-protocol for a planned medical / surgical procedure (eg, renal biopsy).
- Routine health assessment requiring admission for Baseline / trending of health status (eg, routine colonoscopy).
- Medical / surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical / surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

The Investigator is encouraged to discuss with the Sponsor or Medical Monitor any AEs for which the issue of seriousness is unclear or questionable.

10.1.4 Definition of Adverse Events of Special Interest

AESIs are AEs of scientific or medical concern for which ongoing monitoring and rapid communication is important. These may include events that are either specific to the IP or events that, in general, may be of clinical significance with any medicinal product under development. As such, an AESI may or may not be related to the IP**.** AESIs should be reported following expedited reporting procedures as described for SAEs (Section 10.3.2) regardless of seriousness and causality.

For clazakizumab, the following AESIs have been defined: LFT abnormalities, neutropenia, thrombocytopenia, hyperlipidemia, GI perforations, hypersensitivity and anaphylaxis, malignancy, and opportunistic infections. Each of these AESIs is discussed in detail in the following sections. Details regarding a temporary or permanent dose reduction to 6.25 mg SC Q4W are provided in Section 7.5.

10.1.4.1 Liver Function Test Abnormalities, Neutropenia, Thrombocytopenia, and Hyperlipidemia

Throughout the trial, subjects will have regular hematology and biochemical laboratory tests to monitor for abnormal LFTs, neutropenia, thrombocytopenia, and hyperlipidemia. In general, these and any other abnormal test results that meet CTCAE (Version 5.0) definition

of Grade 3 (severe) or higher should be considered an AESI and IP should be withheld or discontinued, in consultation with the Medical Monitor.

Specifically, as detailed in Section 5.6, IP should be withheld or discontinued for subjects who meet any of the following criteria.

If the following laboratory abnormalities are observed an AESI should be reported:

- AST / ALT > 5 x ULN.
- Total bilirubin > 3 x ULN.
- AST / ALT > 3 to ≤ 5 x ULN and total bilirubin ≥ 2 x ULN (or INR > 1.5).
- Neutrophil count < 1000 cells per mm^3.
- Platelets < 50,000 cells per mm^3.
- Total cholesterol > 400 mg/dL (> 10.34 mmol/L), irrespective of Baseline level.
- Triglyceride > 500 mg/dL (> 5.7 mmol/L), irrespective of Baseline level.

10.1.4.2 Gastrointestinal Perforation

Gastrointestinal perforation is an identified risk of treatment with anti-IL-6 antibodies and must be reported as an AESI (see Section 8.1.5).

10.1.4.3 Hypersensitivity and Anaphylaxis

Hypersensitivity reactions and anaphylaxis meeting the definition of the Joint NIAID / FAAN Second Symposium [Sampson et al, 2006] on Anaphylaxis should be reported as AESIs:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
  - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
  - Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia (collapse), syncope, incontinence).

10.1.4.4 Malignancy

Any new malignancy or progression of preexisting malignancy (excluding non-melanoma skin cancers [squamous cell or basal cell carcinoma]) should be reported as AESIs.

10.1.4.5 Opportunistic Infections

Throughout the trial, monitoring for potential infections will follow the recommendations of the American Society of Transplantation [Humar and Michaels, 2006] and the KDIGO guideline [Kidney Disease: Improving Global Outcomes, 2009]. Recognized viruses that cause significant morbidity in kidney transplant recipients such as BKV, CMV and EBV will be monitored by PCR at regular 4- to 24-week intervals as detailed in the SOE.

The following infections should be reported as AESIs:

- Any bacterial pneumonia or bronchitis.
- Any gram-negative bacteria GI infections (including Salmonella (enterica serotypes, Typhimurium and Enteritidis), Shigella, Campylobacter, Escherichia coli, and Clostridium difficile).
- BKV nephropathy.
- CMV infections / disease (eg, hepatitis, colitis, pneumonitis, retinitis).
- Cryptosporidiosis with Cryptosporidium.
- Invasive candidiasis.
- Invasive mycosis which includes cryptococcosis, histoplasmosis, aspergillosis and coccidioidomycosis.
- JC virus infection (progressive multifocal leukoencephalopathy).
- Hepatitis B virus and HCV infections.
- Human papillomavirus (HPV) disease.
- HIV infection.
- Pneumocystis pneumonia with Pneumocystis jirovecii.
- Mycobacterium tuberculosis infections and other mycobacterium infections (eg, Mycobacterium kansasii, Mycobacterium avium).
- Non-CMV viral diseases including herpes simplex virus Type 1 (HSV-1) and Type 2 (HSV-2) disease, varicella zoster virus disease, human herpesvirus-8 (HHV-8) disease.
- Toxoplasmosis infections with Toxoplasma gondii.
- Severe respiratory syndrome coronavirus 2 (SARS-CoV-2) infections (COVID-19).

The above list is not meant to be complete and other infections which are not commonly observed in the kidney transplant population should also be considered an AESI by the Investigator or Sponsor.

Specifically, as detailed in Section 5.6.4, IP should be permanently discontinued for subjects who meet any of the following laboratory criteria and these abnormalities should be reported as AESIs:

- BKV ≥ 10,000 copies/mL (≥ 3200 IU/mL; ≥ 3.51 log IU/mL) or biopsy-proven BKV nephropathy.
- EBV ≥ 10,000 copies/mL (≥ 20,400 IU/mL; ≥ 4.31 log IU/mL) or post-transplant lymphoproliferative disorder or primary EBV infection in seronegative recipient.

10.2 Classification of Adverse Events

10.2.1 Severity Classification

The severity of all AEs should be assessed and graded according to the National Cancer Institute's CTCAE Version 5.0 [NCI, 2017] (see Table 12).

Table 12 Adverse Event Severity Grading

Grade (Severity)	Description
Grade 1 (mild)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (moderate)	Minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
Grade 3 (severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
Grade 4 (life-threatening)	Life-threatening consequences: urgent intervention indicated.
Grade 5 (death)	Death related to AE.

AE=Adverse event.
Source: National Cancer Institute's CTCAE Version 5.0 [NCI, 2017].

The term severe is often used to describe the intensity (severity) of a specific event; however, the event itself may be of relatively minor medical significance (eg, a severe headache). This is not the same as "serious", which is based on the subject / event outcome or action criteria as described in Section 10.1.3. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

Note: AEs of severity Grades 4 and 5 fulfill the definition of an SAE and require expedited reporting (see Section 10.3.2).

10.2.2 Relationship to Investigational Product

For all collected AEs, the clinician who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his / her clinical judgment. The degree of certainty about causality will be graded using 2 categories (related / unrelated) as shown in Table 13.

Table 13 Adverse Event Relationship to Investigational Product

Term	Relationship	Description
Related	Yes	The temporal relationship of the clinical event to IP administration indicates a causal relationship, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
Unrelated	No	The temporal relationship of the clinical event to IP administration does not indicate a causal relationship, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

IP = investigational product.

10.2.3 Outcome Categorization

Outcome of AEs should be classified as follows: recovered / resolved (ie, without sequelae); recovered / resolved with sequelae; recovering / resolving; not recovered / not resolved; fatal; or unknown (if follow-up is not possible).

If the outcome of an SAE is reported as recovered / resolved with sequelae, the Investigator should specify the kind of sequelae on the SAE form. If the outcome of an SAE is reported as unknown, it should be recorded as continuing at the end of the study.

10.2.4 Preexisting and Worsening of Medical Condition

A preexisting medical condition is one that is present at the Screening Visit and prior to randomization. Such conditions should be recorded on the medical history eCRF. A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

Note: If a preexisting medical condition meets the definition of an SAE (see Section 10.1.3) it must also be immediately reported to CSLB (or its delegate [eg, CRO]) within 24 hours of site awareness (see Section 10.3.2).

10.2.5 Symptoms of the Disease Under Study

Signs and symptoms of the disease under study will not be classed as AEs if they are within the normal day-to-day fluctuation of the disease. An explanation of these circumstances must be written in the source documents. Worsening of disease symptoms, however, will be recorded as an AE, and clearly marked on the eCRF as worsening of the signs or symptoms.

10.2.6 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation should be reported as an AE if the change is considered clinically relevant in the opinion of the Investigator.

10.2.7 Physical Examinations and Vital Signs

Worsening of any physical examination findings or vital signs, or any new physical examination findings are to be reported as an AE if the change is considered clinically relevant in the opinion of the Investigator, or in the case of vital signs, if a shift from a normal to a pathological value is observed, or a further worsening of an already pathological value is observed and similarly, the change is considered clinically relevant.

10.2.8 Special Situations

All special events including medication error must be documented in the subject's eCRF and source documentation. If any such event meets the criteria for seriousness, the event must be reported as an SAE.

Special situations which may apply are: overdose, medication error, food or drug interaction, or an unexpected therapeutic effect.

10.3 Reporting Procedures for Adverse Events, Serious Adverse Events and Pregnancy

10.3.1 Reporting of Adverse Events

All AEs either observed by the Investigator or one of his / her medical collaborators, or reported by the subject spontaneously, or in response to a direct question, will be noted in the subject's eCRF and source documents. This applies to all AEs regardless of presumed

relationship to the study treatment, including the IP and placebo arm. Adverse events leading to dose modification, withholding, or discontinuation of IP should also be collected.

For all AEs, the date of onset, relationship to IP, any action taken, date of resolution (or the fact that it is continuing or has become chronic), outcome, intensity (worst at any point during the event), and whether the AE was serious or not at any time during the event will be recorded. In order to establish the duration of any SAE, the dates of hospitalization and discharge or dates of meeting other SAE criteria will be recorded.

Where possible, the Investigator should report a diagnosis rather than individual signs and symptoms or abnormal laboratory values. However, if an aggregate of signs and / or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the eCRF. If a diagnosis is known, the underlying medical diagnosis of an event should be recorded by preference in the listing of individual symptoms.

The Investigator should use standard medical terminology / concepts and avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in each event field in the eCRF.

The AE reporting period will begin at the time the ICF is signed by the subject, and 1 Screening procedure is performed, and continues for 5 months after the last dose or date of withdrawn consent. All AEs that occur during the Screening Period are to be recorded as medical history. Any AE that meets the definition of an SAE (see Section 10.1.3) must also be immediately reported to CSLB (or its delegate [eg, CRO]) within 24 hours of site awareness (see Section 10.3.2).

Serious adverse events persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilization has occurred (or the subject is lost to follow-up and cannot be contacted) and recorded in the source documents. Non-serious AEs ongoing at the end of the Follow-up period (5 months after the last dose) will be recorded as ongoing and will not be followed up further.

If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc.

To avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as "How are you feeling?" It is also important to question the subject in a non-leading way

about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms / conditions reported during assessments and deemed to be clinically significant by the Investigator will be considered AEs.

10.3.2 Reporting of Serious Adverse Events

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).

The occurrence of an SAE, whether related or unrelated, must be immediately reported to CSLB (or its delegate [eg, CRO]) within 24 hours of site awareness by email or facsimile as follows:

Email: adverse.events.global@cslbehring.com (email is the preferred option)
FAX: +49-6421-39-4775

The Investigator is responsible for submitting an SAE to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) per local reporting requirements. Detailed SAE reporting procedures will be specified in separate study instructions.

All SAEs ("related" or "not related") will be reported once the ICF is signed, and 1 screening procedure has been completed. In addition, all SAEs will be reported for 5 months after the last dose or consent is withdrawn. If the Investigator has not seen the subject at a clinic visit at the end of the reporting period, the Investigator must make reasonable efforts to contact the subject to inquire about SAEs. In case of withdrawal of consent, the reporting period ends at the time of withdrawal.

All SAEs will be followed until satisfactory resolution or until the site Investigator deems the event to be chronic or stable, or the subject is lost to follow-up. Other supporting documentation of the event may be requested by the Sponsor and should be provided as soon as possible. In circumstances where the Investigator is unable to contact the subject, the Investigator must provide a written statement to CSLB confirming that the subject is lost to follow-up.

The onset date of the SAE is defined as the date the signs and symptoms / diagnosis became serious. The resolution date of the SAE is defined as when the symptoms resolve, or the event is considered chronic or stable, and / or if the seriousness criteria are no longer applicable.

SAEs that are ongoing at the time of death will have an outcome of "unknown" recorded. SAEs resulting in a fatal outcome will have an outcome of "fatal" recorded.

Any SAE considered to have a causal relationship (ie, "related") to the IP and discovered by the Investigator at any time after the study will be reported. A rationale for the assessment of a causal relationship must be provided by the Investigator. Any safety information that is obtained after the end of the Follow-up period (ie, 5 months after the last dose of IP) will be documented in the safety database only.

A death occurring during the study or which comes to the attention of the Investigator within 5 months after the last dose or date of withdrawn consent, whether considered treatment related or not, must be reported to CSLB. Preliminary reports will be followed by detailed descriptions which will include copies of hospital case reports, autopsy reports / certificates and other documents when requested and applicable.

Additional follow-up information, if required or available, must be submitted within 24 hours of the Investigator (or site) awareness of the information.

The Investigator is encouraged to discuss with the study Medical Monitor when the issue of seriousness is unclear or questionable.

10.3.3 Reporting of Pregnancy

Any pregnancy occurring in a female subject, or in the female partner of a male subject during the study or for 5 months after the last dose of IP, should be reported to CSLB (or its delegate [eg, CRO]) within the same timelines as an SAE (ie, within 24 hours of the Investigator being notified). A pregnancy form should be used to record and report all pregnancies. The Investigator should counsel the subject (or in the case of a male subject, the subject's partner) and discuss the risks of continuing with the pregnancy and any possible effects on the fetus. A female subject must immediately inform the Investigator if she becomes pregnant during the study. Monitoring of the pregnancy in a female subject should continue until conclusion of the pregnancy. In case of a pregnancy in the female partner of a male subject, the Investigator should obtain informed consent of the pregnant partner prior to monitoring of the pregnancy.

Women who have a confirmed positive pregnancy test during the study will be permanently discontinued from IP and remain in the study and continue to attend all regular clinic visits and undergoing all assessments per the SOE and must continue to comply with all aspects of the protocol.

The outcome of all such pregnancies (including normal births) should be followed up and documented. Obtaining a subject's or partner's pregnancy outcome will be done using a special consent form. Every effort should be made to gather information regarding the pregnancy until the outcome has been determined. It will be the responsibility of CSLB, together with the appropriate support of the Investigator, to obtain this information.

Pregnancy in and of itself is not an SAE. However, complications of pregnancy such as abortion (spontaneous or induced), premature birth, or congenital abnormality are considered SAEs and will be reported.

11. Data and Safety Monitoring Board Procedures

A DSMB will be constituted to protect the safety of study subjects. The DSMB will review cumulative study data to evaluate safety, study conduct, scientific validity, and data integrity. The DSMB will receive blinded eCRF data in the form of tables and listings (prepared by an independent statistician) and review subject status changes and dosing decisions (where appropriate). Where appropriate, the DSMB may receive unblinded data (on a subject level or treatment group level) that should be reviewed in a closed session. The data should include, but is not limited to, demographics, subject enrollment, Baseline characteristics, AE data, SAE data (by severity and causality), laboratory data, dose adjustments, protocol adherence, and subject withdrawals. The DSMB will evaluate the progress of the trial, assess data quality and timeliness, subject recruitment, accrual and retention, and subject benefit versus risk. In addition, the DSMB will monitor external factors relevant to the trial, for example scientific and therapeutic developments that may affect subjects safety or ethical status. Based on the observed benefits or adverse effects, the DSMB will make recommendations to CSLB concerning continuation, termination, or modifications of the trial.

A charter document explaining the working procedures and responsibilities of the DSMB will be created and finalized after the first DSMB operational meeting and before any data review meetings.

As detailed in Section 12.11, the DSMB will conduct formal interim safety reviews after approximately 50 subjects per group and 100 subjects per group, respectively, have been randomized and received at least 1 dose of IP. Further safety reviews may be conducted at the discretion of the DSMB. A formal interim efficacy analysis (IA #2) will be conducted on the surrogate eGFR endpoint when approximately 200 subjects have completed at least 52 weeks of study participation. The adequacy of the planned sample size for this analysis will be reevaluated once approximately 100 subjects have been randomized and completed at least 52 weeks of study participation (IA #1). An independent statistician (external to the study Sponsor) will perform these unblinded interim efficacy and safety analyses and will prepare all interim data for the DSMB. Detailed procedures for maintaining the blind will be specified in the DSMB charter and / or Data Access Plan.

12. Statistical Analysis

The purpose of this study is to investigate the superiority of clazakizumab relative to placebo.

12.1 Statistical Methods

All statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute Inc. SAS / STAT, Cary, NC, US). Detailed methodology and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be finalized prior to study completion. A general overview of the planned methodology is provided below. Any deviation from the SAP will be detailed in the final clinical study report.

The primary and secondary efficacy analyses will be based on an Intention-to-Treat (ITT) and Per-protocol (PP) Analysis Set. Safety evaluations will be based on the Safety Analysis Set.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. Two-sided 95% confidence intervals will be provided when relevant.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation, minimum and maximum.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

For summary purposes, Baseline will be defined as the last available predose value; all summaries will be presented by treatment group, unless otherwise specified.

All statistical analyses will be based on the diagnosis and Banff scoring from the central pathologist.

All statistical DSA analyses will be based on the results from the central laboratory.

12.2 Sample Size and Power Calculations

As summarized in Section 2, a non-interventional historical, prospective cohort study (modeling exercise) was conducted to quantify the relationship between change in eGFR and risk of allograft failure in patients diagnosed with acute / active ABMR or CABMR following kidney transplantation. Using data from this modeling exercise, sample sizes based on eGFR data collected for a period of up to 52 weeks after diagnosis of ABMR, and assuming a 50% reduction in the rate of eGFR decline, were estimated for the risk of composite all-cause

allograft loss or irreversible loss of allograft function and "working backwards," for the interim analysis of the surrogate 52-week eGFR endpoint.

Assuming a rate of composite all-cause allograft loss or irreversible loss of allograft function survival of 24.7%% for the placebo arm over a period of approximately 48 months, at least 221 composite all-cause allograft loss or irreversible loss of allograft function events (expected to accrue in 316 subjects) will be required to provide 80% power (two-sided alpha of 0.05) to detect a 31% reduction in the relative risk of allograft loss in the clazakizumab group compared to the placebo group, assuming clazakizumab can reduce the slope of eGFR decline by 50% (see Table 14). A relative risk reduction of 31% would improve the 4-year graft survival rate from 24.7%% to 38.3%. Approximately 350 subjects (175 per group) will be enrolled to allow for 10% loss to follow-up and withdrawals.

Table 14 Sample Size Estimates for Composite All-cause Allograft Loss or Irreversible Loss of Allograft Function Based on eGFR Data Restricted to 52 Weeks Post-Diagnosis of Active ABMR

Scenario	All-Cause Graft Survival or Irreversible Loss at 4-Years Post Diagnosis of Active ABMR	Hazard Ratio, λ	Total Number of Events / Total Number of Subjects Power=80%
Mean eGFR	0 0.247	1.000	–
50% improvement in slope[(a)]	0.383	0.686	221/316

ABMR=Antibody-mediated rejection; eGFR=Estimated glomerular filtration rate.
Notes:

[a] Relative to the average slope change for the mean eGFR scenario, slope = -0.753, based on eGFR data restricted to first 12 months post-diagnosis of ABMR.
Source: Modeling Report, Section 10, Table 9-2-1b.

Once approximately 100 subjects (50 per group) have been randomized and completed at least 52 weeks of study participation, reestimation (IA #1) of the planned sample size of 200 subjects will be conducted using the inverse normal method with pre-specified information rates (0.5556, 1) to control the Type I error rate. Observed data from subjects not completing / not reaching Week 52 will also be included in the analysis. The sample size reestimation ensures a power of 95.9%, when the assumed difference between treatment groups in the 52-week eGFR of 4.515 mL/min/1.73 m^2 and a common standard deviation of 9.252 mL/min/1.73 m^2 (effect size = 4.515/9.252 = 0.488).The average sample size under these assumptions is 202 subjects (corresponding to approximately 224 randomized subjects, assuming 10% loss to follow-up or withdrawals). When the assumed eGFR effect size is 0.368, then the power is 79.6% and the average sample size is 218 subjects (approximately 242 randomized subjects). The sample size for the interim efficacy analysis surrogate

endpoint (IA #2) will not exceed a total of 250 subjects with at least 52 weeks of study participation (approximately 280 randomized subjects).

The interim efficacy analysis (IA #2) will be performed when approximately 200 (100 per group) subjects have been randomized and completed at least 52 weeks of study participation to evaluate the difference between the treatment groups. Observed data from subjects not completing / not reaching Week 52 will also be included in the analysis. As shown in Table 15, a fixed sample size of 180 subjects (90 per group) will have 90% power (two-sided alpha of 0.05) to detect a minimum difference in the 52-week eGFR of 4.515 mL/min/1.73 m^2 between the treatment groups (assuming eGFR declines at a rate of 0.75 mL/min/1.73 m^2/month in the placebo treated group and that clazakizumab reduces eGFR decline by 50%). The sample size determination for the fixed design is based on a two-sided alpha of 0.05 and a common standard deviation of 9.252 mL/min/1.73 m^2 for the mean eGFR change from Baseline to Week 52 (effect size = 4.515/9.252 = 0.488). The planned sample size has been increased to a minimum of 200 subjects to allow 10% for subjects lost to follow-up or withdrawals.

Table 15 Sample Size Estimates for Change in eGFR (mL/min/1.73 m^2) at 52 Weeks After Diagnosis of Active ABMR

Scenario	eGFR Baseline	eGFR 52 Weeks	% Change from Baseline	Slope (eGFR Change / Month)	Sample Size for Power= 90%[a]
Mean eGFR	45.577	36.547	-19.8%	-0.753	
50% improvement in slope[b]	45.577	41.062	-9.9%	-0.376	180

Notes: ABMR=antibody-mediated rejection; eGFR=estimated glomerular filtration rate.

[a] Standard deviation of the difference in eGFR from Baseline at 12 months after diagnosis of ABMR = 9.252, when restricted to 12-month eGFR data.

[b] Relative to the average slope change for the mean eGFR scenario, slope = -0.753, based on eGFR data restricted to first 12 months after diagnosis of ABMR.

Source: Modeling Report, Section 10, Table 9-2-1a.

12.3 Pharmacokinetic Analyses

For all subjects, serum concentrations of clazakizumab will be listed and summarized by nominal timepoint. The following descriptive statistics will be presented for plasma concentration summaries: n, arithmetic mean, standard deviation (SD), CV%, median, geometric mean, minimum, and maximum.

For subjects participating in the PK / PD Substudy, serum concentration-time data will be used to perform noncompartmental analysis using WinNonLin® version 5.2 (or higher). PK parameters will be calculated and summarized descriptively.

When applicable, the following PK parameters will be derived and summarized (for those participating in the PK / PD Substudy):

- Time of maximum concentration (T_{max}, $T_{max\ ss}$).
- Maximum concentration (C_{max}, $C_{max\ ss}$).
- Trough concentration (C_{trough}, $C_{trough\ ss}$).
- Area under the concentration-time curve ($AUC_{0\text{-}tau}$) at steady state.

If the data allow, additional PK parameters will be derived. The following descriptive statistics will be presented for all PK parameters, except for T_{max}: n, arithmetic mean, SD, CV%, median, geometric mean, minimum and maximum. For T_{max}, n, median, minimum and maximum will be summarized.

12.4 Pharmacodynamic Analyses

For subjects in the PK / PD Substudy, plasma IL-6 (total and free) and serum hsCRP will be summarized for all timepoints. The following descriptive statistics will be presented: n, arithmetic mean, SD, CV%, median, geometric mean, minimum, and maximum. A graphical profile of mean (SD) may also be presented. Exploratory analyses and / or modeling approaches may be used to investigate the relationship between serum clazakizumab concentrations with plasma IL-6 and / or serum hsCRP.

12.5 Analysis Sets

All decisions regarding definition of analyses sets will be made prior to unblinding.

12.5.1 Intention-to-Treat Set

The ITT set will consist of all subjects who meet the following criteria:

- Received at least 1 dose of IP.
- Had a Baseline assessment and at least 1 post-Baseline assessment.

Subjects in the ITT set will be analyzed using the intention-to-treat principle (ie, according to randomized treatment assignment). The ITT set will be used for tables of efficacy and demography, as well as relevant listings. The ITT will be the primary set for analysis of the primary efficacy endpoint.

12.5.2 Per-Protocol Set

The PP set will consist of all subjects who satisfy the ITT criteria and have no major protocol deviations that impact the primary efficacy endpoint for the final or interim analysis (as defined in the SAP).

Subjects in the PP set will be analyzed using the ITT principle (ie, according to randomized treatment assignment).

12.5.3 Safety Analysis Set

The Safety Analysis Set consists of all randomized subjects who have received at least 1 dose of IP. The subjects in the Safety Analysis Set will be analyzed according to the actual treatment received.

12.5.4 Pharmacokinetic Analysis Set

The PK Analysis Set consists of all subjects in the Safety Analysis Set with at least 1 quantifiable PK concentration of IP after administration.

12.5.5 Pharmacokinetic / Pharmacodynamic Substudy Analysis Set

The PK / PD Substudy Analysis Set consists of all subjects in the Safety Analysis Set who consent to be a part of the PK / PD Substudy and have at least 1 quantifiable PK concentration of IP after administration.

Protocol violations that may impact PK analysis will be defined in detail in the Blinded Data Review Meeting before database lock.

12.6 Baseline and Demographic Characteristics

Baseline disease and demographic characteristics will be summarized using descriptive statistics for the ITT set, grouped according to treatment group. The number and percent of subjects in each category of the randomization stratification factors will also be summarized by treatment group.

Medical history will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA, Version 21 or later) System Organ Class (SOC) and PT, according to treatment group. Prior medications will be categorized using WHO Drug (March 2018 or later) and summarized according to treatment group. Note: All AEs that occur during the Screening Period are to be recorded as medical history.

12.7 Investigational Product

The total amount of IP given will be calculated for each subject and will be compared to the amount expected to be given for each subject. Treatment compliance will be calculated for each subject and summarized using descriptive statistics.

12.8 Concomitant Therapy

Concomitant medications will be categorized using WHO Drug (March 2018 or later) and be summarized according to treatment group.

12.9 Efficacy Evaluations

Primary Estimand

The primary interest is to quantify the treatment effect of clazakizumab using a composite clinical endpoint. The primary estimand in line with the primary objective of the study is described as follows:

- Population: the target patient population defined by the eligibility criteria and the ITT analysis set.
- Variable: Time-to-event of composite all-cause allograft loss or irreversible loss of allograft function or all-cause death.
- Intercurrent event: intercurrent events are captured through the variable definition.
- Population level summary: hazard ratio of clazakizumab relative to placebo for composite all-cause allograft loss or irreversible loss of allograft function or all-cause death.

Primary Efficacy Endpoint

The primary efficacy endpoint is the time to composite all-cause allograft loss or irreversible loss of allograft function, defined as occurrence of any of the following components:

- eGFR < 15 mL/min/1.73 m^2*
- return to dialysis*
- allograft nephrectomy
- retransplantation
- death from any cause, or
- a sustained (≥ 60 days) 40% decline in eGFR from Baseline.

*total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days.

If the eGFR < 15 mL/min/1.73 m^2 is the only component reached, the value must be sustained over at least 60 days and must be confirmed by a repeat measurement after ≥60 days from the date of the first measurement. The confirmatory measurement of eGFR < 15 mL/min/1.73 m^2 done at least 60 days from the initial measurement must be processed by the central laboratory.

A stratified log rank test will be used to compare the median time-to-event between each treatment arm. Incidence rates and hazard ratios will also be presented.

To assess the robustness of the primary efficacy analysis, the primary efficacy variable will be repeated in sensitivity analyses using the PP set. An additional sensitivity analysis will address the nature of composite all-cause allograft loss or irreversible loss of allograft function as a recurrent event.

All efforts will be made to minimize missing data. Subjects who permanently discontinued treatment with IP, and who have not reached an endpoint of composite all-cause allograft loss or death, will remain in the study. Following the EOT / Early Withdrawal Visit within 4 weeks of receiving the last dose of IP, all subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after receiving the last dose of IP. In addition, all subjects will be contacted by telephone call 1, 2, and 4 months after last dose for IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data. Subjects who permanently discontinued IP treatment due to loss of their allograft will undergo EOT assessments and be contacted monthly for 5 months after the last dose of IP, followed by an in-clinic SFV per protocol.

Additional details will be documented in the SAP.

12.9.1 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed:

- Time to composite all-cause allograft loss, defined as:
  - eGFR < 15 mL/min/1.73 m^{2*}
  - return to dialysis*
  - allograft nephrectomy
  - retransplantation, or

  - death from any cause.
- Incidence and time to irreversible loss of allograft function as defined by a 40% decline in eGFR from Baseline.
- Incidence of composite all-cause allograft loss or irreversible loss of allograft function, defined by the occurrence of any of the following components:
  - eGFR < 15 mL/min/1.73 m^{2*}
  - return to dialysis*
  - allograft nephrectomy
  - retransplantation
  - death from any cause, or
  - a sustained (≥ 60 days) 40% decline in eGFR from Baseline.
- Incidence and time to death-censored allograft loss, defined as:
  - eGFR < 15 mL/min/1.73 m^{2*}
  - return to dialysis*
  - allograft nephrectomy, or
  - retransplantation.
- Change in mean eGFR from Baseline to EOT.
- Change in spot UACR from Baseline to EOT.
- Change in DSA titers and MFI scores from Baseline to EOT.
- Change in Banff lesion grading score (2015 criteria [Loupy et al, 2017]) of pre-treatment to post-treatment (Week 52) kidney biopsies.
- Incidence of acute rejection episodes (TCMR and ABMR) from Baseline to EOT.
- Overall subject survival.

*total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days.

If the eGFR < 15 mL/min/1.73 m^2 is the only component reached, the value must be sustained over at least 60 days and must be confirmed by a repeat measurement after ≥60 days from the date of the first measurement. The confirmatory measurement of

eGFR < 15 mL/min/1.73 m^2 done at least 60 days from the initial measurement must be processed by the central laboratory.

12.9.2 Pharmacokinetic / Pharmacodynamic Endpoints

The pharmacokinetic endpoints for those participating in the PK / PD Substudy will include the following:

- Maximum concentration (C_{max}, $C_{max\ ss}$).
- Trough Concentration (C_{trough}, $C_{trough\ ss}$).
- Area under the concentration-time curve ($AUC_{0\text{-}tau\ ss}$) at steady state.
- Time of maximum concentration (T_{max}, $T_{max\ ss}$).

Details of the analysis of secondary endpoints will be documented in the SAP.

12.9.3 Exploratory Analyses

Exploratory analyses may be considered prior to unblinding and will be described fully in the SAP.

Analyses will be performed to evaluate the PD of clazakizumab (IL-6 [total and free] and / or hsCRP, or others) following SC injection in kidney transplant recipients with CABMR.

Analyses will be performed to evaluate the relationship between clazakizumab PK parameters and PD parameters (IL-6 [total and free] and / or hsCRP) using a PK / PD modeling approach.

hsCRP and IL-6 (free and total) levels, plasma clazakizumab concentrations, presence of anti-clazakizumab antibodies, and other evaluations / assessments will be presented descriptively and fully described in the SAP.

Exploratory Endpoints

PK / PD Endpoints:

The PD endpoints for subjects who consent to participate in the PK / PD Substudy will include the following: evaluation of IL-6 (total), IL-6 (free), and hsCRP.

- Baseline and change from Baseline of free interleukin 6 (IL-6) in plasma.
- Baseline and change from Baseline of total interleukin 6 (IL-6) in plasma.

- Baseline and change from Baseline of hsCRP levels in serum.
- Correlation of hsCRP and IL-6 (total and free) to plasma clazakizumab plasma concentration.

Other Exploratory Endpoints

- HRQoL associated with the treatment of CABMR to Week 52 as well as to EOT.
- Change from Baseline in eGFR at 2 years.
- 40% decline in eGFR accompanied by the Investigator's decision to supplement the therapy by additional treatment.

12.9.4 Additional Analyses

CNI and MPA levels will be measured during the study. An analysis will be conducted to analyze the concentrations of these drugs. A comparison of these concentrations between the clazakizumab and placebo groups will be used to determine whether or not there have been any meaningful drug-drug PK interactions after initiation of IP. The analysis will also investigate and account for any significant differences in the doses of these drugs during the trial between the clazakizumab and placebo groups.

12.10 Safety Evaluations

The following safety endpoints will be evaluated and analyzed using descriptive statistics:

- TEAE, serious TEAEs, and AESIs.
- Viral infection monitoring for BKV, CMV, and EBV by plasma PCR.
- Laboratory tests including LFTs, CBC, plasma lipids, high-sensitivity CRP.
- Vital signs, ECGs, and physical examination.
- Incidence of anti-clazakizumab antibodies.

All AEs will be coded using MedDRA Version 21 or later and presented according to SOC and PT. All AEs, including laboratory test abnormalities, will be graded according to the CTCAE Version 5.0 or later [NCI, 2017].

The AE reporting period will begin at the time the ICF is signed by the subject, and 1 screening procedure is performed, continues for 5 months after the last dose (ie, SFV; or

date of withdrawn consent). Only TEAEs (ie, AEs occurring on or after the date of the first dose of IP) will be summarized in the clinical study report.

Frequency distributions and individual listings of all TEAEs and laboratory marked abnormalities will be generated and summarized according to treatment group.

Clinical laboratory test results at each time point and changes from Baseline will be provided. Shift tables for the hematology and biochemistry laboratory parameters, comparing values low, normal and high using the standard reference ranges, will be presented for the Baseline laboratory measurement versus the endpoint measurement for each subject.

No formal statistical tests on the treatment difference will be performed for any safety analyses. All safety presentations will be performed on the Safety Analysis Set.

Change from Baseline in vital signs, ECG, and physical examinations will also be presented descriptively.

12.11 Safety Reviews and Interim Analyses

Once approximately 50 subjects per group have been randomized and received IP, an interim safety review will be conducted by the DSMB. A second safety review will be conducted after approximately 100 subjects per group have been randomized and received IP. Further safety interim reviews will be determined at the discretion of the DSMB. Two formal interim analyses will also be conducted:

IA #1 for sample size reestimation: After approximately 100 subjects (50 per group) have been randomized and completed at least 52 weeks of study participation, a formal interim analysis will be conducted by an independent statistician to assess the adequacy of the sample size for the interim efficacy analysis of the 52-week eGFR endpoint (see IA #2 below). Observed data from subjects not completing / not reaching Week 52 will also be included in the analysis. The DSMB will review and approve the recommendation of the independent statistician. IA #1 may result in an increase in the number of subjects included in IA #2. Details of the sample size reestimation are provided in Section 12.2.

IA #2: An interim efficacy analysis of the 52-week eGFR endpoint (ie, change in mean eGFR from Baseline to Week 52) is planned when approximately 200 subjects (100 per group) have been randomized and completed at least 52 weeks of study participation. Observed data from subjects not completing / not reaching Week 52 will also be included in the analysis. Details of the sample size estimation are provided in Section 12.2. The number of subjects included

in this interim efficacy analysis may be increased by IA #1. If IA #2 shows a statistically significant ($p \leq 0.05$) and clinically meaningful treatment effect on eGFR between the clazakizumab and placebo treatment groups, the results will be submitted to regulatory authorities for expedited marketing approval. If this analysis does not reach statistical significance, then the study will continue until 221 composite all-cause allograft loss or irreversible loss of allograft function events have been observed. Any decision to stop the study in the event of non-significant effect on eGFR or to increase the sample size for the primary efficacy endpoint (time to composite all-cause allograft loss or irreversible loss of allograft function) would be made based on the recommendation of the DSMB after review of the totality of the data, ie, observed effect on eGFR, updated predicted survival based on the model using data observed in the study, and safety data. Note: the DSMB can recommend stopping the study for safety reasons at any time.

The interim efficacy endpoint will be analyzed using a mixed model repeated measures approach. The model will include terms for treatment, stratification factors, Baseline eGFR and other pre-defined covariates.

Sensitivity analyses will include the following:

- Missing values imputed using the mean of the observed values at that time point within the same treatment group.
- The delta adjustment method will be used to estimate the tipping point beyond which the active treatment would have an unfavorable effect.
- Nonparametric rank-based method where subjects will first be ranked on the time point that they last provided data, and then by the value of eGFR at that visit. A Wilcoxon rank sum test will then be applied to compare treatment groups using the ranks.

A consulting group external to the study Sponsor will perform these unblinded interim efficacy and safety analyses and will prepare all interim data for the DSMB.

A DSMB charter will be created and finalized after the first DSMB operational meeting and before any data review meetings. Detailed procedures for maintaining the blind will be specified in the DSMB charter and / or Data Access Plan.

13. Study Ethical Considerations

13.1 Ethical Conduct of the Study

The study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki [World Medical Association, 2013] and the International Council for Harmonisation [ICH, 1996] guidelines for Good Clinical Practice (GCP) CSLB will ensure that the study complies with all local, federal or country-specific regulatory requirements.

The Investigator must ensure the anonymity of all subjects participating in the study. Each subject will be assigned a unique subject identification number that should be used on all forms associated with the subject's samples or documents that will be supplied to the Sponsor (or CRO) or to any party completing testing on behalf of the Sponsor (eg, samples for central laboratory analyses). Data privacy will be maintained according to local and federal requirements and will not be released without the written permission of the subject (or the subject's guardian), except as necessary for monitoring and auditing by CSLB, its designee, the Food and Drug Administration (FDA) or other applicable Regulatory Authority, or the IRB / IEC.

All unpublished information concerning the IP, as well as any information concerning the business or operations of CSLB or its affiliates that have been provided by or on behalf of the Sponsor to the Principal Investigator and all employees and coworkers involved with this study ("Study Personnel"), are confidential and will remain the confidential information and sole property of CSLB. This includes, without limitation, information concerning the clinical indications for the IP, its formula, methods of manufacture, regulatory, marketing and strategic information, and all other scientific, nonclinical or clinical data relating to it. Study Personnel must agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission is obtained from Sponsor's authorized representative, and not to disclose, or use Sponsor's confidential information for any purpose other than performance of the study. Prior written agreement from the Sponsor's authorized representative must be obtained for the disclosure of any said confidential information to other parties.

13.2 Informed Consent

A written informed consent in compliance with Part 50 of Title 21 of the Code of Federal Regulations (CFR), with the Declaration of Helsinki, ICH guidelines, federal and / or local regulations, and advance approval by the IRB / IEC shall be obtained from each subject prior to entering the study or performing any unusual or non-routine procedure that involves risk to the subject, including washout of any medications.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the Principal Investigator or authorized designee is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study and sign and date the ICF.

The Principal Investigator is responsible for maintaining the originally signed ICF document according to record retention requirements. Each subject will be given a copy of the ICF.

If more than 30 days elapses between date of consent and Screening Visit, the subject should be asked to re-sign and re-date the consent form at Screening to reaffirm continued interest in study participation.

If any non-administrative, institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor and / or its designee, if appropriate, prior to IRB / IEC submission. Once reviewed, the consent will be submitted by the Principal Investigator or authorized designee to his or her IRB / IEC for review and approval prior to the start of the study. If the ICF is revised during the course of the study, all actively participating subjects must sign the revised form, unless otherwise indicated, ie, administrative changes.

13.3 Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB / IEC prior to participation of human subjects in research studies. Prior to the study onset, the protocol, ICF, advertisements or materials to be used for subject recruitment, and any other written information to be provided to the subject must be approved by the IRB / IEC. Any amendments to the protocol or ICF will require review and approval by the IRB / IEC before the changes are implemented to the study. Documentation of all IRB / IEC submissions / approvals and of the IRB / IEC compliance with ICH Guideline E6 will be maintained by the site and will be available for review by CSLB or its designee.

All IRB / IEC approvals should be authorized by the IRB / IEC chairman or designee and must identify the IRB / IEC name and address, the clinical protocol by title and / or protocol number, detail the specific documents reviewed, and the date that approval and / or a favorable opinion was granted.

The Principal Investigator or authorized designee is responsible for obtaining continuing review of the clinical research at intervals not exceeding 1 year or as otherwise specified by

the IRB / IEC. The Principal Investigator or sub-Investigator must supply CSLB or its designee with written documentation of continued review of the clinical research.

The IRB / IEC is expected to maintain the confidentiality of the protocol and related information.

14. Quality Control and Quality Assurance

The Investigator must ensure that all trial-related site source data, study-related documents and reports will be available, and that the provision of direct access for monitoring and auditing by CSLB or its designees will be permitted. In addition, the Investigator must ensure that all trial-related site source data, study-related documents, and reports will be made available for inspection by the appropriate Regulatory Authority and review by the IRB / IEC.

The Investigator is responsible for notifying CSLB in advance of an impending regulatory inspection. He / she may request that CSLB provide support for preparation, if necessary, and is required to provide updates on the ongoing activities during the inspection and submit any citations / objectionable findings (ie, FDA 483) and is required to share any follow-up responses to the outcome.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the Investigator's records by the Study Monitor (source document verification). The Study Monitor will also review the Investigator's drug accountability records to ensure that the drug supplies are stored and dispensed appropriately. A comprehensive validation program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, CSLB or its designates may review data as deemed necessary.

15. Administrative Procedures

15.1 Sponsor's Responsibilities

15.1.1 Study Supplies

Study sites will be provided with supplies required to manage the study. This will include but not be limited to the following:

- Investigator file(s) (for filing of all study-related documentation).
- Contact list of all relevant study personnel.
- Documentation and directions for use of relevant study questionnaires.
- eCRF and completion guidelines.
- All study forms (eg, SAE, pregnancy, drug accountability, etc.).

15.1.2 Insurance

CSLB confirms that it carries liability insurance which protects non-employee physicians or Investigators against claims for which they may become liable as a result of damages caused by CSLB products used in clinical studies. Insurance coverage is not extended to damages that the Investigators or third parties may suffer by reason of acts of commission or omission on the part of such Investigators or third parties and that are not in accordance with accepted common medical practices (lege artis procedures). CSLB will reimburse the subject for all study-related injuries provided that the injury does not arise from the subject's misuse of the IP or failure to follow the Investigator's instructions.

15.1.3 Financial Disclosure and Obligations

Principal Investigators and sub-Investigators are required to provide financial disclosure information to allow CSLB to submit the complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR and the Qualified Investigator Undertaking (QIU) form. In addition, the Principal Investigator or sub-Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

15.1.4 Investigator Training

All Investigators and their study personnel will receive training regarding the study procedures and GCP / regulations specific to the conduct of clinical trials. This training will be documented and will take place prior to enrollment and throughout the study as necessary.

It is the Investigator’s responsibility to ensure appropriate personnel receive ongoing training on important study updates or protocol modifications.

15.1.5 Study Monitoring

In accordance with current GCP and ICH guidelines, the study will be monitored by the Sponsor and / or Sponsor's representatives at all stages of study conduct from inception to completion. This monitoring will be in the form of site visits and other communication and will include review of original source documents and eCRFs. The Sponsor’s Medical Monitor or representative will notify the Principal Investigator prior to conducting any investigational site visit. The frequency of these visits will depend upon the progress of the study, and will include monitoring to assess facilities and equipment, recruiting, record-keeping, protocol adherence, data collection, AE reporting, and other factors.

The Study Monitor, as a representative of CSLB, has the obligation to follow the study closely. In doing so, the Study Monitor will visit the Principal Investigator and study facility at periodic intervals, in addition to remote review of data and maintaining necessary telephone, fax, email, and letter contact. Subject confidentiality will be maintained in accordance with local requirements.

It is the Study Monitor's responsibility to inspect source documents and the eCRFs throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The Study Monitor must have access to source documents, laboratory test reports and other subject records needed to verify the entries on the eCRF. The Study Monitor will also perform drug accountability and review the Investigator’s regulatory files to assure completeness of documentation in respect to clinical study conduct. The Investigator (or his / her deputy) agrees to co-operate with the Monitor to ensure that any problems detected during monitoring visits are resolved.

15.1.6 Medical Monitoring

CSLB will provide an independent Medical Monitor, a medical expert who advises the study Investigators and study monitors regarding protocol and subject safety questions. The role of the Medical Monitor is to review all AEs / SAEs on a regular basis throughout the study, to advise the Investigators on study-related medical questions or problems as needed, and to evaluate cumulative subject safety data and make recommendations regarding the safe continuation of the study. The Medical Monitor will remain blinded throughout the conduct of the clinical study unless unblinding is warranted to optimize management of an AE / SAE or for other safety reasons.

15.2 Investigator's Responsibilities

Medical supervision is the responsibility of the Principal Investigator named on the FDA Form 1572, trial attestation form and / or QIU. The Investigator may delegate day-to-day activities to a sub-Investigator listed on these forms but retains overall responsibility for ensuring that the study is conducted properly and in accordance with the study protocol. The Investigator is required to provide the Sponsor / CRO with his / her own curriculum vitae and applicable licensure, as well as those of the personnel assuming significant responsibility in the study (eg, sub-Investigators). The Investigator is responsible for ensuring that the study is conducted according to applicable health authorities (eg, Health Canada, Therapeutic Goods Administration, European country-specific health authorities, or FDA), sound medical practices, and in compliance with applicable regulations (eg, 21 CFR, ICH, European Union Directive and relevant country-specific requirements).

15.2.1 Reporting and Recording of Data

It is the responsibility of the Investigator to record essential information in the medical records in accordance with national regulations and requirements. The Investigator is responsible for ensuring the accuracy, completeness, legibility and timelines of the data recorded in the eCRF.

The Principal Investigator agrees to maintain accurate source documentation as part of the case histories and to accurately enter this information in the eCRFs. These source documents are distinct from the eCRFs and are designed to record all observations and other data pertinent to the investigation on each subject. The CRO will supply the eCRFs for site completion via the electronic data capture system. These eCRFs are to be completed as instructed in the eCRF completion guidelines, which will be distributed to the sites under separate cover.

The eCRFs will be reviewed and the source documents verified by the Study Monitor during routine monitoring visits, in accordance with the Clinical Monitoring Plan, to ensure that data in the eCRFs are accurate and complete.

The Investigator (or delegate) will have access to all eCOA data entered at site and / or all data reported within the subject eDiary via a secure, role-based web portal provided by an external eCOA system provider. The eCOA system provider will transfer a copy of the source data across to CSL's clinical data warehouse at a pre-defined frequency via a secure data channel for systematic review by the CSL clinical team.

The eCOA provider engaged for this study is responsible for providing a solution that conforms to all pertinent regulations. The solution is not in any way intended as a substitute for normal medical care of the subject. The vendor provides the service of hosting of the eCOA data on behalf of the study Investigators, until such a time as the Investigator is in receipt of a certified archive copy of all diary data relating to subjects at that site and has confirmed it is readable.

15.2.2 Study Records

It is the responsibility of the Investigator to ensure that a current disposition record of IP (those supplied by CSLB) is maintained at each study site where IP is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include the following:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label identification number or batch number.
- Amount dispensed to and used by each subject, including unique subject identifiers.
- Amount transferred to another area / site for dispensing or storage.
- Non-study disposition (eg, expired, lost, wasted).
- Amount destroyed at study site or returned to CSLB, if applicable.
- Dates and signature / initials of person responsible for IP dispensing / accountability, as per the Delegation of Authority Form.

Samples should be retained for bioavailability / bioequivalence, with appropriate tracking details (collection date / time etc) and be shipped to the central laboratory when requested.

CSLB will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

15.2.3 Record Retention

Essential documents should be retained until at least 25 years after the formal discontinuation or completion of the clinical trial. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with CSLB.

CSLB will notify the Investigator / institution when the study records are no longer needed.

If the Investigator withdraws from the study (eg, relocation, retirement), the records must be transferred to a mutually agreed upon designee (eg, another Investigator, IRB, EC, IEC). Notice of such transfer will be given in writing to CSLB.

The Investigator must inform CSLB immediately if any documents are lost, damaged, to be transferred to another facility, or to be transferred to a different owner.

The Investigator must contact CSLB prior to destroying any records associated with the study.

15.2.4 Protocol Violations and Deviations

The Principal Investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol and should take measures to prevent the deviation from recurring. A deviation from the protocol is an unintended and / or unanticipated departure from the procedures and / or processes approved by the Sponsor and the IRB / IEC and agreed to by the Principal Investigator. Protocol violations and deviations will be communicated by the Medical Monitor throughout the study. The Principal Investigator will be notified of violations and / or deviations in writing by the Medical Monitor. The IRB / IEC should be notified of all protocol violations and deviations according to local IRB / IEC reporting requirements.

16. Procedure for Modification of Protocol or Premature Termination of the Study

16.1 Protocol Waivers, Deviations and Violations

Protocol waivers shall not be permitted except where necessary to eliminate an immediate hazard to subjects (see Section 15.2.4). Deviations from the protocol will be assessed as minor or major on a case-by-case basis. The criteria describing the deviation(s) and how they will be handled will be documented in the SAP.

16.2 Protocol Amendments

The study shall be conducted as described in this approved protocol. Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of CSLB. Each applicable Regulatory Authority / IRB / IEC will review and approve amendments prior to their implementation. Regulatory Authority / IRB / IEC approval need not be obtained prior to removal of an immediate hazard to subjects.

16.3 Study Termination

CSLB reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include (but are not limited to) unsatisfactory subject enrollment with respect to quality and / or quantity, a site is unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and / or incomplete.

In terminating the study, CSLB and the Investigator will assure that adequate consideration is given to the protection of the subject's interests. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

17. Policy for Publication and Presentation of Data

CSLB is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles [PRMA, 2014]. Where possible, authorship will be agreed at the beginning of the study. The authors will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by CSLB before submission for publication. Names of all Investigators participating in the study will be included in the publication. The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria [ICMJE, 2018] for authorship. That is, all authors must meet each of the following 3 criteria:

- Made a substantial contribution to conception and design or acquisition of data, or analysis and interpretation of data.
- Drafted the article or revised it critically for important intellectual content.
- Approved the final version for publication.

Members of the study steering committee generally fulfill the authorship criteria through their involvement in protocol design and review, monitoring of and sometimes direct involvement with recruitment, and thus they will usually be part of the publication committee. If studies are multicenter, it may be appropriate to assign group authorship.

In addition, certain CSLB employees involved in the design and conception of the protocol, study management and data analysis and interpretation are qualified authors and will be included in the publication committee eg, the lead physician, statistician and study project manager or their equivalents.

17.1 Disclosure of Data

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted below is prohibited. Subject confidentiality will be further assured by utilizing subject identification code numbers to correspond to treatment data in the computer files.

However, such medical information may be given to the subject's personal physician, or to other appropriate medical personnel responsible for the subject's welfare.

In addition, data generated as a result of this study are to be available for inspection upon request by FDA or local health authority auditors, the Sponsor's study monitors, or by the IRB / IEC. Therefore, absolute confidentiality cannot be guaranteed.

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19. Appendices

Appendix 1 Signatures

Signature on Behalf of Sponsor

Study Title: A Pivotal Phase 3 Trial to Evaluate the Safety and Efficacy of Clazakizumab for the Treatment of Chronic Active Antibody-Mediated Rejection in Kidney Transplant Recipients

Protocol Number: CSL300_3001

I have read the Clinical Study Protocol, Amendment 9 titled "A Pivotal Phase 3 Trial to Evaluate the Safety and Efficacy of Clazakizumab for the Treatment of Chronic Active Antibody-Mediated Rejection in Kidney Transplant Recipients" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

(S

PPD

PPD

(Printed name)

PPD

(Title)

Signature of Principal Investigator

Study Title: A Pivotal Phase 3 Trial to Evaluate the Safety and Efficacy of Clazakizumab for the Treatment of Chronic Active Antibody-Mediated Rejection in Kidney Transplant Recipients

Protocol Number: CSL300_3001 Site Number:

I have read the Clinical Study Protocol, Amendment 9 titled "A Pivotal Phase 3 Trial to Evaluate the Safety and Efficacy of Clazakizumab for the Treatment of Chronic Active Antibody-Mediated Rejection in Kidney 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 on Harmonisation) and applicable regulatory requirements.

Changes to the Clinical Study Protocol will only be implemented after written approval is received from CSL Behring (CSLB) 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 2 SUMMARY TABLE OF ALL SCHEDULED STUDY VISITS

Study Day / Week	Visit Number	Mandatory In-Clinic Visit[a]	Dosing with Investigational Drug	Pregnancy Test, AEs, and Concomitant Medications	eGFR	Additional Assessments Per SOE
Year 1						
Up to -42 days (+ 2 days)	Visit 1 (Screening)[a]	X		X	X	X
Day 1	Visit 2 (Baseline)[a]	X	X	X	X	X
Week 1	Visit 3[b, d]					X
Week 4	Visit 4[a, d]	X	X	X	X	X
Week 8	Visit 5[d]		X	X	X	X
Week 12	Visit 6[a, d]	X	X	X	X	X
Week 16	Visit 7[d]		X	X	X	
Week 20	Visit 8[d]		X	X	X	X
Week 24	Visit 9[a, d]	X	X	X	X	X
Week 28	Visit 10[d]		X	X	X	X
Week 32	Visit 11[d]		X	X	X	
Week 36	Visit 12[d]		X	X	X	X
Week 40	Visit 13[d]		X	X	X	
Week 44	Visit 14[d]		X	X	X	X
Week 48	Visit 15[a, d]	X	X	X	X	X
Week 52	Visit 16[a ,d]	X	X	X	X	X
Year 2						
Week 56	Visit 17[d]		X	X		
Week 60	Visit 18[d]		X	X	X	X
Week 64	Visit 19[d]		X	X		
Week 68	Visit 20[d]		X	X	X	X
Week 72	Visit 21[d]		X	X		
Week 76	Visit 22[a, d]	X	X	X	X	X
Week 80	Visit 23[d]		X	X		X
Week 84	Visit 24[d]		X	X	X	X
Week 88	Visit 25[d]		X	X		
Week 92	Visit 26[d]		X	X	X	X
Week 96	Visit 27[d]		X	X		
Week 100	Visit 28[a, d]	X	X	X	X	X
Week 104	Visit 29[d]		X	X		

Study Day / Week	Visit Number	Mandatory In-Clinic Visit[a]	Dosing with Investigational Drug	Pregnancy Test, AEs, and Concomitant Medications	eGFR	Additional Assessments Per SOE
Year 3						
Week 108	Visit 30[d]		X	X	X	X
Week 112	Visit 31[d]		X	X		
Week 116	Visit 32[d]		X	X	X	X
Week 120	Visit 33[d]		X	X		
Week 124	Visit 34[a, d]	X	X	X	X	X
Week 128	Visit 35[d]		X	X		
Week 132	Visit 36[d]		X	X	X	X
Week 136	Visit 37[d]		X	X		
Week 140	Visit 38[d]		X	X	X	X
Week 144	Visit 39[d]		X	X		
Week 148	Visit 40[a, d]	X	X	X	X	X
Week 152	Visit 41[d]		X	X		
Week 156	Visit 42[d]		X	X	X	X
Year 4						
Week 160	Visit 43[d]		X	X		
Week 164	Visit 44[d]		X	X	X	X
Week 168	Visit 45[d]		X	X		
Week 172	Visit 46[a ,d]	X	X	X	X	X
Week 176	Visit 47[d]		X	X		
Week 180	Visit 48[d]		X	X	X	X
Week 184	Visit 49[d]		X	X		
Week 188	Visit 50[d]		X	X	X	X
Week 192	Visit 51[d]		X	X		
Week 196	Visit 52[a, d]	X	X	X	X	X
Week 200	Visit 53[d]		X	X		
Week 204	Visit 54[d]		X	X	X	X
Week 208	Visit 55[d]		X	X		
Year 5						
Week 212	Visit 56[d]		X	X	X	X
Week 216	Visit 57[d]		X	X		
Week 220	Visit 58[a, d]	X	X	X	X	X
Week 224	Visit 59[d]		X	X		
Week 228	Visit 60[d]		X	X	X	X
Week 232	Visit 61[d]		X	X		

Study Day / Week	Visit Number	Mandatory In-Clinic Visit[a]	Dosing with Investigational Drug	Pregnancy Test, AEs, and Concomitant Medications	eGFR	Additional Assessments Per SOE
Week 236	Visit 62[d]		X	X	X	X
Week 240	Visit 63[d]		X	X		
Week 244	Visit 64[a, d]	X	X	X	X	X
Week 248	Visit 65[d]		X	X		
Week 252	Visit 66[d]		X	X	X	X
Week 256	Visit 67[d]		X	X		
Week 260	Visit 68[d]		X	X	X	X
Year 6						
Week 264	Visit 69[d]		X	X		
Week 268	Visit 70[a, d]	X	X	X	X	X
Week 272	Visit 71[d]		X	X		
Week 276	Visit 72[d]		X	X	X	X
Week 280	Visit 73[d]		X	X		
Week 284	Visit 74[d]		X	X	X	X
Week 288	Visit 75[d]		X	X		
Week 292	Visit 76[a, d]	X	X	X	X	X
Week 296	Visit 77[d]		X	X		
Week 300	Visit 78[d]		X	X	X	X
Week 304	Visit 79[d]		X	X		
Week 308	Visit 80[d]		X	X	X	X
Week 312	Visit 81[d]		X	X		
Year 7						
Week 316	Visit 82[a, d]	X	X	X	X	X
Week 320	Visit 83[d]		X	X		
Week 324	Visit 84[d]		X	X	X	X
Week 328	Visit 85[d]		X	X		
Week 332	Visit 86[d]		X	X	X	X
Week 336	Visit 87[d]		X	X		
Week 340	Visit 88[a, d]	X	X	X	X	X
Week 344	Visit 89[d]		X	X		
Week 348	Visit 90[d]		X	X	X	X
Week 352	Visit 91[d]		X	X		
Week 356	Visit 92[d]		X	X	X	X
Week 360	Visit 93[d]		X	X		
Week 364	Visit 94[a, d]	X	X	X	X	X

Study Day / Week	Visit Number	Mandatory In-Clinic Visit[a]	Dosing with Investigational Drug	Pregnancy Test, AEs, and Concomitant Medications	eGFR	Additional Assessments Per SOE
EOT / Early Withdrawal Visit [a, c, f]	EOT	X		X	X	X
SFV[f]	Monthly Follow-up TCs[c]			X[e]		X
Q6M after permanently DC of IP [a, f]		X		X	X	X
CTEV[a, f]		X		X	X	X

AE = adverse event; CNI = calcineurin inhibitor; Con meds = concomitant medications; CTED = common treatment end date; CTEV = common treatment end visit; eGFR = estimated glomerular filtration rate; EOS = End of Study; EOT = End of Treatment; IP= investigational product; Q6M = every 6 months; SAE = serious adverse event; SFV = Safety follow-up visit; SOE = Schedule of Events; TC = telephone call.

Notes:

[a] At some sites, home / workplace visits may be offered as an option instead of in-clinic visits for certain visits during the Treatment Period. This service may not be available for all subjects at all sites. In Year 1 of the study, in-clinic visits are mandatory at Visit 1 (Screening), Visit 2 (Baseline; Day 1), Visit 4 (Week 4), Visit 6 (Week 12), Visit 9 (Week 24), Visit 15 (Week 48), and Visit 16 (Week 52). Thereafter, in-clinic visits are required approximately every 6 months (ie, at Visit 22 [Week 76], Visit 28 [Week 100], Visit 34 [Week 124], Visit 40 [Week 148], Visit 46 [Week 172], Visit 52 [Week 196], Visit 58 [Week 220], Visit 64 [Week 244], Visit 70 [Week 268], Visit 76 [Week 292], Visit 82 [Week 316], Visit 88 [Week 340], and Visit 94 (Week 364]). An in-clinic visit is required at EOT / Early Withdrawal; if a subject meets the primary efficacy endpoint (all-cause composite allograft loss); and, at the discretion of the investigator, if clinically indicated (eg, because of an AE). Other scheduled visits can be home / workplace visits.

[b] This visit is required only if subject is taking a CNI.

[c] Subjects will be contacted monthly by TC (for up to 5 months after last dose of investigational drug) for monitoring of new AEs, SAEs, or pregnancies and may be called in for a clinic visit at the discretion of the Investigator.

[d] Visit has a ±5-day window.

[e] Pregnancy test not required at SFV.

[f] Subjects who permanently discontinued treatment with IP for any reason who have not reached an endpoint of allograft loss, defined as: eGFR < 15 mL/min/1.73 m^{2*}, return to dialysis*, allograft nephrectomy, retransplantation or death from any cause, or subjects with a sustained (≥ 60 days) 40% decline in eGFR from Baseline, who discontinued IP for any reason will not be withdrawn; they will remain in the study as described in Section . *total cumulative duration of sustained eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days. Following the EOT / Early Withdrawal Visit, subjects will be asked to return for 2 in-clinic Safety Follow-up Visits, 3 and 5 months after the last dose of IP. (Note: DSA MFI Scores, UACR, and IL-6 levels are not required at the 3-month Safety Follow-up Visit). In addition, all subjects will be contacted by telephone call at 1, 2, and 4 months after the last dose of IP for monitoring for new AEs, SAEs, or pregnancies. Thereafter, the subject will be asked to return in 6-month intervals until the CTED is reached to collect renal function and allograft status data. If a subject is unable to return for 6-monthly follow-up visits, he / she will be asked to agree to be contacted at CTED to collect allograft and survival status. The CTEV will be performed within 4 weeks after the CTED date is reached.

APPENDIX 3

Il-6 and Antibody-Mediated Rejection in Kidney Transplant Recipients

Date: 04 February 2021

Sponsor Address: CSL Behring, LLC.
1020 1st Avenue
King of Prussia, PA 19406
USA

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LIST OF ABBREVIATIONS

ABMR	Antibody-mediated rejection
ACR	Acute cellular rejection
ADCC	Antibody-dependent cellular cytotoxicity
ATG	Anti-thymocyte globulin
C3a	Complement component 3a
C4d	Complement component 4d
C5a	Complement component 5a
CABMR	Chronic active antibody-mediated rejection
CMR	Cell-mediated rejection
CNI	Calcineurin inhibitor
dnDSA	De novo donor-specific antibodies
DSA	Donor-specific antibodies
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	End-stage renal disease
EU28	European Union (28 countries)
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
g	Glomerulitis
IFN-γ	Interferon-gamma
GVHD	Graft-versus-host disease
HLA	Human leukocyte antigen
IgG	Immunoglobulin G
IL-6	Interleukin 6
IL-17	Interleukin 17
IL-6R	Interleukin 6 receptor
IV	Intravenous
IVIG	Intravenous immunoglobulin
KDIGO	Kidney Disease: Improving Global Outcomes
mAb	Monoclonal antibody

MFI	Mean fluorescence intensity
MHC	Major histocompatibility complex
MLR	Mixed lymphocyte reaction
MMF	Mycophenolate mofetil
NK	Natural killer (cell)
PBMC	Peripheral blood mononuclear cell
PLEX	Plasma exchange
ptc	Peritubular capillaritis
SOC	Standard of care
TCMR	T cell-mediated rejection
TCZ	Tocilizumab
Tfh	Follicular T helper (cell)
Th1	T helper 1 (cell)
Th2	T helper 2 (cell)
TG	Transplant glomerulopathy
Th17	T helper 17 (cell)
TNFα	Tumor necrosis factor alpha
Treg	Regulatory T (cell)
Union	EU28, Norway, Iceland, and Liechtenstein
US	United States
vWF	Von Willebrand factor

1. OVERVIEW

Active antibody-mediated rejection (ABMR), especially chronic active antibody-mediated rejection (CABMR), is now recognized as the most common cause of allograft failure after a successful kidney transplant. Current standard of care (SOC) anti-rejection treatments target cellular-mediated (ie, T cell-mediated rejection [TCMR]) processes and do not affect this antibody-mediated process. Currently, there are no approved or effective treatments for active ABMR, including CABMR. Robust evidence from well-conducted randomized control studies are sparse. The Kidney Disease: Improving Global Outcomes (KDIGO) 2009 guideline [KDIGO, 2009] recognizes the lack of good quality data and suggests the use of one or more of the following (with or without corticosteroids), to treat acute ABMR: plasma exchange (PLEX); intravenous immunoglobulin (IVIG); anti-CD20 antibody; and lymphocyte-depleting antibody. Recent systematic reviews of treatments for ABMR have shown that the situation remains unchanged, even with novel agents targeting B cells, plasma cells and the complement system [Roberts et al, 2012; Wan et al, 2018]. No treatment exists for the treatment of CABMR and there is no evidence that treatments for acute active ABMR are effective for CABMR. Thus, there exists a critical unmet medical need for effective treatments of CABMR.

Based on evidence from both nonclinical and clinical studies, interleukin 6 (IL-6) appears to be a critical cytokine involved in CABMR. IL-6 promotes the development and maturation of B cells to plasma cells that produce donor-specific antibodies (DSA) targeting the allograft. These DSA cause antibody-mediated injury to the allograft via direct activation of endothelial cells, complement-dependent cytotoxicity and / or antibody-dependent cellular cytotoxicity (ADCC) [Gaston et al, 2010; Thomas et al, 2015; Jordan et al, 2017]. Furthermore, IL-6 shapes the T cell immune response resulting in promotion of long-lived pro-inflammatory T cells (eg, follicular T helper cells [Tfh], T helper 17 cells [Th17], T helper 1 cells [Th1], and T helper 2 cells [Th2]) and inhibition of immune regulatory T cells (Treg) that promote immune tolerance. Data from clinical studies using the anti-IL-6 receptor (IL-6R) monoclonal antibody (mAb) tocilizumab (TCZ) suggest the potential benefit of inhibiting IL-6 signaling in the treatment of CABMR.

Estimates of the prevalence of ABMR in kidney transplant recipients in the US and in Europe indicate that ABMR is a rare condition. In the US, the prevalence of DSA+ kidney transplant recipients at the end of August 2017 is estimated to range from approximately 24,343 to 146,056, well below the threshold of 200,000 for designation as a rare condition according to FDA requirements for orphan designation. In Europe, the prevalence of DSA+

kidney transplant recipients at the end of 2017 is estimated to range from approximately 0.44 and 3.52 in 10,000 well below the defined threshold of 5 in 10,000 for designation as a rare condition according to the EMA requirements for orphan designation. Not all DSA-positive subjects are expected to develop ABMR.

The sections below present a summary of the clinical setting and unmet medical need for effective treatment of CABMR in kidney transplant recipients, followed by summaries of the estimated prevalence of ABMR in kidney transplantation in both the US and Europe. Finally, summaries of both nonclinical and clinical evidence demonstrating the role of IL-6 in mediation of ABMR / CABMR in solid organ transplantation, particularly kidney transplantation, are provided. A comprehensive summary of the therapeutic implications of IL-6R blockade with respect to allograft rejection is also available in a review by Jordan et al, 2016 [Jordan et al, 2017].

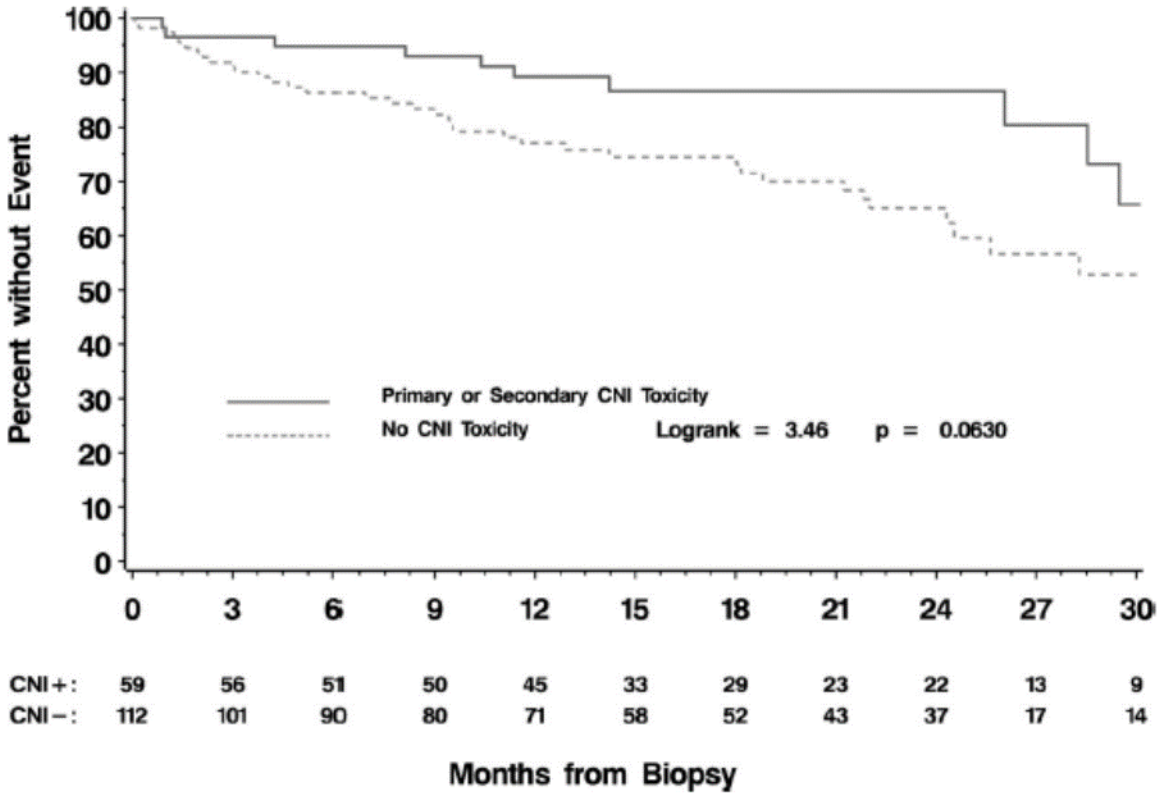
2. CLINICAL SETTING AND UNMET MEDICAL NEED

Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD) and is undoubtedly associated with improved survival, better quality of life, and reduced costs when compared with maintenance dialysis [O'Connell et al, 2017]. Kidney transplant recipients have expected remaining lifetimes estimated at 68 to 85% of that in the general population compared to patients with ESRD on dialysis who are expected to live less than one-third as long as the general population without ESRD [USRDS, 2016]. Despite significant progress in the treatment of acute cellular rejections (ACRs), resulting in marked improvements in the short-term survival of kidney allografts, long-term graft survival has not improved. Graft survival in the first year post-transplant is over 95%, but death-censored graft failure rates beyond the first year have remained relatively unchanged since the late 1980s: ie, 3 to 5% per year for deceased donor grafts and 2 to 3% per year for living donor grafts. By 10 years, 20 to 30% of all kidney allografts will have failed [Stegall et al, 2014].

In the past, studies showed that the patients who experienced a primarily T cell-mediated early ACR episode, had less favorable long-term graft survival than those who remained rejection-free. Thus, it became medical dogma that, to improve long-term graft survival, minimizing ACR should be the goal of post-transplant immunosuppression treatment. However, while newer immunosuppression treatment protocols have lowered ACR rates routinely to < 10% in the first year, late graft loss rates remained relatively unchanged [Meier-Kriesche et al, 2004; Lamb et al, 2011].

In recent years, the understanding of the causes of late kidney allograft loss has undergone a significant change. As histologic studies showed that progressive fibrosis and vasculopathy (called chronic allograft nephropathy) were the major causes of late graft loss, and because calcineurin inhibitors (CNIs) were known to cause fibrosis, it became widely accepted that this late allograft loss was due to CNI nephrotoxicity. This led to multiple studies testing the hypothesis that minimizing the dose of CNIs or avoiding these drugs altogether might improve CNI nephrotoxicity and thus improve long-term graft survival. Although some studies suggested that avoidance of CNIs was safe and associated with better renal function over time, other trials showed increased ACR in the patients on CNI-sparing and CNI-free therapies and minimal, if any, improvement in renal function [Gaston et al, 2010; Meier-Kriesche et al, 2004]. Indeed, the DeKAF study [Gaston et al, 2010] showed that patients with CNI nephrotoxicity had better long-term graft survival than the patients without CNI nephrotoxicity (see Figure 1).

Figure 1 Kaplan-Meier Analysis of the Impact of Primary or Secondary Local Diagnosis of CNI Nephrotoxicity on Kidney Allograft Survival After For-Cause Biopsy

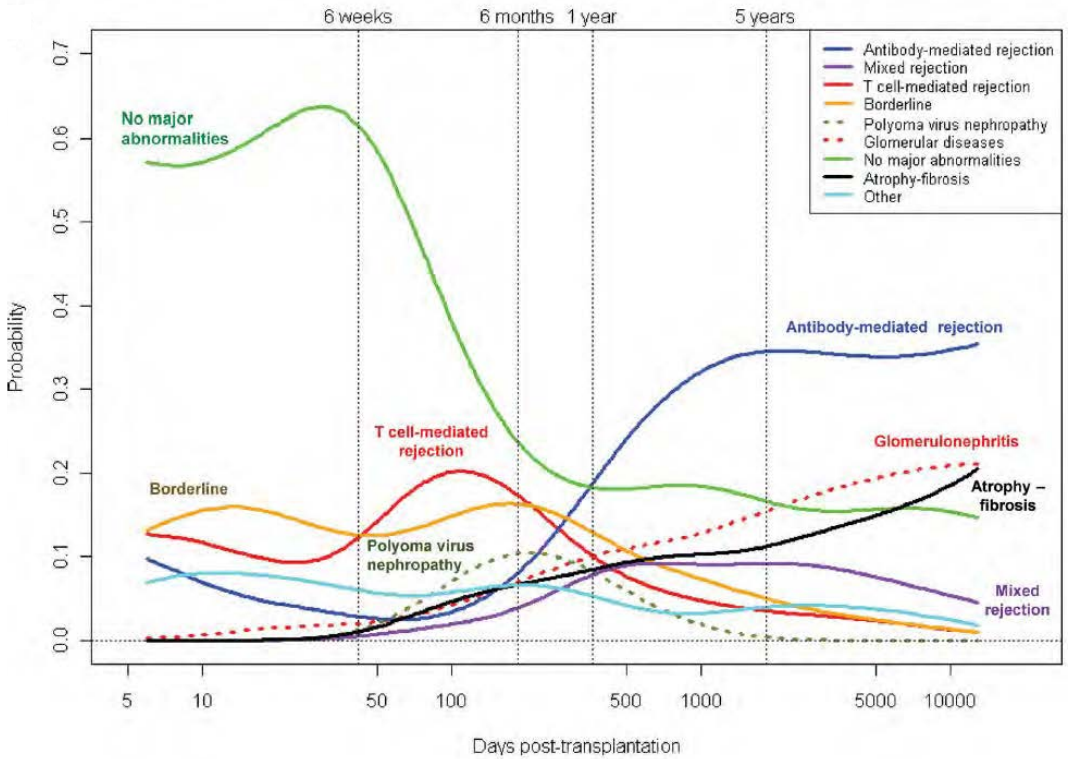


CNI = calcineurin inhibitor.
Source: Gaston et al, 2010.

Over the last several years, it has become clear that insufficient control of the humoral immune response by current immunosuppressive drugs (which primarily target the T cells) is the main pathogenic factor responsible for late graft loss. Important advances in the development of sensitive assays for the identification of DSA improved understanding of the histopathology of ABMR. The growing implementation of molecular diagnostic approaches have led to a realization that ABMR is the most common cause of late kidney allograft failure, and that there is no treatment currently available to prevent or treat this condition [Einecke et al, 2009; Hidalgo et al, 2009; Gaston et al, 2010; Loupy et al, 2012; Sellarés et al, 2012; Wiebe et al, 2012; Thomas et al, 2015; Wiebe et al, 2015]. It is estimated that more than 5,000 renal allografts are lost each year in the US, and approximately 75 to 80% are lost due to antibody-mediated injury [Loupy et al, 2012; Wiebe et al, 2012; Aubert et al, 2017]. In contrast, TCMRs are common early but progressively disappear over time such that by

10 years post-transplant, TCMR episodes are rare (see Figure 2) [Sellarés et al, 2012; Halloran et al, 2015]. These investigations have also determined that ABMR is primarily caused by the recipient developing DSA, most commonly against human leukocyte antigens (HLA) and less commonly against non-HLA antigens present in the donor graft [Opelz, 2005; Colvin, 2007; Sun et al, 2011; Loupy et al, 2012]. These DSA may be present before transplant (ie, preformed because of previous blood transfusion, pregnancy, or previous transplant) or develop post-transplant (de novo DSA [dnDSA]). Antibody-mediated rejection due to preformed DSA tends to occur early and is associated with superior graft survival compared with ABMR due to dnDSA - which usually occurs later (after 1 year post-transplant) and is associated with histological features of chronic injury (such as transplant glomerulopathy (TG) and interstitial fibrosis / tubular atrophy) [Aubert et al, 2017; Haas et al, 2017].

Figure 2 Distribution of Histologic Diagnosis Expressed as Probability Plots Conditional on Time of Biopsy Post-Transplantation



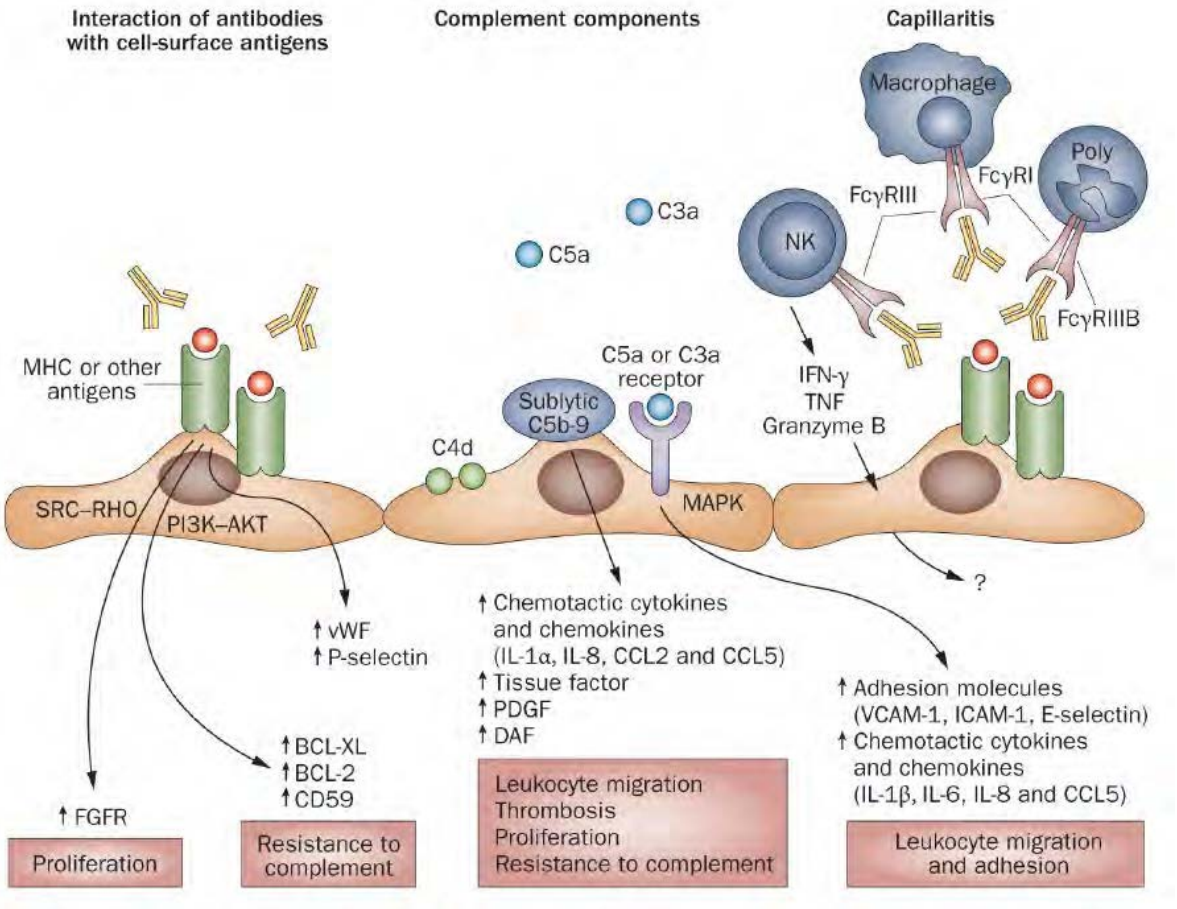
ABMR = antibody-mediated rejection; C4d = complement component 4d.
Notes:
Distribution of histopathology diagnoses and adherence status in biopsies expressed as probability plots conditional on the time of biopsy post-transplantation. The ABMR category includes C4d-positive ABMR, C4d-negative ABMR and probable ABMR.
Source: Sellarés et al, 2012.

The reported rate of development (ie, incidence) and prevalence of dnDSA after kidney transplantation varies widely in the literature, reflecting the different methodological assays used for detecting DSA, different characteristics of the cohort studied, duration of follow-up, and the center's interest in detecting the presence of these antibodies. Wiebe et al., in a study of over 500 adult and pediatric consecutive renal transplants between January 1999 and July 2012, showed that the incidence of dnDSA development is approximately 2% per annum post-transplant, such that at 10 years post-transplant, approximately 20% of recipients will have developed dnDSA [Wiebe et al, 2015]. However, in a smaller cohort, Everly et al. found higher incidence rates: ie, 11% of kidney recipients developed dnDSA after the first year and approximately 20% are expected to develop dnDSA by the fifth-year post-transplant [Everly et al, 2013]. In an international collaborative study of 45 transplant centers, the prevalence of DSA against HLA antigens in the kidney transplant population varied from approximately 10 to 60%, with an average of 27% [Ozawa et al, 2007].

It is widely recognized that DSA causes antibody-mediated injury to the allograft via direct activation of vascular endothelial cells, complement-dependent cytotoxicity, and / or by ADCC [Gaston et al, 2010; Thomas et al, 2015]. These mechanisms of antibody-mediated injury are interrelated and are likely to synergize to cause maximal inflammation. For example, direct endothelial cell activation by DSA may trigger adhesion of leukocytes, which can be enhanced when those leukocytes bind antibody through Fc gamma receptors (FcγRs). Activation of complement at the endothelial cell surface may cause production of C3a and C5a anaphylatoxins which can act on leukocytes as chemoattractants or further enhance endothelial cell activation.

The histological manifestations of ABMR in the kidney allograft reflect the signatures of antibody-mediated injury, specifically vascular endothelial cell changes, and leukocyte infiltrates, with or without complement deposition. These histological features include TG, peritubular capillary basement membrane multilayering, arterial intimal fibrosis, and microvascular inflammation, with or without complement component 4 (C4d) staining (Banff 2015 criteria [Loupy et al, 2017]). Figure 3 illustrates the mechanisms whereby DSAs causes injury to the transplanted kidney.

Figure 3 Mechanisms of DSA Mediated Endothelial Injury in Renal Allografts



BCL-2 = B cell lymphoma 2; BCL-XL = B cell lymphoma-extra large; C3a = complement component 3a; C4d = complement component 4d; C5a = complement component 5a; C5b-9 = complement component C5b and C9 complex; CCL2 = chemokine ligand 2; CCL5 = chemokine ligand 5; CD59 = MAC-inhibitory protein DAF = decay accelerating factor; FcγR = Fc gamma receptor; FGFR = fibroblast growth factor receptor; ICAM-1 = intercellular adhesion molecule 1; IFN-γ = interferon-gamma; IL-1α = interleukin 1 alpha; IL-6 = interleukin 6; IL-8 = interleukin 8; MAPK = mitogen activated protein kinase; MHC = major histocompatibility complex; NK = natural killer cell; PDGF = platelet-derived growth factor; Poly = polynuclear cell; TNF = tumor necrosis factor; VCAM-1 = vascular cell adhesion protein 1; vWF = von Willebrand factor.

Notes:

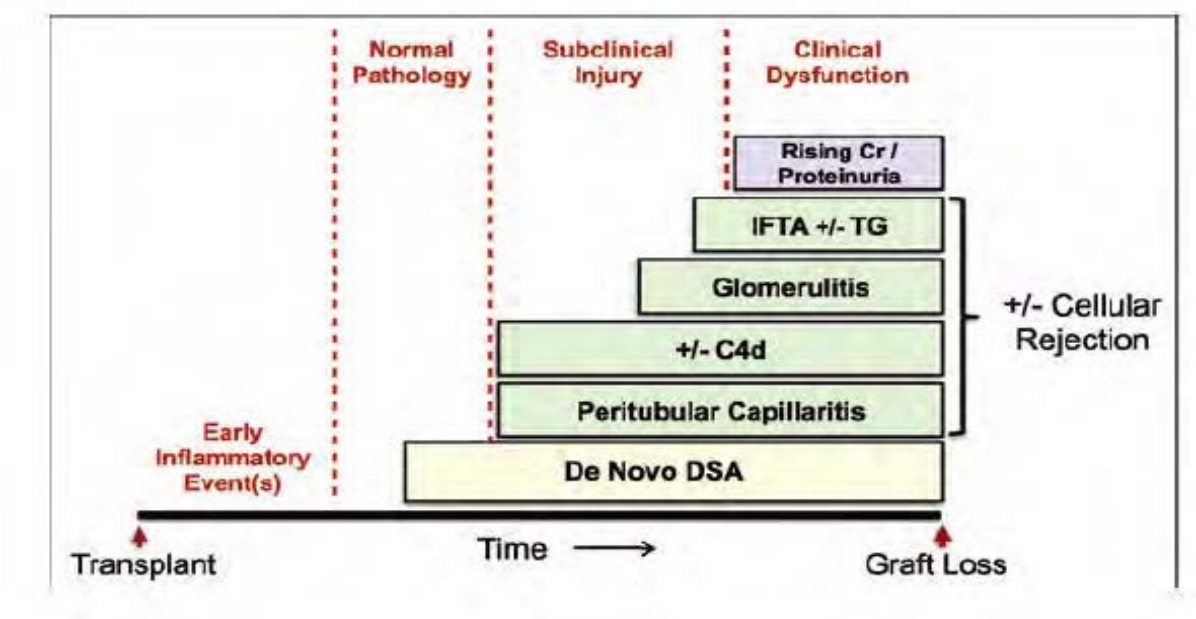
Anti-MHC antibodies can cause direct injury to the capillary endothelium or indirect injury via complement fixation or recruitment of inflammatory cells with Fc receptors.

Source: Farkash and Colvin, 2012.

Wiebe et al. have proposed a continuum of antibody-mediated damage based on a model adapted from the primate studies of Smith et al. [Smith et al, 2008; Wiebe et al, 2012]. Post-transplant dnDSA development is preceded by an antibody-free period. It is likely that inflammatory events (ie, preceding cellular rejection or graft infection) lead to elevated interferon-gamma (IFN-γ) levels, which upregulate HLA expression on endothelial cells and stimulate B cell allorecognition and subsequent long-lived plasma cells producing dnDSA.

At this point, dnDSA onset may be overlooked without routine post-transplant monitoring of stable grafts. Nevertheless, biopsies in stable grafts with dnDSA generally reveal histologic changes consistent with microvasculature injury (see Figure 4).

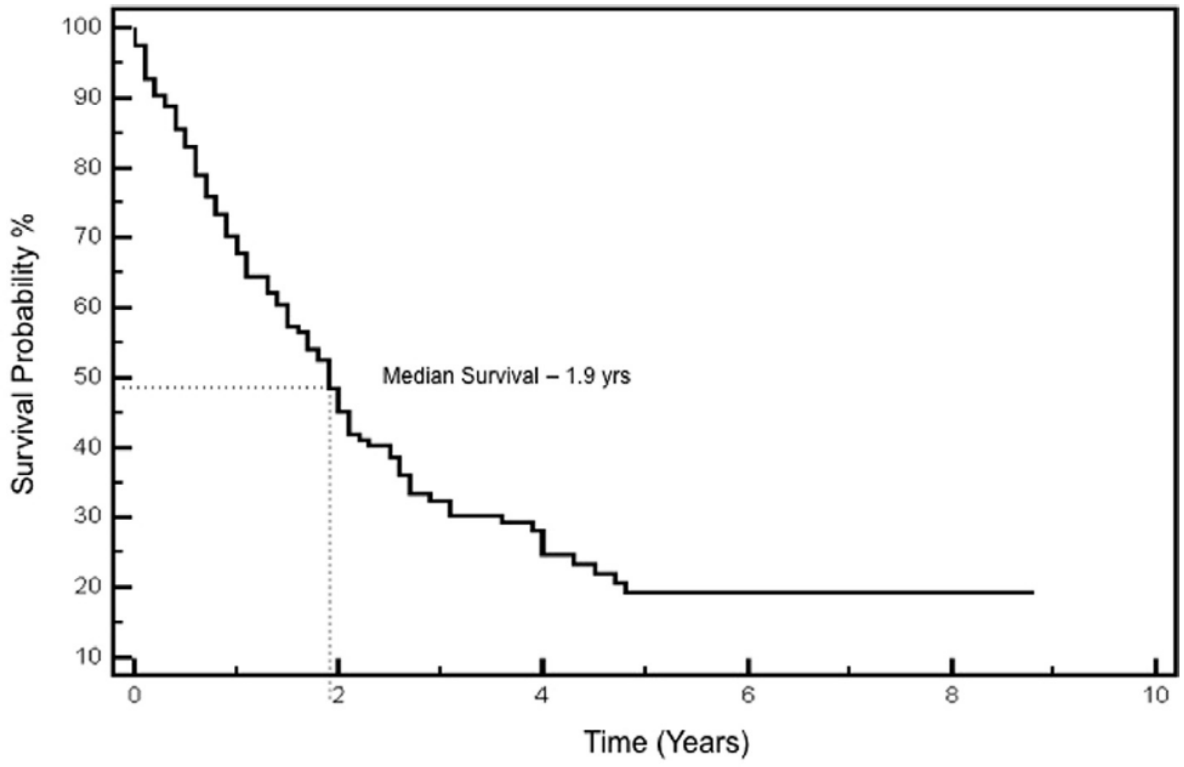
Figure 4 Proposed Natural History of De Novo DSA



C4d = complement component 4d; Cr = creatinine; DSA = donor-specific antibodies; IFTA = interstitial fibrosis and tubular atrophy; TG = transplant glomerulopathy.
Notes:
This figure shows a proposed model for patients developing de novo DSA as they evolve from transplantation to graft failure.
Source: Wiebe et al, 2012.

The belief that DSA causes ABMR is supported by the strong association between the development of DSA, especially dnDSA, and late kidney allograft loss. In a retrospective pooled analysis, Mohan et al. showed that the presence of DSA detected by solid phase assay, even with negative flow cytometry crossmatch, demonstrated a significant increased risk for biopsy-proven ABMR and graft loss [Mohan et al, 2012]. In an observational study of 123 consecutive patients with biopsy-proven CABMR between 2006 and 2012, with follow-up for a median of 9.5 years, Redfield et al. found that 76% of patients lost their grafts with a median graft survival of 1.9 years after diagnosis of CABMR (see Figure 5) [Redfield et al, 2016].

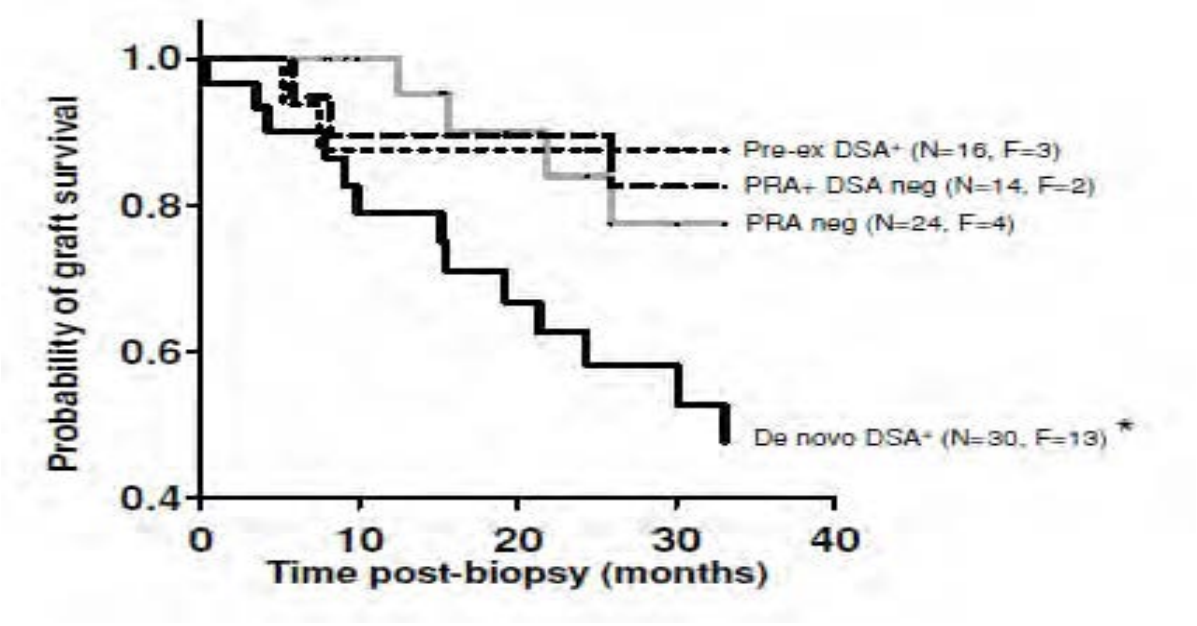
Figure 5 Kidney Graft Survival Following CABMR Diagnosis



CABMR = chronic active antibody-mediated rejection; yrs= years.
Source: Redfield et al, 2016.

In a study of 145 patients between 7 days and 31 years post-transplant, Hidalgo et al. detected DSA in 54 (37%) patients, of which 32 were dnDSA (22% of original patient population and 59% of DSA+ subgroup) [Hidalgo et al, 2009]. De novo DSA were more frequent in the patients who had late biopsies versus early biopsies, and were associated with microcirculation, inflammation and glomerular damage. Importantly, dnDSA correlated with reduced graft survival (see Figure 6).

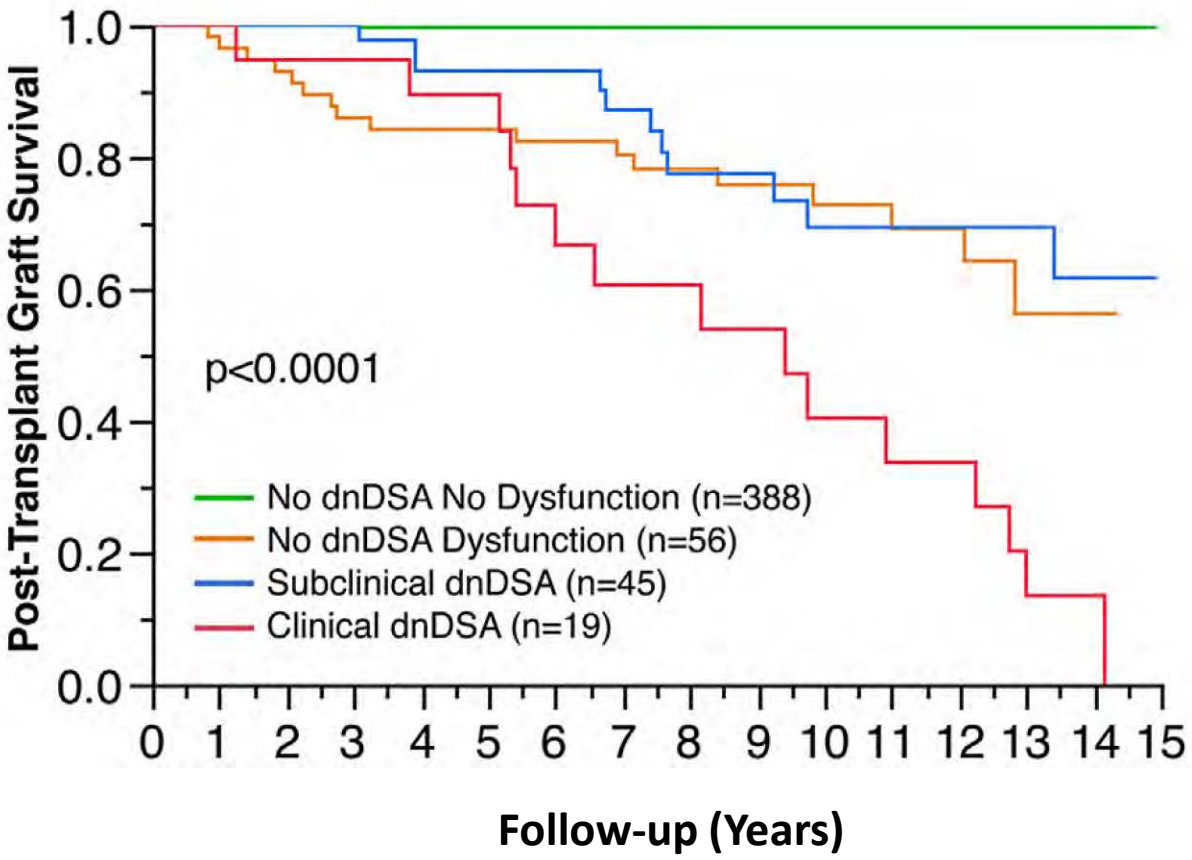
Figure 6 Probability of Graft Survival in Patients Who Underwent a Late Biopsy and Were Assessed for DSA



DSA = donor-specific antibodies; F = the number of failed grafts; HLA = human leukocyte antigen; neg=Negative; PRA = panel-reactive antibodies; Pre-ex = pre-existing.
*p = 0.001 (log rank test).
Notes:
Probability of graft survival in patients in each DSA subgroup was compared to patients with no detectable HLA antibodies (PRA neg).
Source: Hidalgo et al, 2009.

In a study of a larger consecutive cohort of 508 patients, Wiebe et al. discovered dnDSA in 64 (13%) patients [Wiebe et al, 2015]. In patients with dnDSA, the rate of estimated glomerular filtration rate (eGFR) decline was significantly increased prior to dnDSA onset (-2.89 versus 0.65 mL/min/1.73 m^2/year, $p < 0.0001$) and accelerated post-dnDSA onset (-3.63 versus -2.89 mL/min/1.73 m^2/year, $p < 0.0001$), supporting the notion that dnDSA were contributing to the ongoing alloimmunity and allograft damage. Patients with "clinical" dnDSA (ie, evidence of renal dysfunction) had the highest risk of graft loss (see Figure 7).

Figure 7 Death-Censored Graft Survival by Clinical Phenotype and dnDSA Status

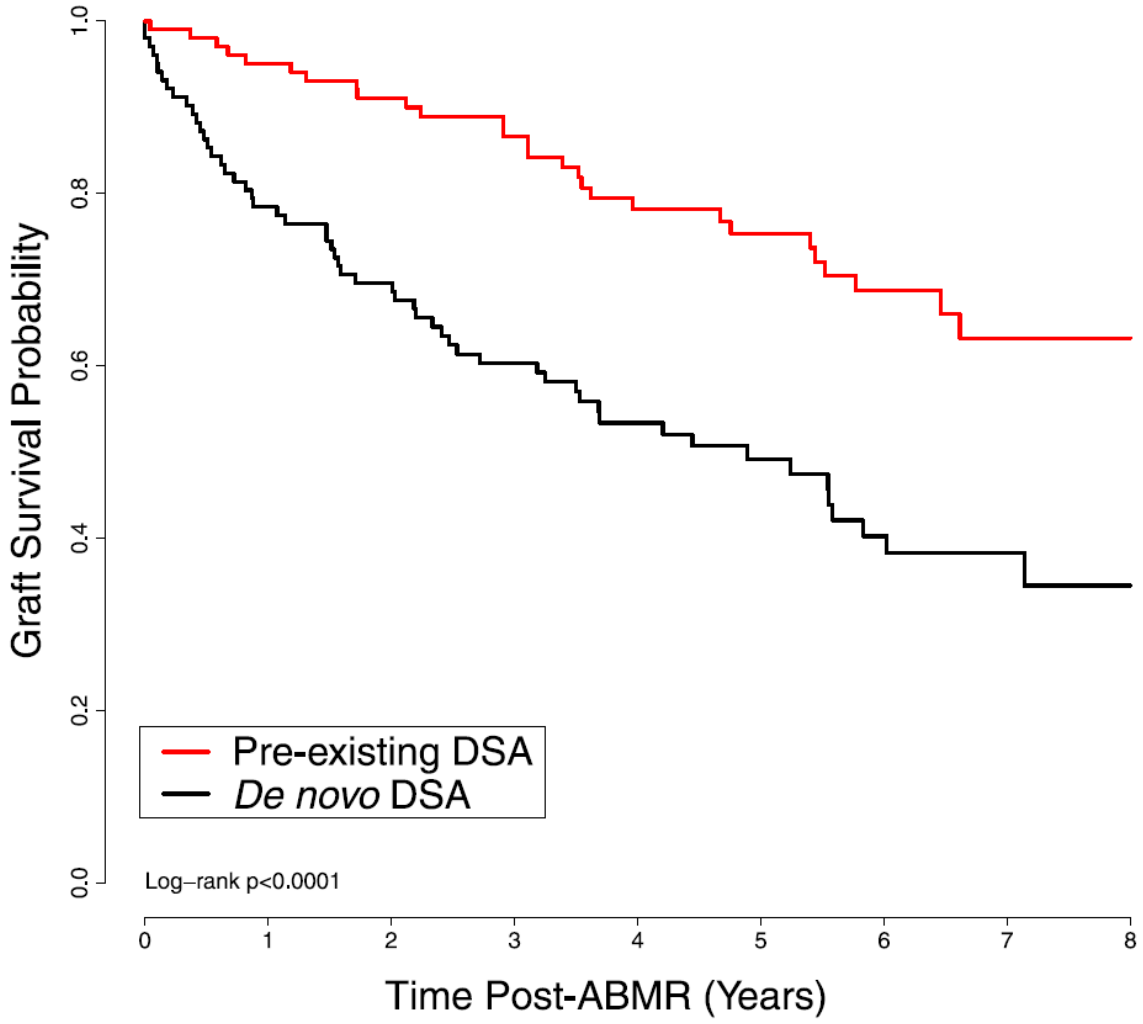


dnDSA = de novo donor-specific antibodies.
Notes:
Kaplan-Meier plot of renal allograft survival by clinical phenotype and dnDSA status.
Source: Wiebe et al, 2015.

Although most studies have identified dnDSA to be significantly associated with increased risk of graft loss, recipients with preformed DSA are also at greater risk of graft loss. Loupy et al, 2009] in their study of 806 kidney transplantations performed between 2002 to 2007, compared a cohort of 54 patients with preformed DSA to a control group of patients without preformed DSA [Loupy, et al 2009]. Four-year graft survival was significantly lower in the group with preformed DSA compared to the control group: survival was 86.2% and 96.2%, respectively, (p = 0.01, log rank test). In another study of 402 consecutive deceased donor kidney transplant recipients, Lefaucher et al. observed a worse 8-year graft survival (61%) among patients with preexisting anti-HLA DSA compared to both sensitized patients without anti-HLA DSA (93%) and non-sensitized patients (84%) [Lefaucheur et al, 2010]. Notwithstanding, in a study of 771 kidney biopsy specimens from 2 North American and 5 European centers, Aubert et al. compared patients with a biopsy-proven ABMR and pre-formed DSA versus patients with rejection and dnDSA [Aubert et al, 2017]. At 8 years after ABMR diagnosis, patients with preformed DSA ABMR had significantly superior graft

survival compared with the patients with dnDSA ABMR (ie, 63% versus 34%, respectively, p = 0.001) (see Figure 8).

Figure 8 Probability of Graft Survival According to DSA Characteristics



ABMR = antibody-mediated rejection; DSA = donor-specific antibodies; HLA = human leukocyte antigen.
Notes:
Early occurrence of preexisting anti-HLA DSA ABMR and superior graft survival compared with de novo anti-HLA DSA ABMR.
Source: Aubert et al, 2017.

That the development of DSA is fundamentally linked with ABMR in kidney allografts is recognized by the Banff 2015 criteria [Loupy et al, 2017] for diagnosing ABMR. All 3 of the following features must be present: histologic evidence of tissue injury, evidence of current / recent antibody interaction with vascular endothelium, and serologic evidence of DSAs (HLA or other antigens), irrespective of whether preformed or dnDSA. The diagnosis

of ABMR is further subdivided into acute / active or chronic active ABMR (ie, CABMR), differentiated by the presence of chronic tissue injury such as TG, severe peritubular capillary basement multilayering, and / or arterial intimal fibrosis in CABMR.

Currently, there are no approved or effective treatments for active ABMR, including CABMR. The KDIGO 2009 guideline [KDIGO, 2009] recognizes the lack of good quality data and suggests the use of one or more of the following (with or without corticosteroids), to treat acute ABMR: PLEX; IVIG; anti-CD20 antibody; and lymphocyte-depleting antibody. Recent systematic reviews of treatments for ABMR have shown that the situation remains unchanged, even with novel agents targeting B cells, plasma cells and the complement system [Roberts et al, 2012; Wan et al, 2018]. In the RITUX ERAH study, there was no early or late (up to 5 years) benefit with rituximab (an anti-CD20 mAb) administered with IVIG, PLEX and corticosteroids in kidney transplant recipients with early acute ABMR [Sautenet et al, 2016; Bailly et al, 2017]. More specifically, no evidence of efficacy was seen in studies in CABMR with eculizumab (a complement inhibitor), bortezomib (a proteasome inhibitor), IVIG, rituximab and PLEX [Kulkarni et al, 2017; Piñeiro et al, 2017; Eskandary et al, 2018; Moreso et al, 2018]. No treatment exists for the treatment of CABMR and there is no evidence that treatments for acute active ABMR are effective for CABMR. Thus, there exists a critical unmet medical need for effective treatments of CABMR.

3. ESTIMATED PREVALENCE OF ABMR – A RARE CONDITION

It is estimated that more than 5,000 renal allografts are lost each year in the US alone, and approximately 75 to 80% are lost due to antibody-mediated injury [Loupy et al, 2012; Wiebe et al, 2012; Aubert et al, 2017]. Epidemiological data on ABMR in kidney transplant recipients is sparse and is not included in rare disease databases such as Orphanet. The prevalence of ABMR in kidney transplant recipients has therefore been approximated by estimating the prevalence of kidney transplant recipients with DSA (ie, DSA+ recipients) living in the US and in the EU28, Norway, Iceland and Liechtenstein (defined as "the Union" hereafter in this report).

Estimation of the Proportion of Kidney Transplant Recipients With ABMR

The reported rate of development (ie, incidence) and prevalence of dnDSA after kidney transplantation varies widely in the literature. Approximately 2% of kidney transplant recipients per annum have been reported to develop DSA [Wiebe et al, 2015], and in an international collaborative study of 45 transplant centers conducted in 2004 and 2005 by Ozawa et al, the prevalence of kidney transplant recipients with DSA varied from approximately 10 to 60%, with an average of 28% [Ozawa et al, 2007]. Not all kidney transplant recipients with DSA will develop ABMR; therefore, applying the most conservative figure of 60% to prevalence data for kidney transplant recipients provides a conservative upper estimate of the prevalence of kidney transplant recipients with ABMR.

Estimation of the Prevalence of Kidney Transplant Recipients With ABMR in the US

Prevalence data on kidney transplant recipients in the US was obtained from 2 key US sources: the United States Renal Data System (USRDS) 2016 Annual Report (which provides data current as of 31 December 2013) [USRDS, 2016] and the United Network for Organ Sharing (UNOS) data on the number of kidney transplants performed in 2015 to 2017 [UNOS, 2015; UNOS, 2016; UNOS, 2017] (see Table 1). By combining these data and estimating the prevalence of DSA+ recipients based on Ozawa et al., a conservative upper estimate of the prevalence of ABMR patients at the end of August 2017 can be made (see Table 1) [Ozawa et al, 2007].

Table 1 Estimated Prevalence of Kidney Transplant Recipients in the US in August 2017 According to Data from the USRDS and UNOS and Estimated Prevalence of DSA-Positive Recipients

	Number of Individuals
Cumulative number of recipients with a functioning kidney transplant in 2014 (based on USRDS data)	200,907
Number of kidney transplants in 2015 (UNOS)	17,878
Number of kidney transplants in 2016 (UNOS)	19,060
Number of kidney transplants from January 2017 to August 2017	13,110
Estimated total number of living kidney transplant recipients with a functioning kidney transplant in August 2017[(a)]	243,426
Estimate prevalence of DSA+ recipients in August 2017[(b)]	24,343 – 146,056

DSA = donor-specific antibodies; UNOS = United Network for Organ Sharing; USRD = United States Renal Data System.
Notes:
[a] Rough estimate applying the overall 1-year graft survival rate reported by the USRDS for 2013 (ie, 97%) to the total number of estimated recipients: ie, 0.97 x (200,907 + 17,878 + 19,060 + 13,110) = 243,426.
[b] Based on range of 10 to 60% as reported by Ozawa et al, 2007.
Source: Ozawa et al, 2007; USRDS, 2016; UNOS, 2015-2017.

Using the assumption of 10 to 60% being DSA+, the prevalence of DSA+ kidney transplant recipients at the end of August 2017 in the US is estimated to range from approximately 24,343 to 146,056, well below the threshold of 200,000 for designation as a rare condition according to FDA requirements for orphan designation. As stated previously, not all DSA-positive subjects are expected to develop ABMR.

Estimation of the Prevalence of Kidney Transplant Recipients With ABMR in the Union

Prevalence data on kidney transplant recipients in the Union was obtained primarily from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) 2015 Annual Report [ERA-EDTA, 2017]. By estimating the prevalence of DSA+ recipients based on Ozawa et al, 2007, an estimate of the prevalence of ABMR patients at the end of 2017 can be made (see Table 2).

Table 2 Estimated ABMR Prevalence in the Union at the End of 2017 According to Data from the ERA-EDTA Estimated Prevalence of DSA-Positive Recipients

Source of ERA-EDTA Data	Estimated Number of Individuals in the Union with Functioning Kidney Grafts	
	Pre-2016[a]	2017[b]
RRT summary data	197,060	226,372
Individual patient data	279,598	304,535
Aggregate patient data	229,043	256,660

Source of ERA-EDTA Data	Estimated 2015 Kidney Transplant Prevalence (per 10,000)	Estimated Prevalence at the End of 2017[c]		
		Projected 2017 Kidney Transplant Prevalence (per 10,000)	Projected 2017 DSA+ (10%) (per 10,000)	Projected 2017 DSA+ (60%) (per 10,000)
RRT summary data	3.82[d]	4.36	0.44	2.62
Individual patient data	5.42[e]	5.87	0.59	3.52
Aggregate patient data	4.44[f]	4.95	0.50	2.97

ABMR = antibody-mediated rejection; DSA = Donor-specific antibodies; ERA-EDTA = European Renal Association – European Dialysis and Transplant Association; GODT = Global Observatory on Donation and Transplantation; RRT = renal replacement therapy; Union = EU28, Norway, Iceland, and Liechtenstein.

Notes:

[a] The number of individuals with functioning grafts pre-2016 was estimated by applying the ERA-EDTA prevalence rates for kidney transplant recipients to the total population of the Union at the end of 2015 (ie, 515,862,387 according to Eurostat).

[b] The number of individuals with functioning grafts at the end of 2017 was estimated by adding the total number of kidney transplants performed in 2016 (based on GODT data) and 2017 to the pre-2016 number of individuals. The kidney transplant incidence for 2017 was assumed to equal the incidence for 2016 and the 1- and 2-year graft survival probabilities from the ERA-EDTA were applied.

[c] The projected prevalence for the end of 2017 was calculated by taking the estimated number of individuals in 2017 and dividing it by the predicted population at the end of 2017. The predicted population at the end of 2017 was calculated by applying the same population growth as was seen in 2016.

[d] Based on Table A.3.1 of the ERA-EDTA 2015 Annual Report.

[e] Based on Table B.4.8 of the ERA-EDTA 2015 Annual Report.

[f] Based on Table C.4.7 of the ERA-EDTA 2015 Annual Report.

Source: ERA-EDTA, 2015; Eurostat: Population on 1 January 2016 / 2017 [Eurostat, 2017]; Global Observatory on Donation and Transplantation [GODT, 2017]; Ozawa et al, 2007.

Using the assumption of 10 to 60% being DSA+, the prevalence of DSA+ kidney transplant recipients in the Union at the end of 2017 is estimated to range from approximately 0.44 and 3.52 in 10,000, which is well below the defined threshold of 5 in 10,000 for designation as a rare condition according to the EMA requirements for orphan designation. As stated previously, not all DSA-positive subjects are expected to develop ABMR.

4. IL-6 IN MEDIATION OF ABMR

IL-6 is a pleiotropic cytokine that regulates the immune response, inflammation, hematopoiesis, and bone metabolism [Keller et al, 1996]. IL-6 also has a range of effects on the adaptive immune response. It stimulates B cell differentiation and secretion of antibodies and prevents apoptosis of activated B cells [Hirano et al, 1985; Muraguchi et al, 1988; Kawano et al, 1995]. IL-6 also activates and induces proliferation of T cells and, in the presence of interleukin 2, induces differentiation of mature and immature T cells into cytotoxic T cells [Lotz et al, 1988; Okada et al, 1988].

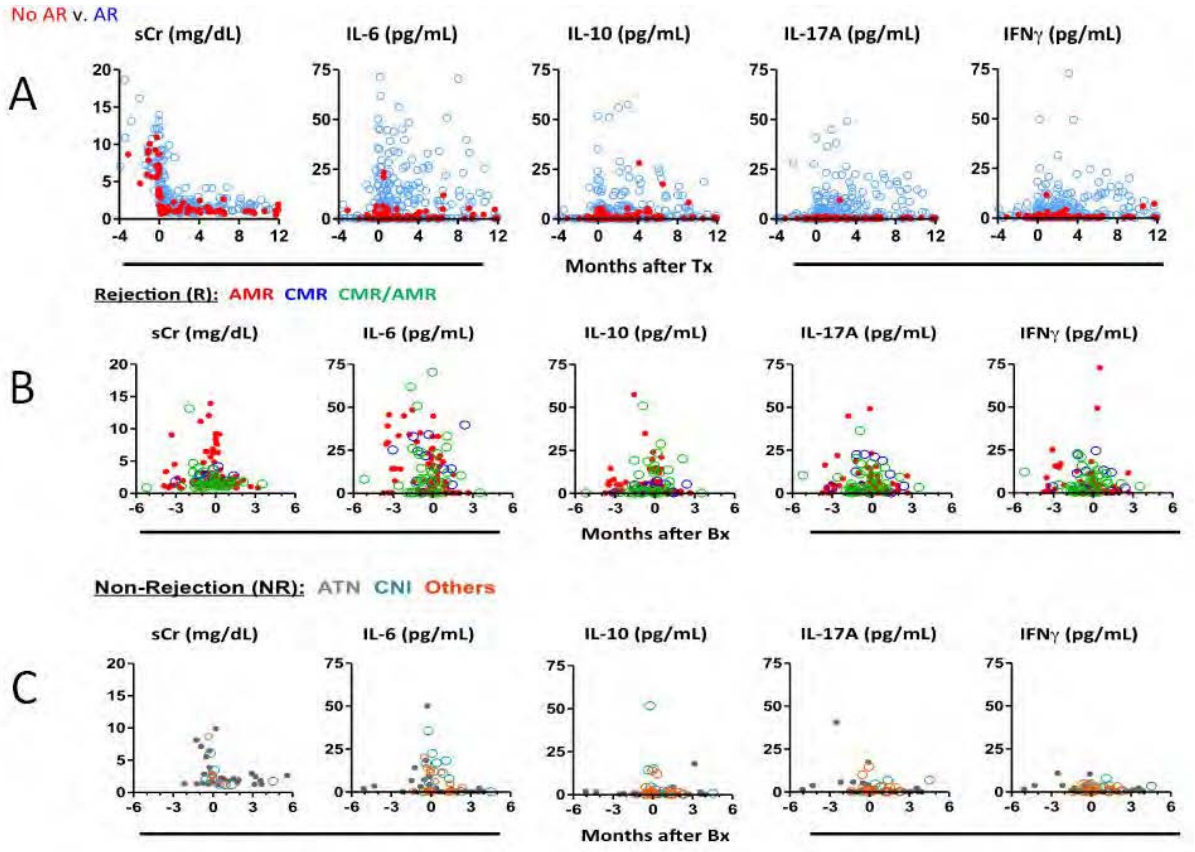
IL-6 appears to be a critical cytokine involved in the humoral rejection of kidney allografts (ie, ABMR). IL-6 promotes the development and maturation of B cells to plasma cells that produce DSA targeting the allograft. These DSA damage the allograft via complement and non-complement mediated pathways and induce graft endothelial cells to produce inflammatory (eg, p-selectin, vascular cell adhesion molecule-1) and pro-thrombotic (eg, von Willebrand factor [vWF]) molecules [Gaston et al, 2010; Thomas et al, 2015; Jordan et al, 2017]. Furthermore, IL-6 shapes the T cell immune response resulting in promotion of long-lived pro-inflammatory Th cells (eg, Tfh cells, Th17, Th1, and Th2 cells) and inhibition of immune Treg cells that promote allograft tolerance.

Both nonclinical and clinical evidence demonstrating how IL-6 / IL-6R interactions relate to CABMR in solid organ transplantation, especially kidney transplantation, are discussed below.

4.1 Expression of IL-6 in Allografts With and Without ABMR

Jordan et al (personal communication) have investigated the role of IL-6 over-expression in the mediation of ABMR. Initial studies centered on measurement of serum cytokine levels in peripheral blood of patients at various times post-kidney transplant (see Figure 9).

Figure 9 Serum Cytokine Levels in Kidney Transplant Recipients with Normal Graft Function and Allograft Rejection

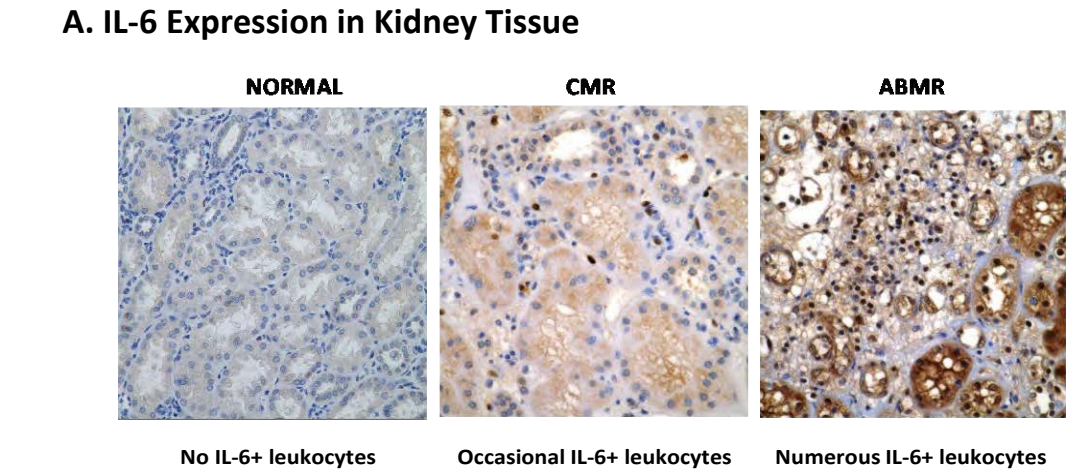


AMR = antibody-mediated rejection; AR = acute rejection; ATN = acute tubular necrosis; Bx = biopsy; CMR = cell-mediated rejection; CNI = calcineurin inhibitor; IFNγ = interferon-gamma; IL = interleukin; sCr = serum creatinine; Tx = transplant.
Source: , unpublished data.

In Figure 9, Panel A, serum cytokines are shown for post-transplant patients who had for cause biopsies (blue dots) versus those who did not have biopsies (red dots). As can be seen, the IL-6 levels are quite low in patients with quiescent allografts. However, in Figure 9, Panel B, patients with ABMR show significant elevations of IL-6 serum levels in concert with ABMR onset. The X axis shows time before, time at biopsy and initiation of treatment for those showing rejection (time zero), and time after biopsy. IL-6 levels appear to diminish with treatment of ABMR. Figure 9, Panel C shows serum cytokine levels in patients who had biopsies that did not show allograft rejection. These data suggest that elevations of serum IL-6 levels may be involved in the pathogenesis of ABMR and could be used as an early marker for allograft dysfunction mediated by antibody injury.

To determine if IL-6 is expressed in the biopsies of patients undergoing allograft rejection, Jordan et al also examined renal biopsy material from patients with normal kidneys, patients with cellular rejection, and patients with ABMR. Sections were stained with anti-sera directed at IL-6 and evaluated by morphometric scanning microscopy (see Figure 10).

Figure 10 IL-6 Expression in the Kidney: Normal Versus CMR and ABMR



ABMR = antibody-mediated rejection; CMR = cell-mediated rejection; IL-6 = interleukin 6; tx = transplant.
Source: Jordan et al, unpublished data.

Briefly, Jordan et al showed that the number of IL-6$^+$ cells were significantly increased in biopsies demonstrating ABMR compared to cell-mediated rejection (CMR) or normal kidney tissue. Figure 10, Panel A shows representative staining of normal kidney tissue, tissue from a patient with cellular rejection, and a biopsy from a patient with ABMR. In this instance, there are numerous IL-6$^+$ cells in the biopsy of ABMR compared with CMR and normal tissue. Figure 10, Panel B shows data from a larger analysis of ABMR biopsies compared to other diagnoses. Using morphometric scanning analysis, Jordan et al were able to show a significant increase in IL-6 expression in biopsies with ABMR. Altogether, these data suggest that IL-6 might play an important role in antibody-mediated injury to allografts.

Along with the data presented in Figure 9 which demonstrates elevated levels of IL-6 in the sera of patients with ABMR, these findings suggest the possibility of IL-6 blockade as a potentially important therapy in management of ABMR.

4.2 Evidence from Nonclinical Studies Supporting the Role of IL-6 in ABMR

4.2.1 Nonclinical Studies with Anti-IL-6R mAbs

4.2.1.1 Anti-IL-6R Antibodies Attenuate Antibody Recall Responses in a Mouse Model of Allo-Sensitization

Kim et al, 2014 investigated the ability of an anti-IL-6R mAb (mMR16-1) to modify immune responses in a mouse model of allo-sensitization in which C57 black mice were presensitized with a skin allograft from C57 black HLA-A2 transgenic mice [Wu et al, 2013; Kim et al, 2014; Jordan et al, 2017]. Sensitized mice were then re-exposed to a second graft with 1 cohort receiving treatment with anti-IL-6R mAb and a second cohort receiving a control antibody.

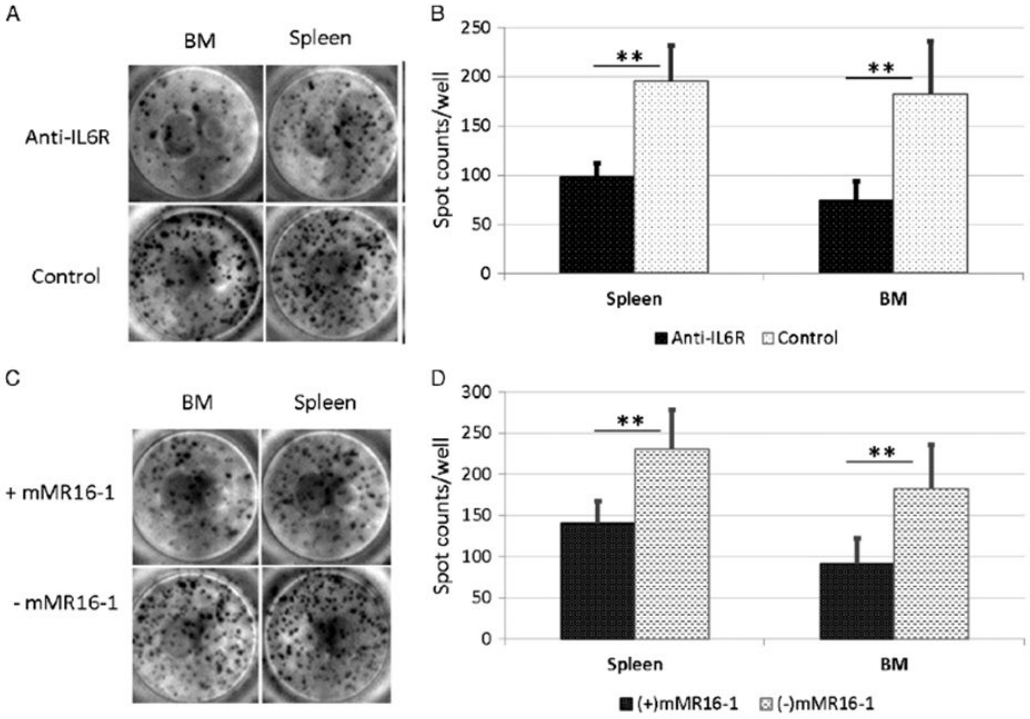
Re-exposure of sensitized control mice to HLA-A2+ skin allografts resulted in a surge of DSA (anti-HLA-A2 immunoglobulin G [IgG]) [Kim et al, 2014]. Titers of DSA were significantly lower in the anti-IL-6R-treated mice compared with isotype controls. Flow cytometry analysis of anti-IL-6R-treated mice demonstrated a significant increase in Treg cells (Foxp3+ CD4+) and a significant decrease in both Th17 cells (interleukin 21+ CD4+) and Tfh cells (CXCR5+ CD4+) compared to isotype antibody-treated controls.

Finally, using an IgG enzyme-linked immunospot assay (ELISpot), the impact of anti-IL-6R on terminally differentiated plasma cells was demonstrated (see Figure 11). Dramatic reductions were observed in the anti-HLA-A2 antibody in the supernatants of bone marrow and splenic plasma cells for anti-IL-6R-treated animals compared with the isotype controls.

As shown in Figure 12, the addition of anti-IL-6R to the plasma cell cultures of isotype treated animals showed a similar suppressive effect on anti-HLA-A2 production, thereby demonstrating a direct effect of anti-IL-6R on plasma cell antibody production.

Together, these findings suggest a multifaceted mechanism of anti-IL-6R attenuation of antibody recall response to skin allograft, including modulation of a number of immune regulatory and effector cells: ie, decreased Th17 and Tfh cells, increased Treg cells, and reduced B cell progression to plasmablast, plasma cells, and IgG production.

Figure 11 Anti-IL-6R mAb Significantly Suppressed IgG + Plasma Cells in the Bone Marrow and Spleen (ELISpot Assay)



BM = bone marrow; ELISpot = enzyme-linked immune absorbent spot; IgG = immunoglobulin G; IL-6R = interleukin 6 receptor; mAb=Monoclonal antibody

Notes:

Anti-IL-6R mAb significantly suppressed IgG+ plasma cells in the bone marrow and spleen as demonstrated in an ELISpot assay.

A: Representative photos of ELISpots produced by bone marrow cells or splenocytes (spleen) from mice of anti-IL-6R group or control group, showing a decrease of IgG spots in the bone marrow and spleen of anti-IL-6R-treated mice.

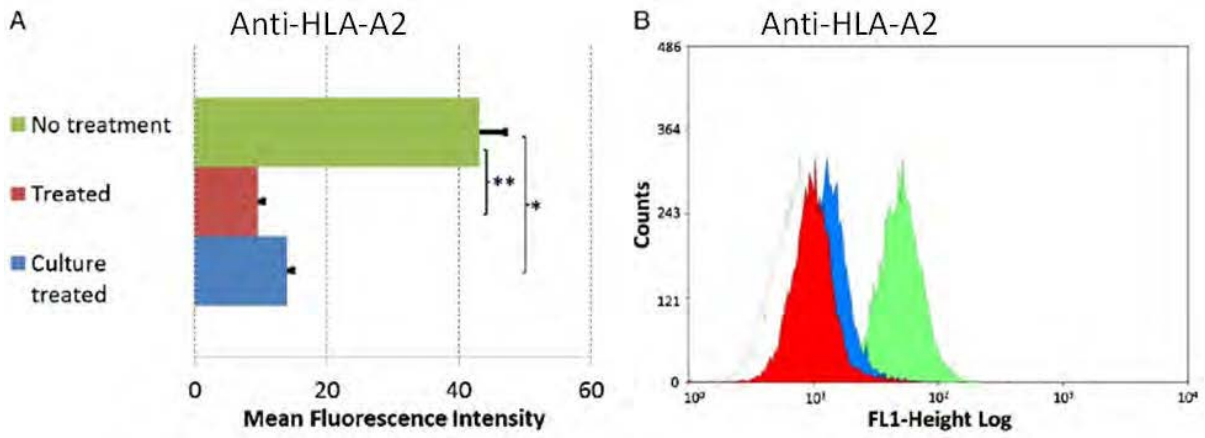
B: Bar-graph presentation of spot-counts from the anti-IL-6R (n = 3) and the control (n = 4) groups, showing statistically significant differences.

C: Photos of ELISpots produced by bone marrow cells or spleen cells from the control mice, showing evidence of suppression of IgG spot formation by in vitro treatment of B cells / plasma cells with anti-IL-6R antibody (mMR16-1) in cultures.

D: Bar graph presentation of spot-counts from the control bone marrow (n = 4) and spleens (n = 4) with (+mMR16-1) or without (mMR16-1) in vitro treatment. **p < 0.01.

Source: Kim et al, 2014, Figure 5.

Figure 12 Anti-IL-6R mAb Inhibits Anti-HLA-A2 Antibody (Flow-Antibody Binding Assay)



DSA = donor-specific antibodies; HLA = human leukocyte antigen; IL-6 = interleukin 6; IgG = immunoglobulin G; mAb = monoclonal antibody.
Notes: Detection of anti-HLA.A2 IgG antibodies in conditioned media of bone marrow cell cultures by flow-antibody binding assay.
A: Bar graphs show that bone marrow cells from no treatment mice (green bar) produced significantly higher levels of DSA(IgG) as compared with that of anti-IL-6R-treated mice (red bar) at Day 14 in recall responses to second skin allografts. Also, in vitro treatment of bone marrow cells from the no treatment mice with anti-IL-6R antibody significantly reduced IgG alloantibodies (blue bar).
B: Representative histograms demonstrating antibody binding to HLA-A2-expressing target cells detected in 96-hr culture supernatants of (1) no treatment bone marrow (green bar); (2) anti-IL-6R-treated mouse bone marrow (red bar); (3) no treatment mouse bone marrow treated with anti-IL-6R in culture (blue bar) and the isotype control (gray line).
*$p < 0.05$; **$p < 0.01$.
Source: Kim et al, 2014, Figure 6.

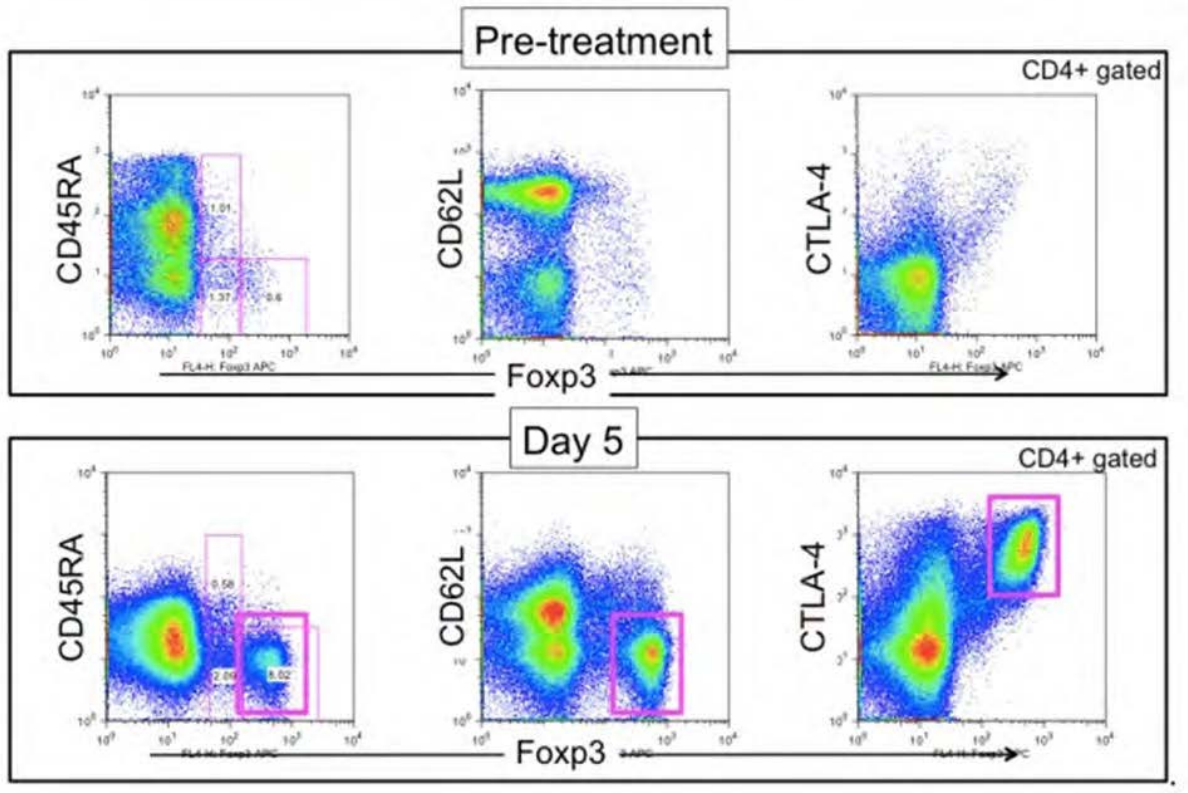
4.2.1.2 Non-Human Primate Lung Allograft Survival Is Prolonged by Anti-IL-6R Antibody and Anti-Thymocyte Globulin Treatment Possibly Through Expansion of Peripheral Regulatory T Cells

Aoyama et al. examined the effect of anti-IL-6R mAb (TCZ) and / or anti-thymocyte globulin (ATG) treatment in cynomolgus monkeys before and after transplantation with equine lung [Aoyama et al, 2016]. Tocilizumab treatment in combination with ATG was associated with an increase in peripheral Treg cells (see Figure 13) that was not observed in animals treated with ATG alone. As shown in Figure 14, graft survival was prolonged in animals who received TCZ + ATG in addition to SOC treatment with tacrolimus + steroids + mycophenolate mofetil (MMF) compared to animals who received SOC alone or SOC + ATG. Briefly, all animals treated with SOC alone lost their grafts by Day 100 with 20% survival at Day 60, and all animals in this group were also DSA+. Animals receiving SOC + ATG had 60% survival at Day 120 and were also DSA+. However, those that received TCZ in addition to SOC + ATG had 100% survival at Day 120 and were DSA–.

In summary, treatment with an IL-6 blocking antibody in combination with ATG was associated with an increase in peripheral Treg cells, inhibition of DSA generation

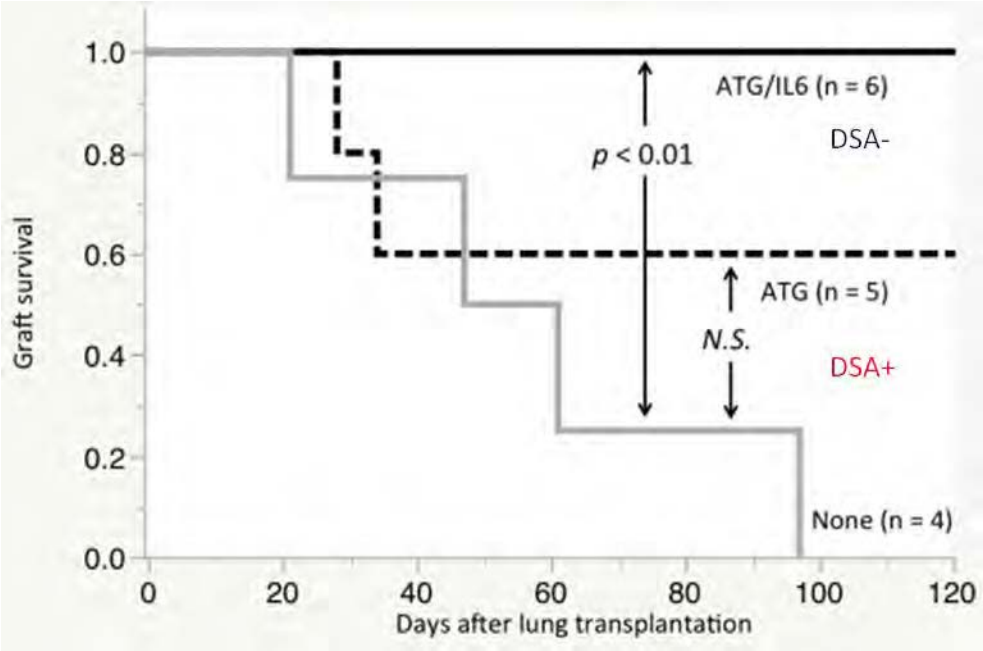
post-transplant, and graft survival. The observed increase in Treg cells is likely responsible for the improved graft survival and lack of DSA development post-transplant.

Figure 13 Flow Cytometry Analysis of Blood from Non-human Primates Before and After Treatment with TCZ and ATG (Before Transplant)



ATG = anti-thymocyte globulin; TCZ = tocilizumab.
Notes: Flow cytometry analysis of blood from cynomolgus monkeys before and after treatment with TCZ plus ATG showing increase in peripheral Treg cells.
Source: Aoyama et al, 2016.

Figure 14 Graft Survival in Non-Human Primates Treated with ATG Plus or Minus TCZ



ATG = anti-thymocyte globulin; DSA = donor-specific antibody; IL6 = interleukin 6; MMF = mycophenolate mofetil; N.S. = not significant; SOC = Standard of Care; TCZ = tocilizumab.
Notes: Survival of lung transplants in cynomolgus monkeys who received standard treatment with tacrolimus + steroids + MMF (ie, SOC), or SOC + ATG, or SOC +ATG + TCZ.
Source: Aoyama et al, 2016.

4.2.2 Additional Nonclinical Studies Supporting the Role of IL-6 in ABMR

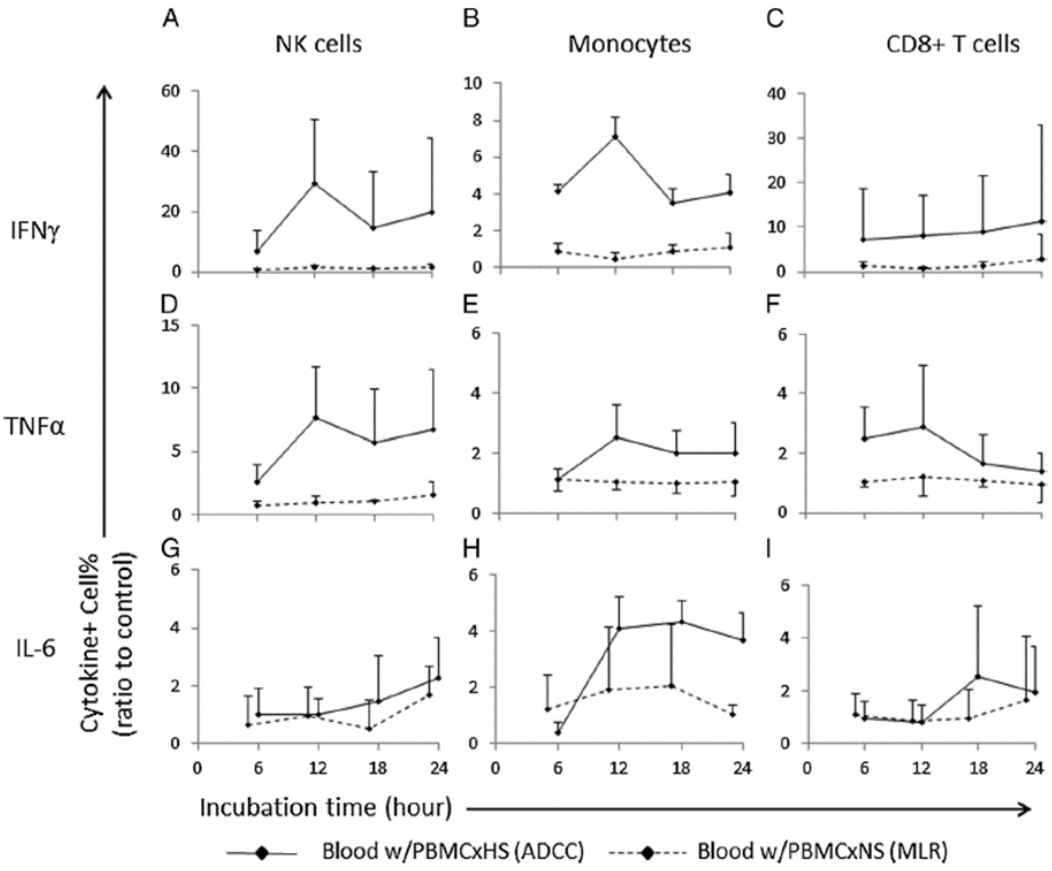
4.2.2.1 Anti-IL-6R Induced Suppression of TNFα Production by Human Monocytes in an In Vitro Model of Anti-HLA Antibody-Induced ADCC

Shin et al. investigated if natural killer (NK) cells, primary cells for ADCC, and other CD16+ (ie, FcγR IIIA+) cells, primarily monocytes and CD8+ T cells, are capable of alloantibody-mediated cell activation, resulting in cytokine production in the in vitro ADCC model, and if TCZ is capable of suppressing these activation events and cytotoxicity in ADCC [Shin et al, 2017]. Whole blood from a normal individual was incubated overnight with irradiated allo-peripheral blood mononuclear cells (PBMCs) pretreated with anti-HLA antibody positive (in vitro ADCC) or negative sera (mixed lymphocyte reaction [MLR]), with or without TCZ or control IgG. Intracellular cytokine production was analyzed by cytokine flow cytometry.

Results showed that IFN-γ+ and / or tumor necrosis factor alpha (TNFα)+ cell% in NK cells, monocytes and CD8+ T cells were elevated in the ADCC compared to the MLR condition (see Figure 15). IL-6+ cells were significantly increased in ADCC versus MLR (10.2 ± 4.8%

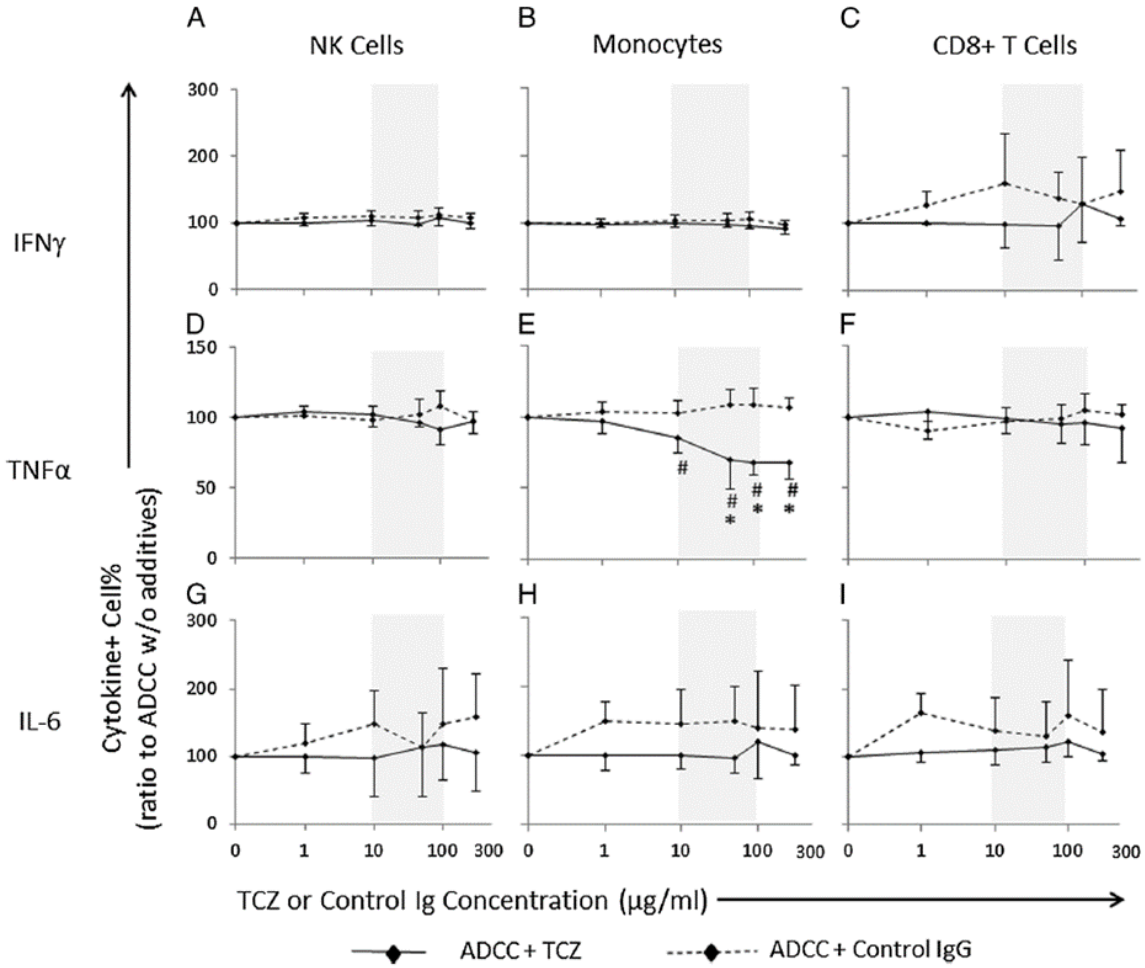
versus 2.7 ± 1.5%, p=0.0003), but only in monocytes. Treatment with TCZ significantly reduced TNFα+ cell% in monocytes in ADCC, but had no effect on other cytokine+ cells (see Figure 16) and showed no effect on cytotoxicity in ADCC. Thus, IFN-γ, TNFα, and IL-6 production induced by HLA antibody-mediated CD16 bearing cell activation in NK cells, monocytes, and CD8+ T cells suggests a potential role for ADCC and these inflammatory cytokines in mediation of ABMR. Tocilizumab suppression of TNFα production in monocytes in the ADCC condition suggests a role of the IL-6 / IL-6R pathway in monocyte activation. Inhibition of this pathway could reduce the inflammatory cascade induced by alloantibody, although the inhibitory effect on cytotoxicity was minimal in vitro.

Figure 15 Cytokine Production in NK cells, Monocytes and CD8+ T Cells in the In Vitro ADCC and MLR Cultures as Detected by CFC



ADCC = antibody-dependent cellular cytotoxicity; CFC = cytokine flow cytometry; HS = human leukocyte antigen (HLA) sensitized; IFNγ = interferon-gamma; IL-6 = interleukin 6; MLR = mixed lymphocyte reaction; NK = natural killer; NS = non-sensitized; PBMC=Peripheral blood mononuclear cells; TNFα=Tumor necrosis factor alpha.
Source: Shin et al, 2017, Figure 2.

Figure 16 The Effect of TCZ on IFNγ, TNFα, and IL-6 Production in NK Cells, Monocytes and CD8+ T Cells in In Vitro ADCC



ADCC = antibody-dependent cellular cytotoxicity; IFNγ = interferon-gamma; IgG = immunoglobulin G; IL-6 = interleukin 6; NK = natural killer; TCZ = tocilizumab; TNFα = tumor necrosis factor alpha.

Notes:
# $p < 0.05$ vs control IgG at each concentration.
* $p < 0.05$ vs ADCC condition without additives.

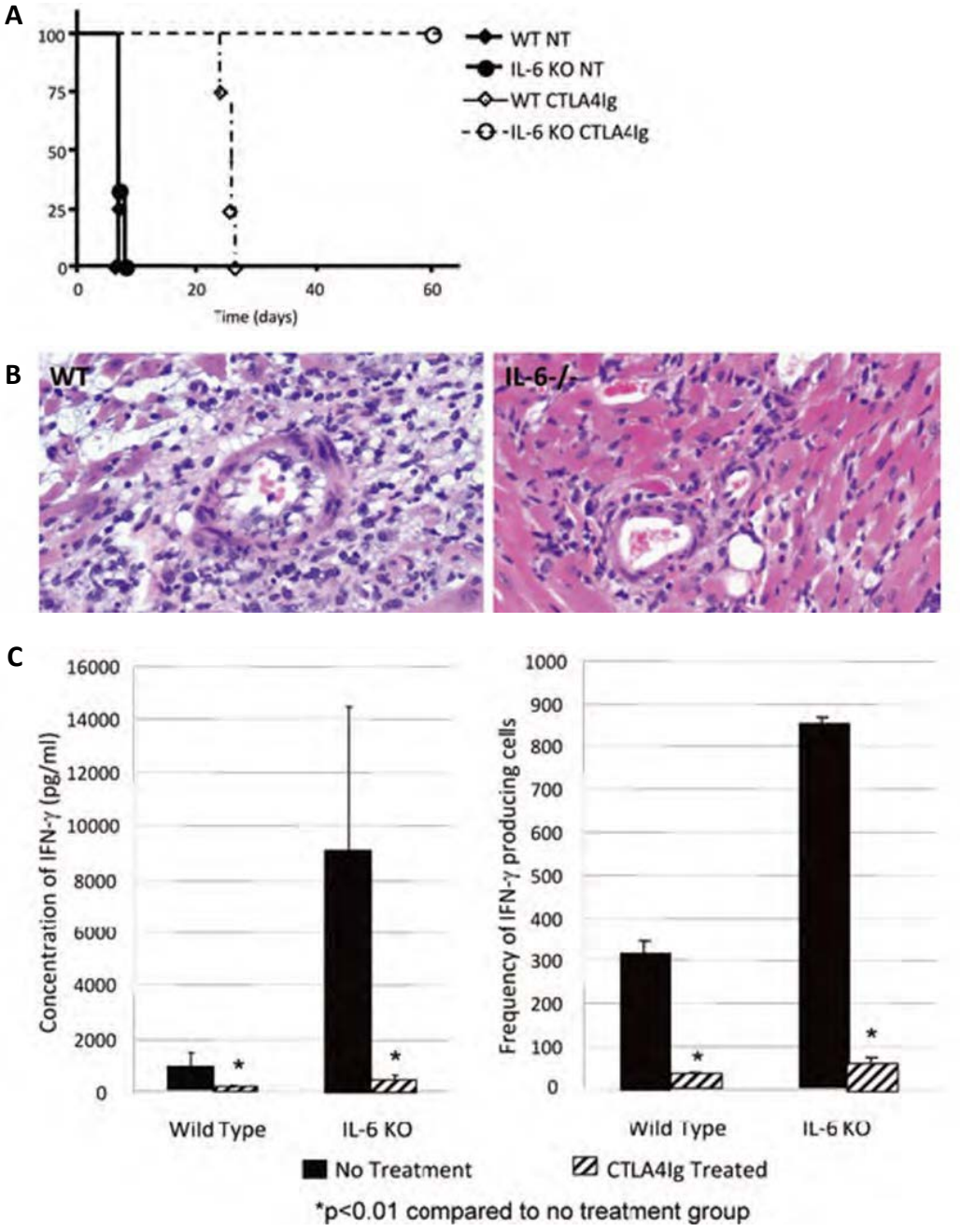
Source: Shin et al, 2017, Figure 4.

4.2.2.2 IL-6 Blockade (in Combination with CD28-B7 Blockade) Promotes Long-Term Allograft Acceptance and Tolerance in Mice

Zhao et al. investigated the role of IL-6 in mediation of experimental cardiac allograft rejection. BALB/c cardiac allografts were transplanted into wild-type or IL-6-deficient (ie, IL-6 -/- knock-out) C57BL/6 mice [Zhao et al, 2012]. In wild-type mice, IL-6 and IFN-γ production were upregulated during rejection. In IL-6 deficient mice, IFN-γ production was greater than that observed in wild-type controls (Figure 17C) suggesting that IL-6 production affects Th1 / Th2 balance during allograft rejection. CD28-B7 blockade by treatment with

CTLA4-Ig (a fusion protein blocking the CD28-B7 pathway) inhibited IFN-γ production but did not affect IL-6. Although wild-type C57BL/6 recipients treated with CTLA4-Ig rejected fully major histocompatibility complex (MHC)-mismatched BALB/c heart transplants, treatment of IL-6 deficient mice with CTLA4-Ig resulted in graft acceptance (see Figure 17A and Figure 17B).

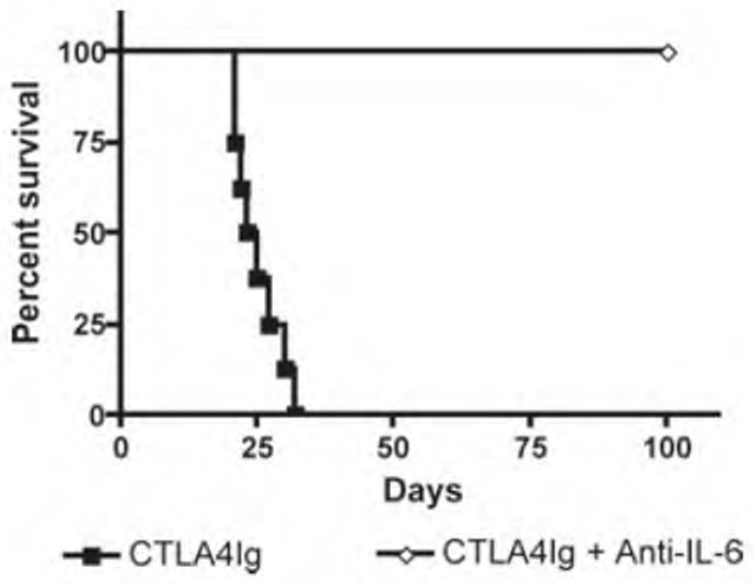
Figure 17 Effect of IL-6 Deficiency on Allograft Tolerance



IFN-γ = interferon-gamma; IL-6 = interleukin 6; KO = knock-out; MHC = major histocompatibility complex; NT = no treatment; WT = Wild type.
Notes:
A. Survival (%) of fully MHC-mismatched BALB/c cardiac allografts in wildtype C57BL/6 and IL-6 -/- knock-out mice with and without treatment with CTLA4Ig (n = 4 to 7 per group).
B. Representative example of allograft pathology at 3 weeks after transplantation showing relatively normal myocardium and vasculature in the IL-6 -/- recipient. C. IFN-γ production (mean ± standard deviation) by splenocytes.
Source: Zhao et al, 2012, Figure 4.

Long-term allograft acceptance was also seen in wildtype mice treated with combined CTLA4 immunoglobulin and anti-IL-6 antibody (see Figure 18). The investigators also noted an increase in Treg cells in animals receiving anti-IL-6 therapy that was not seen in isotype controls. The authors concluded that blocking the effects of IL-6 in combination with costimulatory blockade may be an important strategy to promote long-term allograft acceptance and tolerance.

Figure 18 Neutralization of IL-6 In Vivo Promotes Allograft Survival with Costimulation Blockade



IgG = immunoglobulin G; IL-6 = interleukin 6; mAb = monoclonal antibody; MHC = major histocompatibility complex.
Notes: Survival of fully MHC-mismatched BALB/c cardiac allografts in wildtype C57BL/6 recipients treated with CTLA4Ig and either anti-IL-6 mAb (n = 5) or control IgG (n = 8).
Source: Zhao et al, 2012, Figure 6.

4.2.2.3 Neutralizing IL-6 Reduces Human Arterial Allograft Rejection by Allowing Expansion of CD161+ CD4+ Treg Cells

Fogal et al. investigated the effect of neutralizing IL-6 on human arterial segments transplanted into immunodeficient mice [Fogal et al, 2011]. IL-6 transcripts in transplanted tissue were shown to rapidly increase post-transplantation compared to before transplant

specimens and fall dramatically by 30 days post-transplant. Adoptive transfer of human PBMCs with allospecificity to the arterial alloantigens resulted in T cell infiltrates and intimal expansion 4 weeks later. Neutralization of human IL-6 using a mAb significantly reduced the magnitude of intimal expansion and total T cell infiltration but increased the relative expression of CD161+ Treg cells while decreasing other Th17 markers. In other experiments, culturing of MHC Class II expressing human endothelial cells with allogeneic CD4+ memory T cells resulted in T cell activation and endothelial cell secretion of IL-6. In primary allogeneic T cell endothelial cell cocultures, neutralization of IL-6 with a mouse antihuman IL-6 mAb resulted in enhanced proliferation of CD161+ / CD4+ Treg cells. The authors concluded that IL-6 released from injured allograft vessels appears to enhance allogeneic T cell infiltration and intimal expansion in a model of human allograft rejection by inhibiting an increase in CD161+ Treg cells.

4.2.2.4 Intrarenal B Cell Cytokines Promote Transplant Fibrosis and Tubular Atrophy in a Mouse Model of Kidney Transplant Rejection

Tse et al recently showed that chronic allograft damage in a mouse model of kidney transplant rejection, specifically interstitial fibrosis / tubular atrophy, was mediated by B cells producing intra-graft chemokines and IL-6 [Tse et al, 2015]. B cell depletion with anti-CD20 antibody given after the initiation of chronic allograft damage was able to reduce intra-graft B cells, chemokines, IL-6 levels, and interstitial fibrosis / tubular atrophy. These findings suggest that persistent B cell activation and IL-6 production may be important in mediation of chronic allograft nephropathy and could possibly be important in human CABMR.

4.2.2.5 Antibodies from Donor B Cells Perpetuate Cutaneous Chronic GVHD in Mice

Using a mouse model of chronic graft-versus-host disease (GVHD), Jin et al showed that donor antibodies were responsible for damage to the thymus and skin that was also associated with IgG-induced Th17 infiltration into the skin of affected animals [Jin et al, 2016]. Thus, B cell antibodies appeared to augment cutaneous chronic GVHD. Srinivasan et al reported that donor B cell–derived antibodies also enhance development of bronchiolitis obliterans in a murine model of chronic GVHD [Srinivasan et al, 2012]. In this model, recipient germinal centers were enlarged, and blockade of germinal center formation prevented induction of chronic GVHD. Both studies suggest a potential role for IL-6 in induction of the Th17 and plasmablast pathway for progression of chronic GVHD.

4.3 Evidence from Clinical Studies Supporting the Role of IL-6 in ABMR - Studies with Anti-IL-6R (TCZ)

4.3.1 TCZ Treatment Resulted in Reduction of DSA and Improved Graft Survival in HLA-Sensitized Renal Allograft Recipients with CABMR and TG

Choi et al investigated the effect of TCZ treatment in 36 HLA-sensitized renal allograft recipients with CABMR and TG, each of whom had failed treatment with IVIG + rituximab ± PLEX [Choi et al, 2017a]. These patients were treated with monthly intravenous (IV) infusions of TCZ (8 mg/kg, maximum dose 800 mg) as rescue therapy for 6 to 25 months and monitored for DSA and long-term outcomes for up to 8 years. Baseline features of these 36 patients are shown in Table 3.

All patients had evidence of significant pathological injury at initiation of TCZ treatment, and 17 of 36 (47%) patients were re-transplants. Twenty-five of 36 (69%) patients had more than 2 prior ABMR episodes and 33 of 36 (92%) had received more than 2 rounds of ABMR treatment with pulse steroids, IVIG, rituximab, ± eculizumab and ± PLEX for treatment-resistant ABMR before initiation of TCZ. At the time of CABMR diagnosis, 31/36 (86%) patients had demonstrable HLA-DSA with Class II DSA predominating. Three patients did not demonstrate HLA-DSA but showed elevated levels of anti-angiotensin Type 1 receptor antibodies.

Table 3 Baseline Characteristics of CABMR Patients Treated with TCZ

	N	Patients
Recipient characteristics		
Age (yrs), mean (SD)	36	45.86 (16.64)
Gender male, n (%)	36	19 (52.78)
Graft rank > 1, n (%)	36	17 (47.22)
Donor characteristics		
Decreased donor, n (%)	36	20 (55.56)
Extended-criteria donor, n (%)	36	1 (2.78)
Cold ischemia time > 24 h, n (%)	36	2 (5.56)
Delayed graft function[(a)], n (%)	36	6 (16.67)
Immunology at the time of transplantation		
HLA mismatches, mean (SD)	28[(b)]	4.07 (1.46)
Anti-HLA DSA-positive, n (%)	28[(b)]	18 (64.29)
Time from transplantation to treatment (yrs), mean (SD)	36	6.72 (4.63)

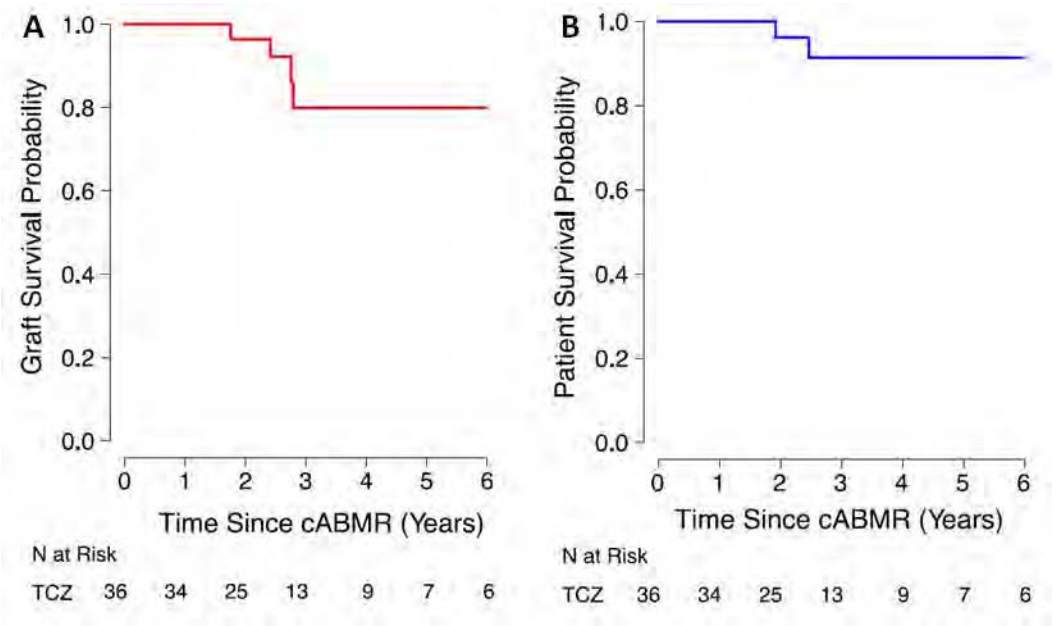
Immunology at the time of ABMR		
Anti-HLA DSA^{+}, n (%)	36	33 (91.67)
Anti-angiotensin Type 1 receptor antibody^{+} / DSA^{-}, n (%)	36	3 (8.33)
Number of anti-HLA DSA, mean (SD)	33[(c)]	1.91 (1.26)
Number of Class 1, mean (SD)	33[(c)]	0.43 (0.66)
Number of Class 2, mean (SD)	33[(c)]	1.45 (0.94)
Renal function at the time of ABMR		
eGFR (mL/min/1.73 m^2), mean (SD)	36	48.43 (34.56)
eGFR (mL/min/1.73 m^2) for adult patients, mean (SD)	32	38.82 (10.37)
eGFR (mL/min/1.73 m^2) for pediatric patients, mean (SD)	4	77.63 (25.86)
Follow-up (yrs), mean (SD)	36	3.26 (2.04)
Graft loss, n (%)	36	4 (11.11)
Received > 2 ABMR treatment sessions before TCZ, n (%)	36	33 (91.67)

ABMR = antibody-mediated rejection; CABMR = chronic active antibody-mediated rejection; DSA = donor-specific antibody; eGFR = estimated glomerular filtration rate; HLA = human leukocyte antigen; SD = standard deviation; TCZ = tocilizumab; yrs = years.
Notes:
[a] Delayed graft function was defined as the use of dialysis in the first postoperative week.
[b] Information available for 28 of 36 patients.
[c] Among the patients with anti-HLA DSAs.
Source: Choi et al, 2017a, Table 1.

Tocilizumab-treated patients demonstrated graft survival and patient survival rates of 80% and 91% at 6 years, respectively (Figure 19). Statistically significant reductions in DSA were seen at 2 years (see Figure 20). Notably, stabilization of renal function (ie, eGFR) was seen over 36 months (see Figure 21), a clinically important finding given that renal function would be expected to decline over time in patients with ABMR and DSA [Fotheringham et al, 2011; Eskandary et al, 2014; Wiebe et al, 2015].

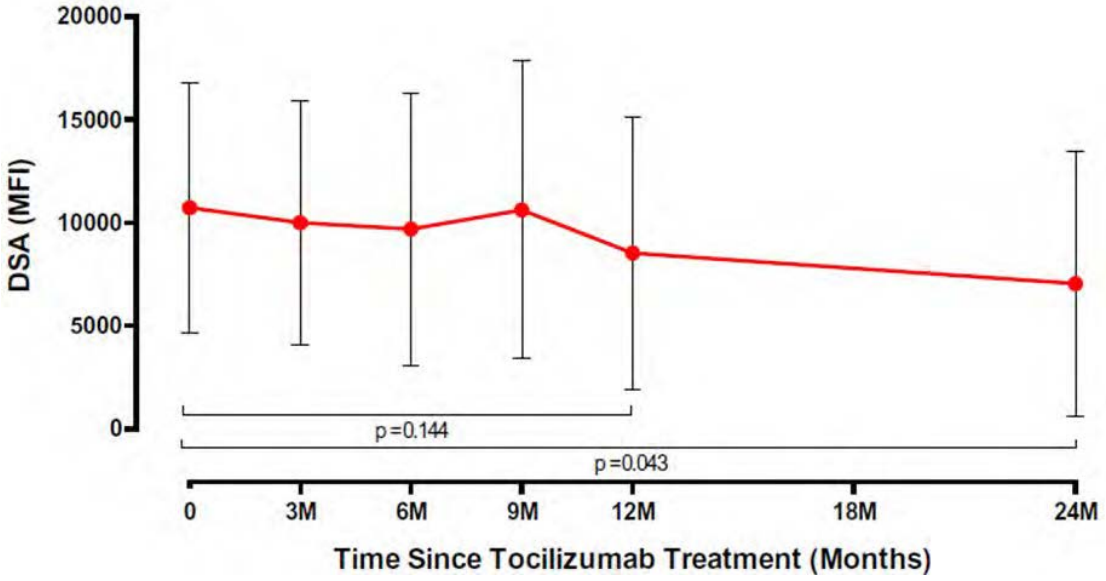
Nine patients also underwent repeat biopsies 1 year after initiation of TCZ treatment to assess the impact of therapy on pathologic features of CABMR (Banff 2013 criteria [Haas et al, 2014]) and to determine if continuation of therapy was advisable. As shown Figure 22, statistically significant improvements in the scores of complement staining (C4d scores) and microvascular inflammation (glomerulitis (g) + peritubular capillaritis (ptc) scores) were observed. These parameters have been shown to be associated with the development of TG and graft loss [Haas and Mirocha, 2011; De Serres et al, 2016].

Figure 19 Kaplan-Meier Analysis of Graft and Patient Survival Over Time Post Treatment with TCZ



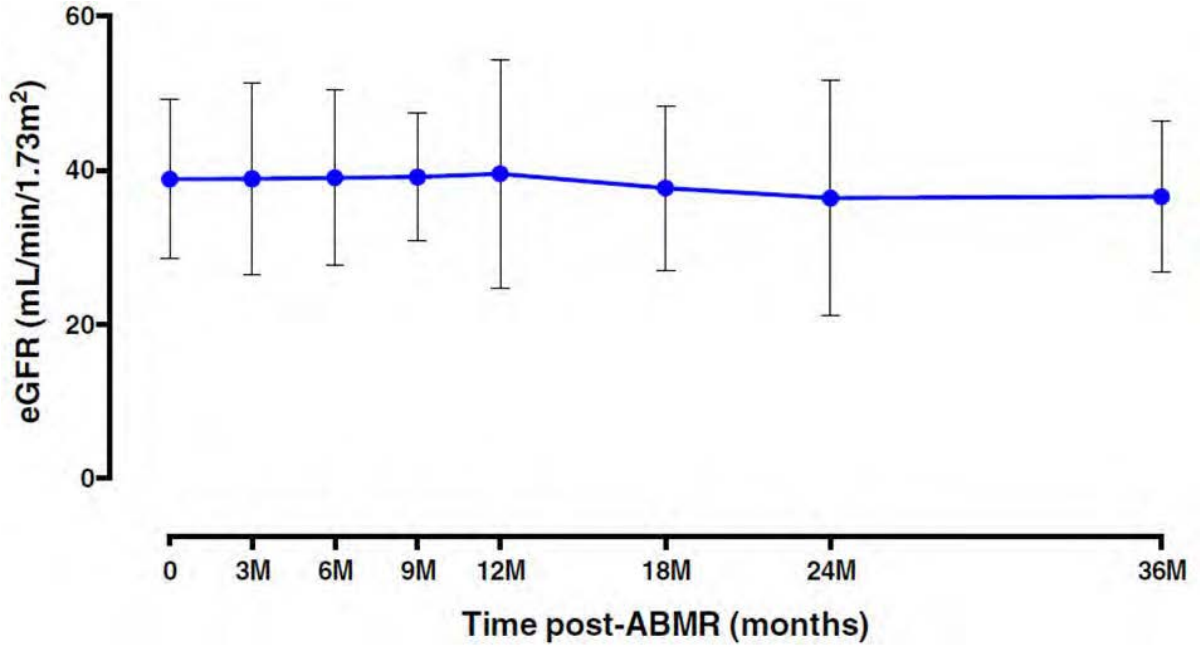
cABMR = chronic active antibody-mediated rejection; TCZ = tocilizumab.
Source: Choi et al, 2017a, Figure 2.

Figure 20 Mean Immunodominant DSA Values for TCZ-Treated Patients



DSA = donor-specific antibodies; MFI = mean fluorescence intensity; TCZ = tocilizumab.
Source: Choi et al, 2017a, Figure 4.

Figure 21 Mean eGFR Value of TCZ-Treated Adult CABMR Patients



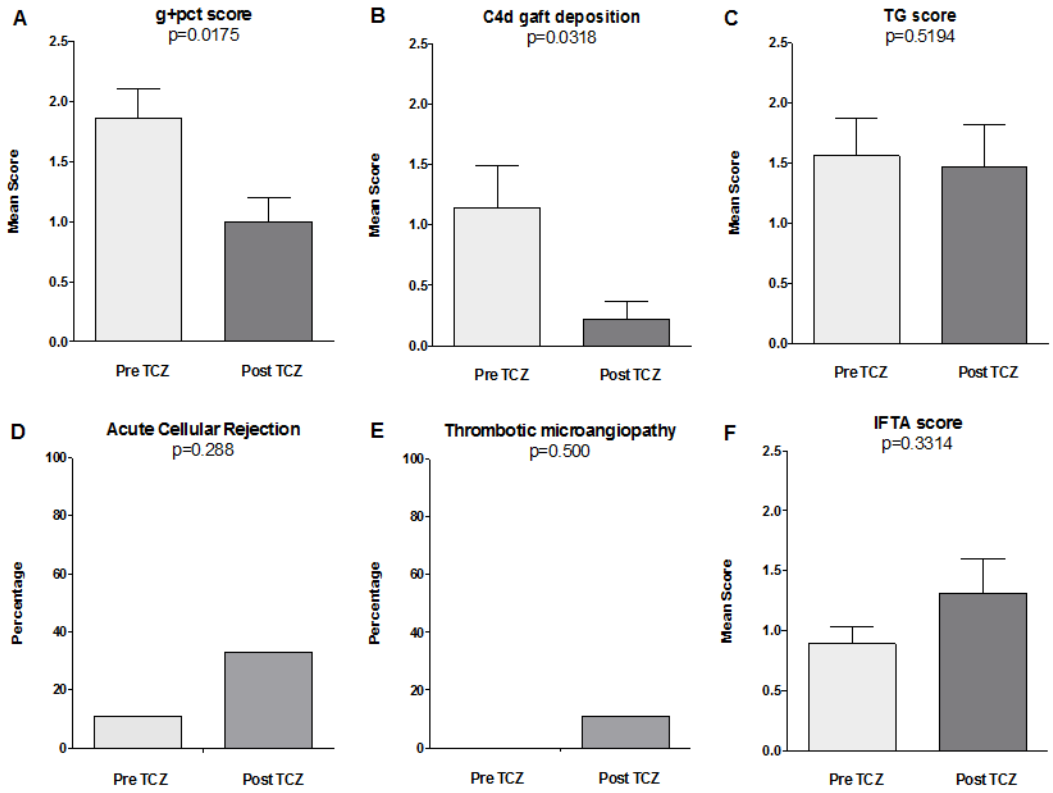
ABMR = antibody-mediated rejection; CABMR = chronic active antibody-mediated rejection; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; TCZ = tocilizumab.

Notes:

Mean eGFR value of TCZ-treated adult CABMR patients (N = 32, > 18 years). eGFR values were maintained over the course of TCZ treatment after CABMR biopsy (36 months). 4 adult patients with graft loss were excluded. eGFR values were calculated by the MDRD equation for all adult patients.

Source: Choi et al, 2017a, Figure 3.

Figure 22 Allograft Phenotype Pre- and Post-TCZ Treatment



C4d = complement component 4d; g = glomerulitis; IFTA = interstitial fibrosis and tubular atrophy; ptc = peritubular capillaritis; TCZ = tocilizumab; TG = transplant glomerulopathy.

Notes:

This figure shows kidney allograft biopsy phenotypes (Banff 13 scoring) before and after TCZ treatment. Allograft biopsies were obtained 1 year post-TCZ treatment and compared with pre-TCZ CABMR biopsies in 9 patients. Significant reductions in g + ptc scores and C4d deposition were seen with TCZ treatment. Other parameters were stable.

Source: Choi et al, 2017b, Figure 1B.

Choi et al recently reported extended experience with a larger cohort of 65 kidney transplant recipients with CABMR and TG, treated monthly with TCZ 4 to 8 mg/kg IV for 3 to 37 doses and followed up to 6 years from TCZ initiation [Choi et al, 2017b]. The mean time from transplant to TCZ treatment and from CABMR diagnosis to treatment was 5.39 ± 4.3 years and 1.37 ± 1.62 years, respectively. Immunodominant DSA levels tended to decrease after therapy. Mean eGFR decreased from 53.18 ± 34.61 mL/min/1.73 m^2 at Month 0 to 50.43 ± 36.37 mL/min/1.73 m^2 at Month 24. At 6 years, 92.6% of TCZ-treated patients had functioning grafts compared to 53.3% of patients in a SOC group (p = 0.0005) that consisted of 39 non-concurrent CABMR patients treated with IVIG + rituximab ± PLEX. Post-TCZ biopsies taken at a mean of 29.5 ± 18.7 months from pre-TCZ, showed significant

reductions in g + ptc scores compared to biopsy at diagnosis. Two deaths occurred in the TCZ group.

Together, these results indicate that inhibition of the IL-6 / IL-6R pathway may represent a novel approach to stabilize renal allograft function and extend patient lives.

4.3.2 Stabilization of Severe CABMR Progression Following TCZ Treatment in Pediatric Renal Transplant Patients Refractory to B Cell Immunotherapy

Puliyanda et al investigated the effect of TCZ on ABMR progression in 6 pediatric kidney transplant recipients with severe CABMR, refractory to treatment with IVIG and rituximab [Puliyanda et al, 2017]. Patients were treated with TCZ 4 to 8 mg/kg IV monthly for 4 to 12 doses and monitored for immunodominant DSA, renal function, and patient and graft survival. At initiation of TCZ treatment, the mean of patients was 14.2 years. The mean time to CABMR from transplant was 2177 days and the mean time to TCZ treatment from CABMR diagnosis was 457 days. Prior to TCZ treatment, all patients had developed strong (mean fluorescence intensity (MFI) > 10,000) dnDSA and continued to have biopsy-proven CABMR despite B cell immunotherapy.

At a median follow-up of 15 months post TCZ, there was no decline in renal function and no change in the immunodominant DSA. Patient and graft survival were 100% and in 4 patients' renal biopsy 3 months after TCZ there was mild to moderate reduction in C4d staining with no worsening of CABMR. Thus, treatment with TCZ was shown to stabilize the progression of ABMR, resulting in no graft loss and no decline in renal function.

4.3.3 Improved Renal Function and Reduced DSAs Following TCZ Treatment in HLA-Sensitized Patients with Acute ABMR

Venkatachalam et al. examined the efficacy of addition of TCZ to treatment of acute ABMR in 5 highly HLA-sensitized kidney transplant recipients [Venkatachalam et al, 2017]. All 5 patients had evidence of high DSA MFIs at the time of biopsy. During an acute rejection episode, monthly infusions of TCZ 8 mg/kg (for 3 to 6 months) was added to background treatment with solumedrol, IVIG and tacrolimus. In addition, 1 patient also received rituximab, 2 patients received thymoglobulin, and 1 patient received a dose of eculizumab for thrombotic microangiopathy-like features on kidney biopsy.

Renal function improved in all 5 patients; DSA remained stable in 1 patient and decreased significantly in 4 patients (see Table 4). Thus, addition of TCZ to standard acute ABMR treatment appeared to be effective.

Table 4 DSA and Creatinine Levels Before and After Treatment with TCZ for Acute ABMR

Patient	Age	Race	iDSA	Pre-TCZ iDSA MFI	Post-TCZ iDSA MFI	Cr at Time of ABMR	Cr 3 months Post Rejection
1	42	African American	DQB5*01:01	23,477	11,580	2.92	1.70
2	67	Caucasian	DQA1* 06:01/ DQB1*01:01	21,663	6,344	1.8	1.2
3	35	Caucasian	DRB5*01:01	5,346	1,089	1.49	0.7
4	35	Asian	B*51:02	16,864	5,013	5.69	2.02
5	39	African American	DRB1*13:03	22,923	5,515	2.1	1.5

ABMR = antibody-mediated rejection; Cr= creatinine; DSA = donor-specific antibodies; iDSA = immunodominant DSA; MFI = mean fluorescence intensity; TCZ = tocilizumab.
Source: Venkatachalam et al, 2017.

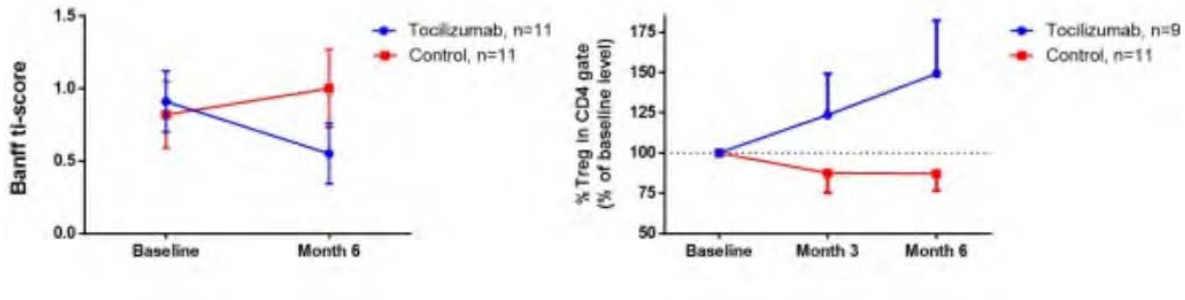
4.3.4 Increased Treg Cells, Decreased CD4+ T Cell Cytokine Production and Decreased Graft Inflammation Following TCZ Treatment in Kidney Transplant Recipients

Chandran et al. examined the effects of TCZ treatment in a small randomized controlled study in stable (eGFR > 30 mL/min/1.73 m^2) kidney transplant recipients with biopsy evidence of subclinical inflammation within 1 year of their transplant and on treatment with tacrolimus + MMF ± prednisone [Chandran et al, 2017]. Subjects received TCZ 8 mg/kg IV monthly for 6 months (n = 11) or no additional treatment (n = 11). PBMCs were collected at baseline, 3 and 6 months after initiation of TCZ treatment and kidney biopsies were performed at baseline and 6 months after initiation of TCZ.

As shown in Figure 23, circulating Treg cells increased over 6 months in the TCZ group (+ 50%) and decreased in the control group (-22.5% [p = 0.012]). Conversely, phorbol myristate acetate / ionomycin stimulated production of interleukin 17 (IL-17) by CD4+ T cells decreased in the TCZ group and increased in the control group. At 6 months, the mean Banff total cortical inflammation score declined 39.5% in the TCZ group and increased 21.9% in the control group. There were no cases of death or graft loss.

In conclusion, TCZ was well tolerated and was associated with a significant increase in circulating Treg cells, a significant decrease in CD4+ T cell cytokine (IL-17) production, and a trend towards decreased graft inflammation.

Figure 23 Increased Circulating Treg Cells and Decreased Graft Inflammation Following TCZ Treatment in Kidney Transplant Recipients



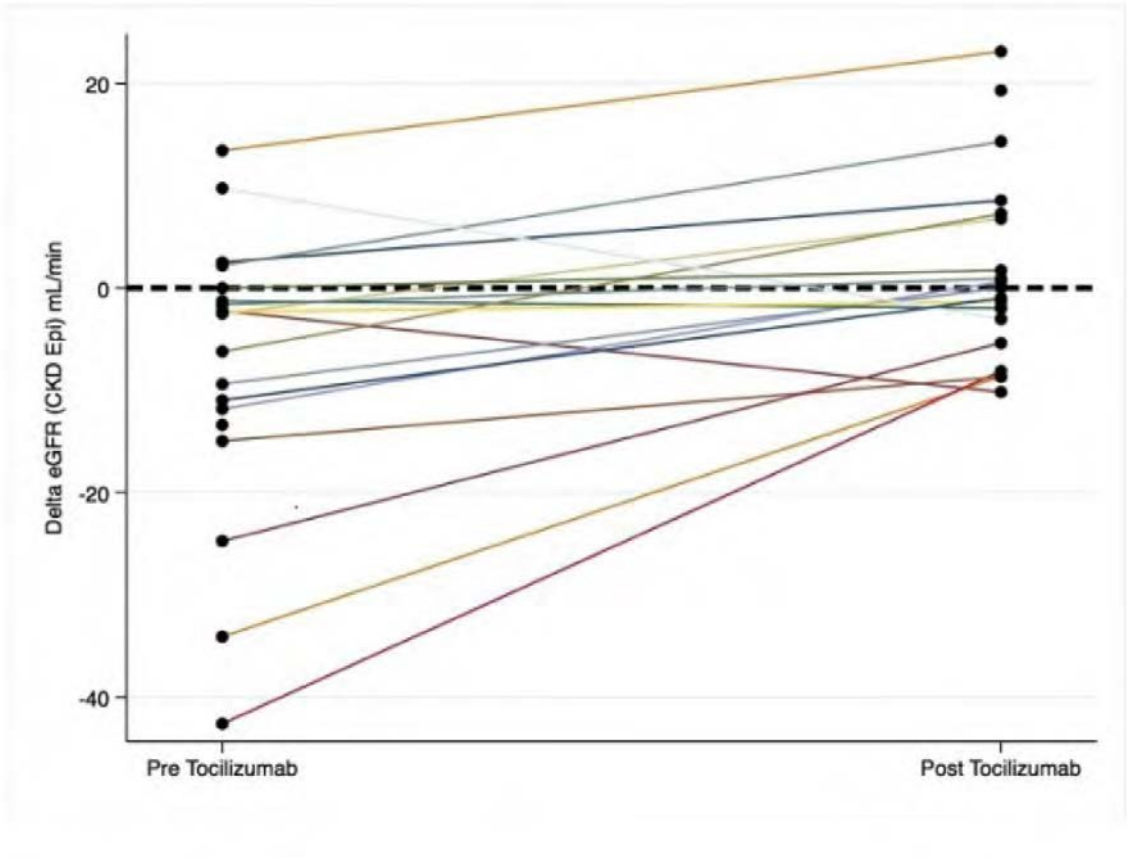
TCZ = tocilizumab; ti-score = total cortical inflammation score; Treg = regulatory T cell.
Source: Chandran et al, 2017.

4.3.5 Stabilization of Renal Function Following TCZ Treatment in Kidney Transplant Recipients with Refractory CABMR

Patel et al investigated the efficacy of the addition of monthly TCZ 8 mg/kg IV to a regimen of tacrolimus, mycophenolate and prednisone in 20 kidney transplant recipients with refractory CABMR [Patel et al, 2017]. All patients had prior ABMR with persistent HLA DSA despite treatment with PLEX (n = 9), IVIG (n = 11), or rituximab (n = 5). TCZ treatment was initiated a mean of 1,648 ± 1,420 days after transplant and was administered for a mean of 323 ± 281 days, and all patients in the study had > 3 months follow-up. Following treatment with TCZ, the rate of eGFR decline decreased to 0.05 mL/min/1.73 m^2/month from 3.9 mL/min/1.73 m^2/month in the 3 months prior to TCZ treatment (see Figure 24). Proteinuria also stabilized with a urine protein creatine ratio of 0.80 at follow-up compared to 1.01 at baseline. No significant changes in DSA were observed. Two graft failures (1 noncompliance and 1 progressive rejection) were reported. There were few infectious complications.

Thus, the addition of TCZ 8 mg/kg IV monthly to a regimen of tacrolimus, mycophenolate and prednisone was shown to stabilize eGFR, despite persistent DSA.

Figure 24 Rate of eGFR Decline Before and After TCZ Treatment



CKD Epi = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; TCZ = tocilizumab.
Source: Patel et al, 2017.

4.3.6 Improved Renal Transplant Rates Following TCZ Treatment in HLA-Sensitized Patients (Resistant to Desensitization with IVIG + Rituximab Therapy ± PLEX) Awaiting Kidney Transplant

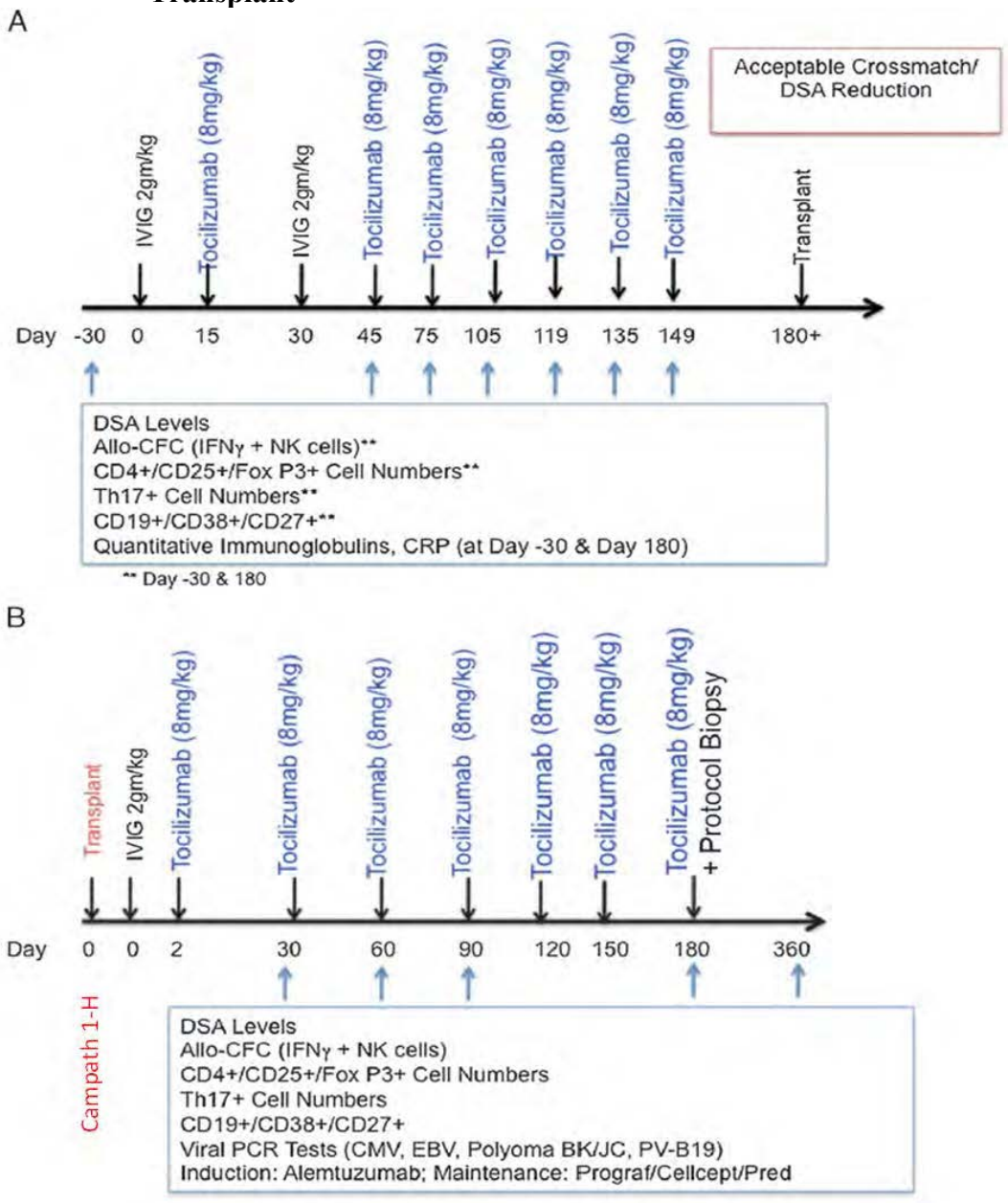
Vo et al. investigated the efficacy of TCZ for reduction of DSA (to a level permissible for renal transplant) in 10 highly-HLA sensitized patients awaiting kidney transplants (see Figure 25) [Vo et al, 2015]. All patients had received previous renal transplants and were resistant to SOC for desensitization (ie, IVIG + rituximab ± PLEX). Two subjects were withdrawn from the study due to non-compliance with the protocol. Of the 8 patients remaining in the study, 5 received transplants during the study. Of note, an additional patient had frequent offers with negative crossmatches, but allocation was not favorable.

Significant reductions in immunodominant DSA were seen in all transplanted patients, with the most significant reduction at 12 months post-transplant. Figure 26A shows the course of immunodominant DSA before treatment, at transplant, and 12 months after transplant, and Figure 26B shows the mean DSA levels.

It is important to note that all patients received additional monthly doses of TCZ for 6 months after transplant. Protocol biopsies at 6 months showed no evidence of CABMR or TG in any of these patients.

Although this study was conducted in a different clinical setting, results of this study show that IL-6 antagonism can reduce the strength and number of immunodominant DSA supporting the potential treatment benefit of IL-6 / IL-6R blockade in the treatment of CABMR in kidney transplant recipients.

Figure 25 Study Design: TCZ Protocol for Desensitization Before- and After Transplant



CFC = cytokine flow cytometry; CMV = cytomegalovirus; CRP = C-reactive protein; DSA = donor-specific antibodies; EBV = Epstein-Barr virus; IFNγ = interferon-gamma; IVIG = intravenous immunoglobulin; NK = natural killer; PCR = polymerase chain reaction; SC = subcutaneous; TCZ = tocilizumab; Th17= T helper cell 17.

Notes:

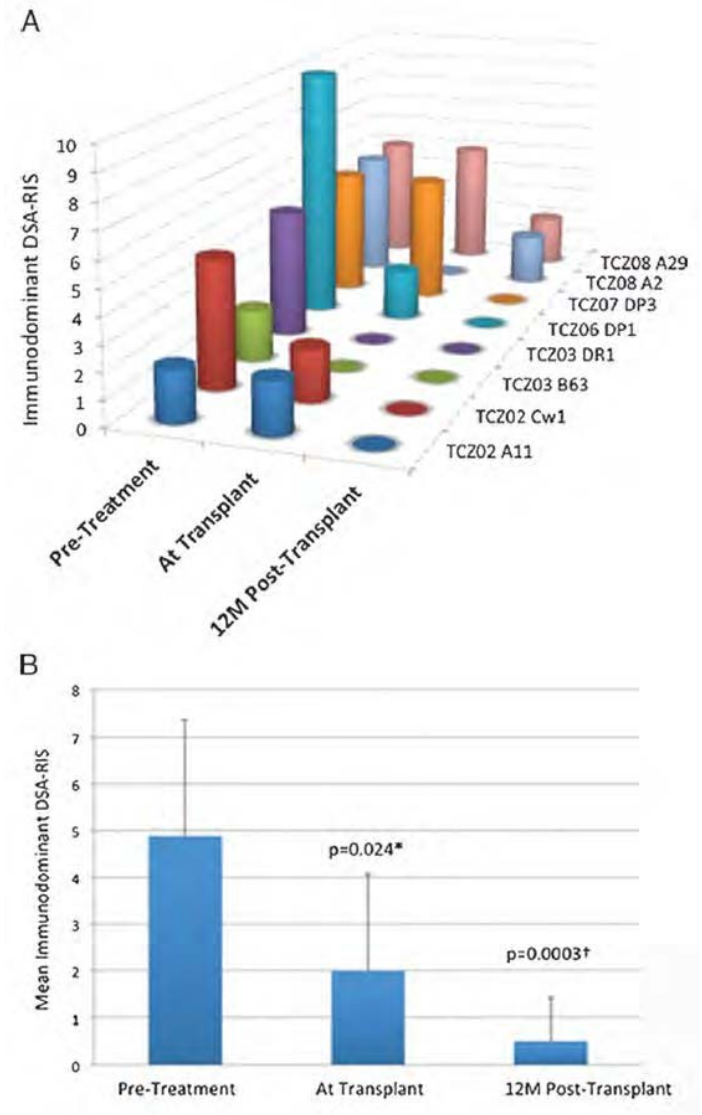
Patients entered into this study received desensitization with IVIG + TCZ for up to 6 months. If renal transplantation was accomplished, patients received an additional 6 months of TCZ after initial induction with Campath 1-H (alemtuzumab) 30 mg SC and IVIG post-transplant. DSA and other immune parameters were measured. Importantly, DSA present before transplant were reduced by TCZ + IVIG treatment.

[a] Before transplant de-sensitization schema.

[b] Post-transplant treatment schema.

Source: Vo et al, 2015; Figure 4.

Figure 26 Reduction in Immunodominant DSA Following TCZ Treatment



ABMR = antibody-mediated rejection; AT1R = angiotensin II receptor Type 1; DSA = donor-specific antibodies; MFI = mean fluorescence intensity; RIS = relative intensity scale; TCZ = tocilizumab.

Notes:

This figure shows the course of immunodominant DSA before treatment, at transplant, and 12 months after transplantation.

A. The course of immunodominant DSA before treatment, at transplant and 12 months after transplant. DSA levels are shown for the 5 individual patients who received a transplant during the study (TCZ02, TCZ03, TCZ06, TCZ07, and TCZ08). The DSA were eliminated in all but 1 patient (TCZ08) who had 2 weak DSA at 12 months without evidence of ABMR on protocol biopsy. Patient TCZ03 had mild ABMR at 12 months without evidence of DSA although AT1R antibody was positive.

B. Mean immunodominant DSA scores for TCZ-treated and transplanted patients shown before treatment, at transplant and 12 months post-transplant. Significant reductions in DSA number and strength were seen at transplant* and 12 months after transplantation†. The DSA values were calculated based on number and strength of DSA present at timepoints indicated. Strong DSA (> 10,000 MFI) were given a score of 10, moderate DSA (5000-10,000 MFI) were given a score of 5, weak DSA (<5000 MFI) were given a score of 2 whereas no DSA received a score of 0.

Source: Vo et al, 2015, Figure 2.

5. CONCLUSIONS

Active ABMR, especially CABMR, is now recognized as the most common cause of allograft failure after a successful kidney transplant. Active ABMR and CABMR are part of a continuum of injury which, left untreated, results in the loss of the transplanted allograft. ABMR in kidney transplant recipients is a rare condition, and currently, there are no approved or effective treatments for active ABMR, including CABMR.

Based on evidence from both nonclinical and clinical studies, IL-6 appears to be a critical cytokine involved in CABMR. Notably, Kim et al. [Kim et al, 2014] demonstrated that blockade of IL-6 /I L-6R interactions in an animal model of alloimmunity resulted in a significant reduction of alloantibodies, reduction of antibody production by splenic and bone marrow plasma cells, direct inhibition of plasma cell anti-HLA antibody production, and induction of Treg cells with inhibition of Tfh cells. Jordan et al (unpublished) have shown a significant increase in IL-6 expression in kidney biopsies with ABMR. Several small studies have shown stabilization and / or improvement of renal function in ABMR and CABMR following treatment with TCZ [Choi et al, 2017a; Choi et al, 2017b; Patel et al, 2017; Puliyanda et al, 2017; Venkatachalam et al, 2017]. In the largest of these studies, Choi et al. [Choi et al, 2017a; Choi et al, 2017b] demonstrated that treatment with anti-IL-6R mAb (TCZ) resulted in reduction of DSAs, stabilized graft function, and improved graft survival in HLA-sensitized renal allograft recipients with CABMR and TG. Chandran et al. showed that treatment of kidney transplant recipients with TCZ was associated with a significant increase in circulating Treg cells, a significant decrease in CD4+ T cell cytokine (IL-17) production, and a trend toward decreased graft inflammation [Chandran et al, 2017]. Vo et al. showed that renal transplant rates in HLA-sensitized patients (resistant to desensitization SOC) were improved following treatment with TCZ [Vo et al, 2015]. These data, together with additional studies summarized in Section 4, provide scientific evidence that a sound rationale exists for the treatment of CABMR with an anti-IL-6 mAb.

In summary, the current treatments commonly being used for the treatment of CABMR are not evidenced-based. Considering the costs and potential for serious toxicity with the current treatments, this highlights the need for well-designed randomized controlled studies to investigate the safety and efficacy of any new drugs for the treatment of CABMR – a serious and rare condition with an unmet clinical need. Blocking the activity of IL-6 in kidney transplant recipients with ABMR has been investigated in a number of small uncontrolled clinical trials. Promising signals of efficacy have been seen with this anti-IL-6 approach.

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APPENDIX 4

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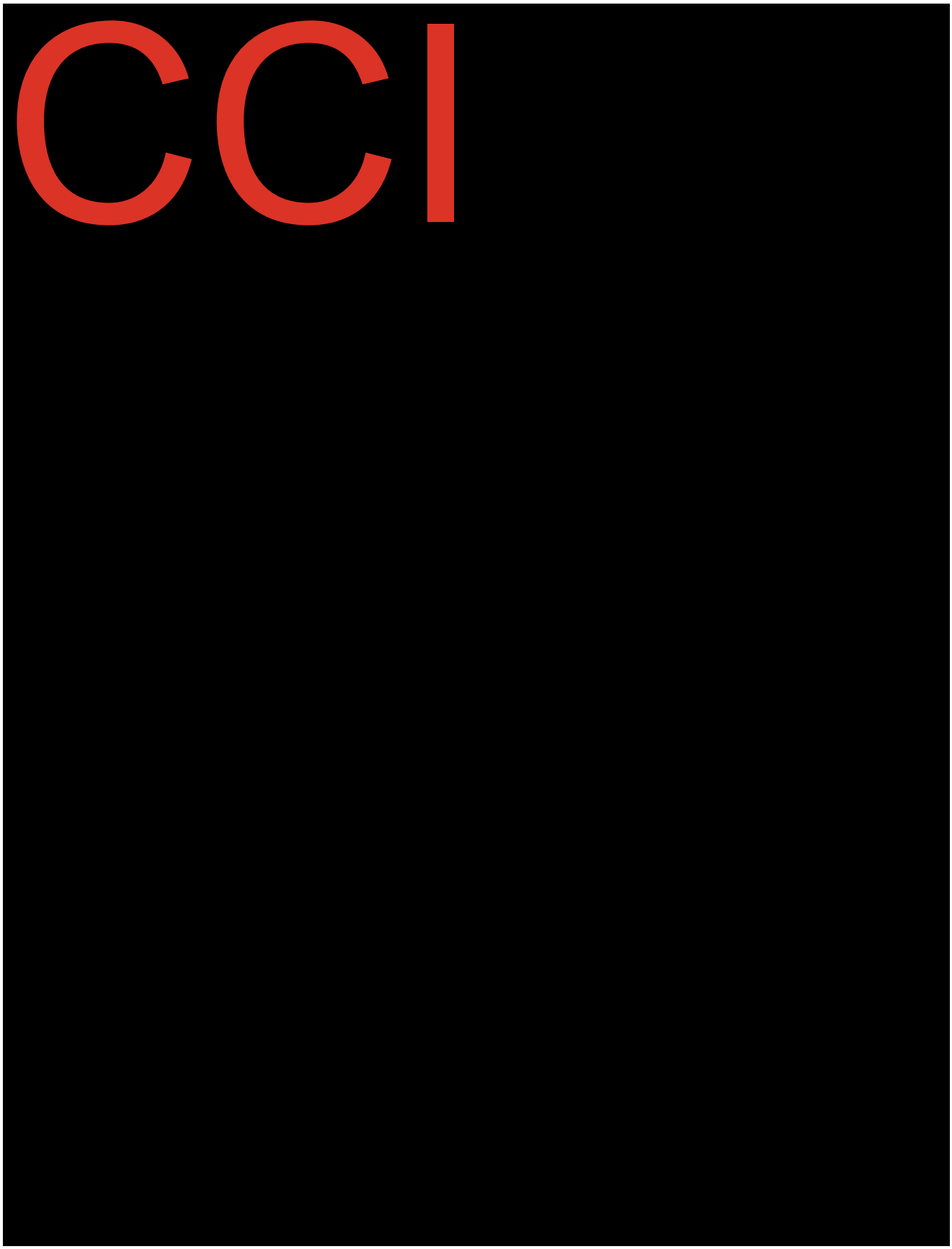
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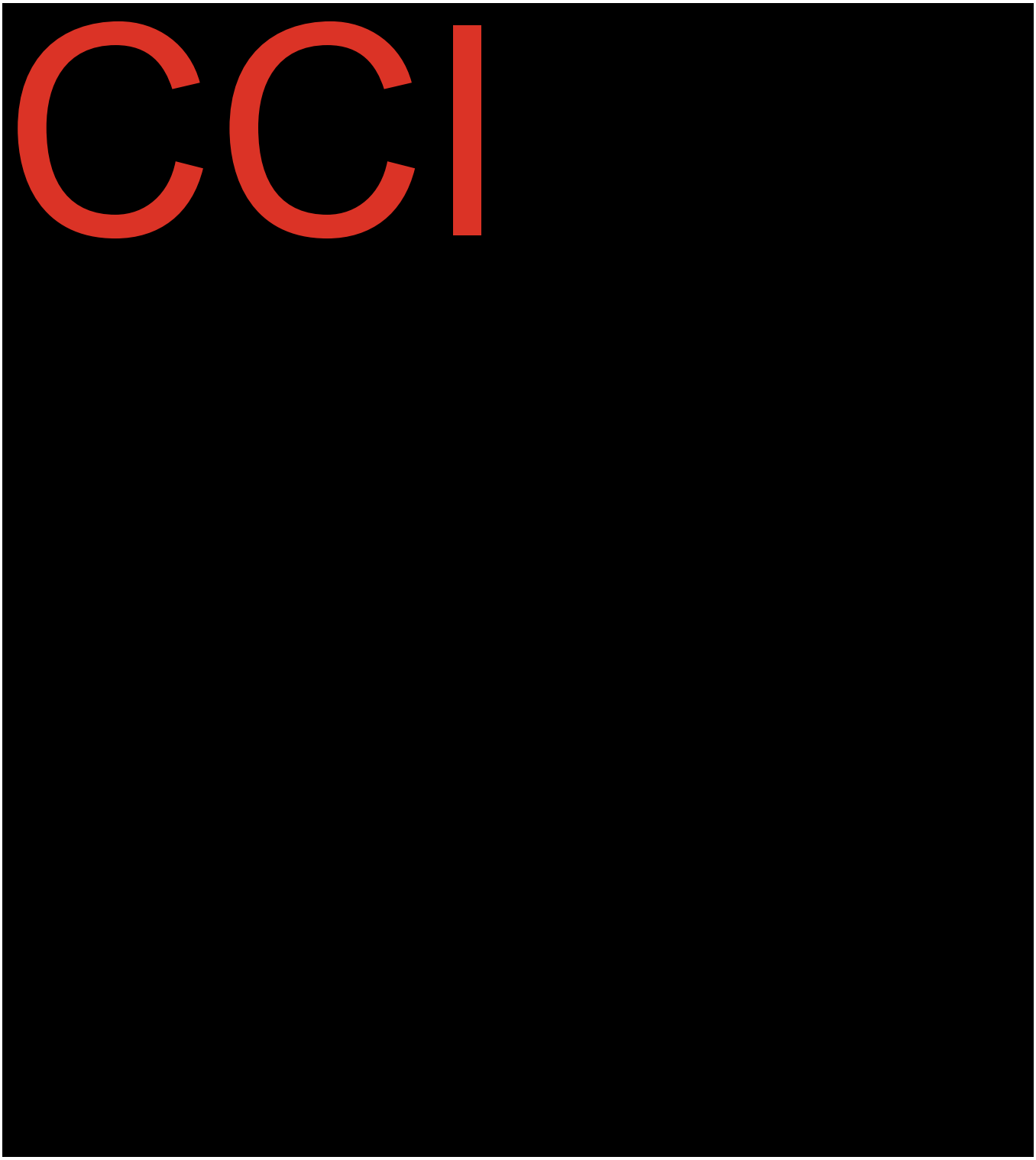
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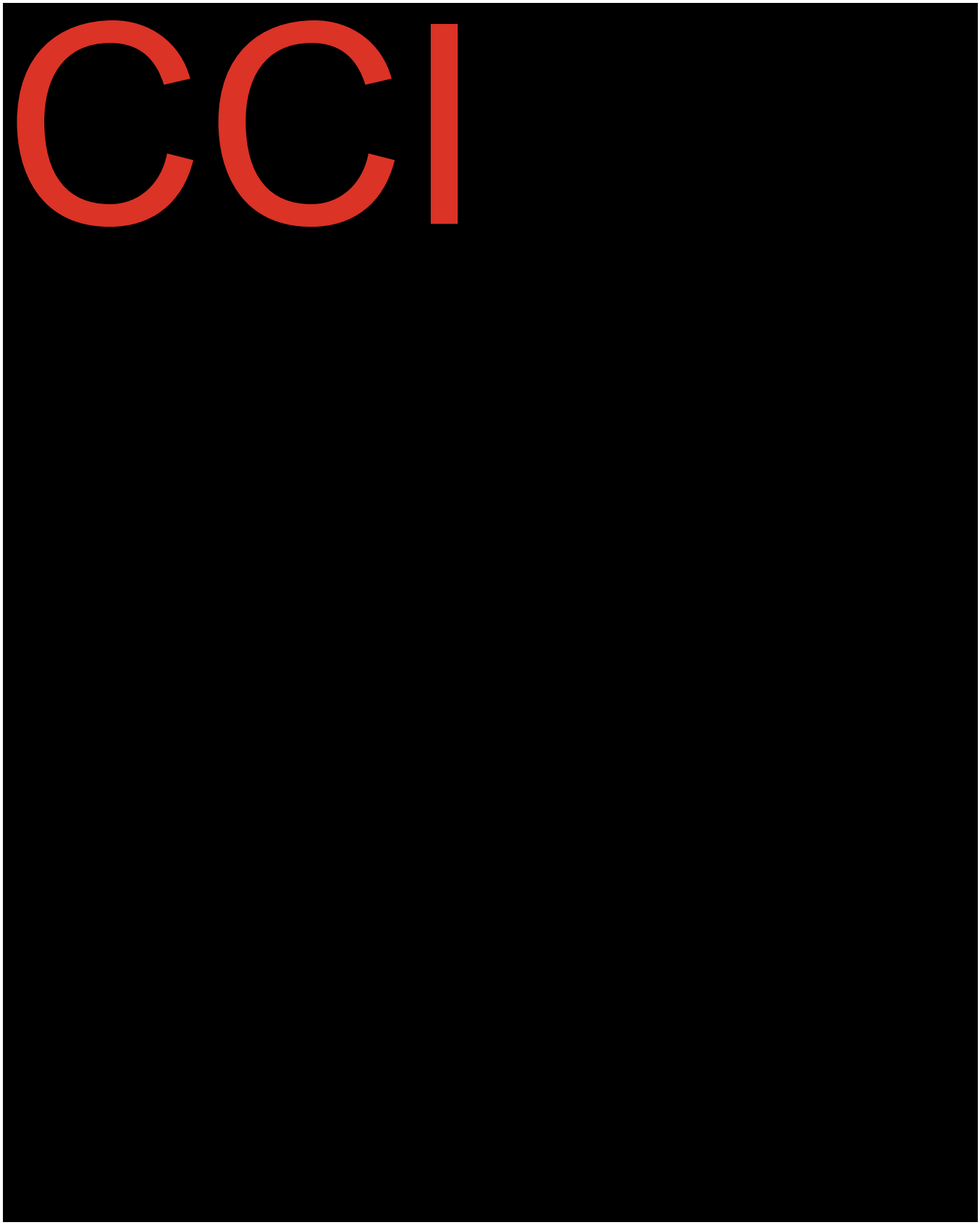
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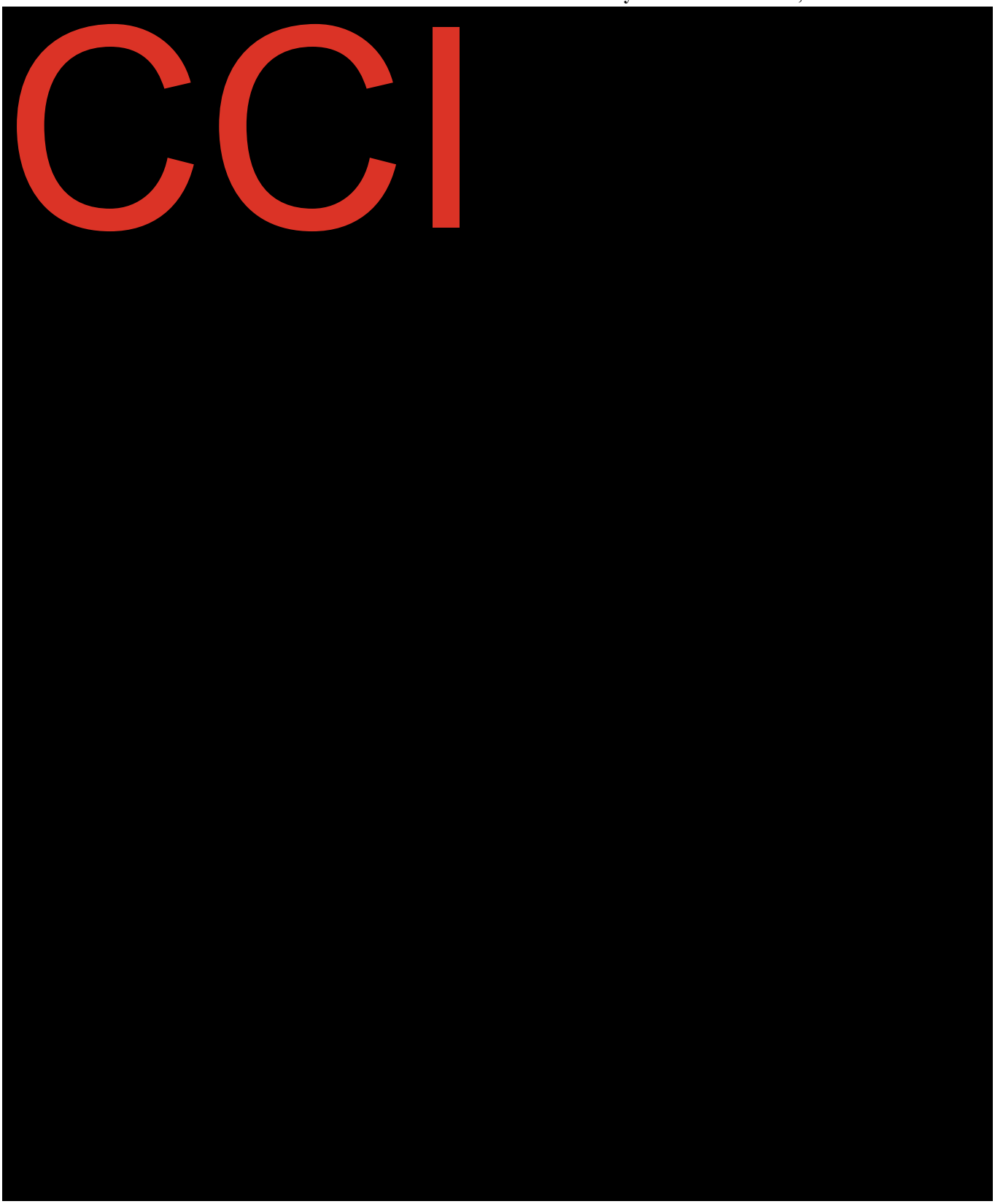
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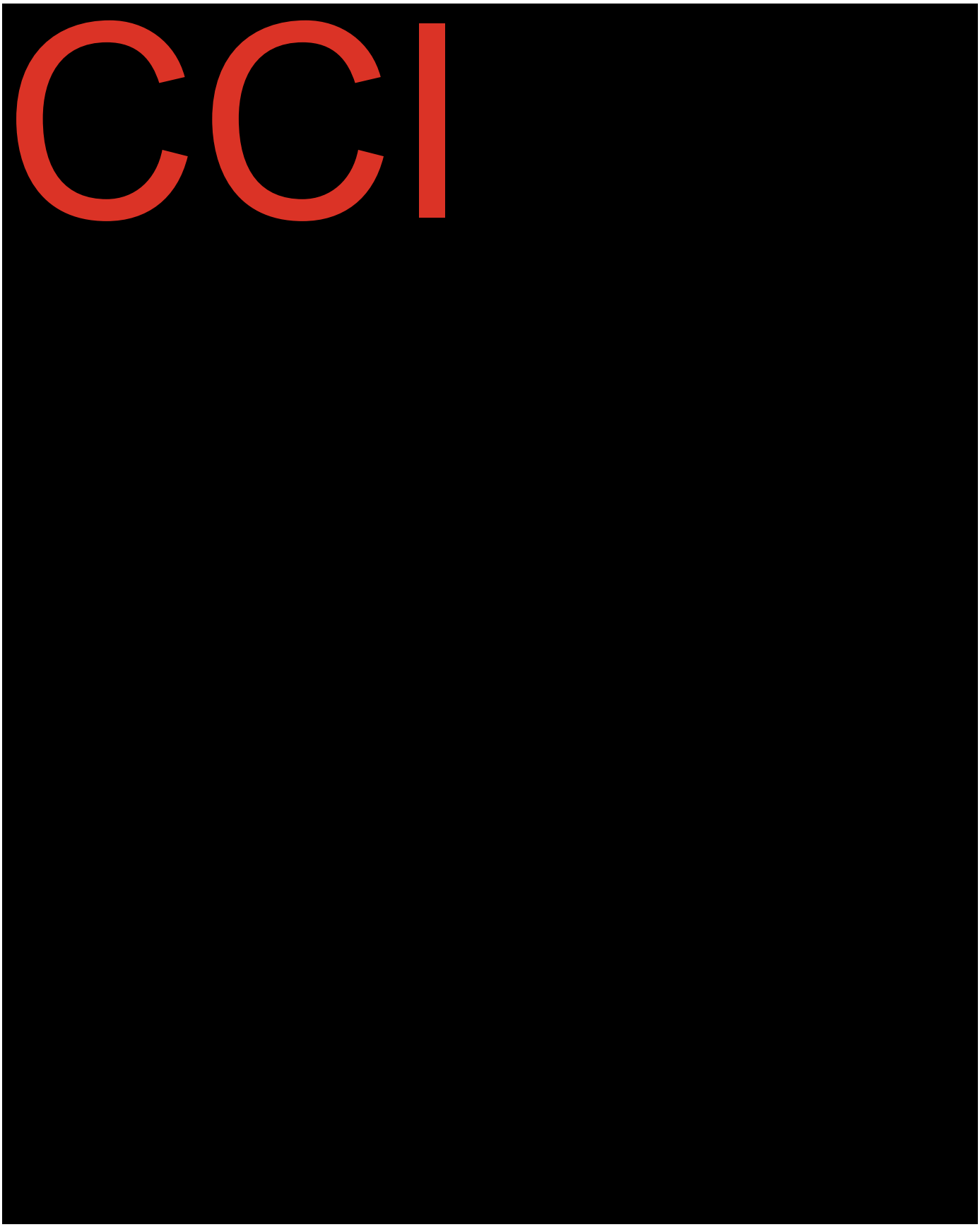
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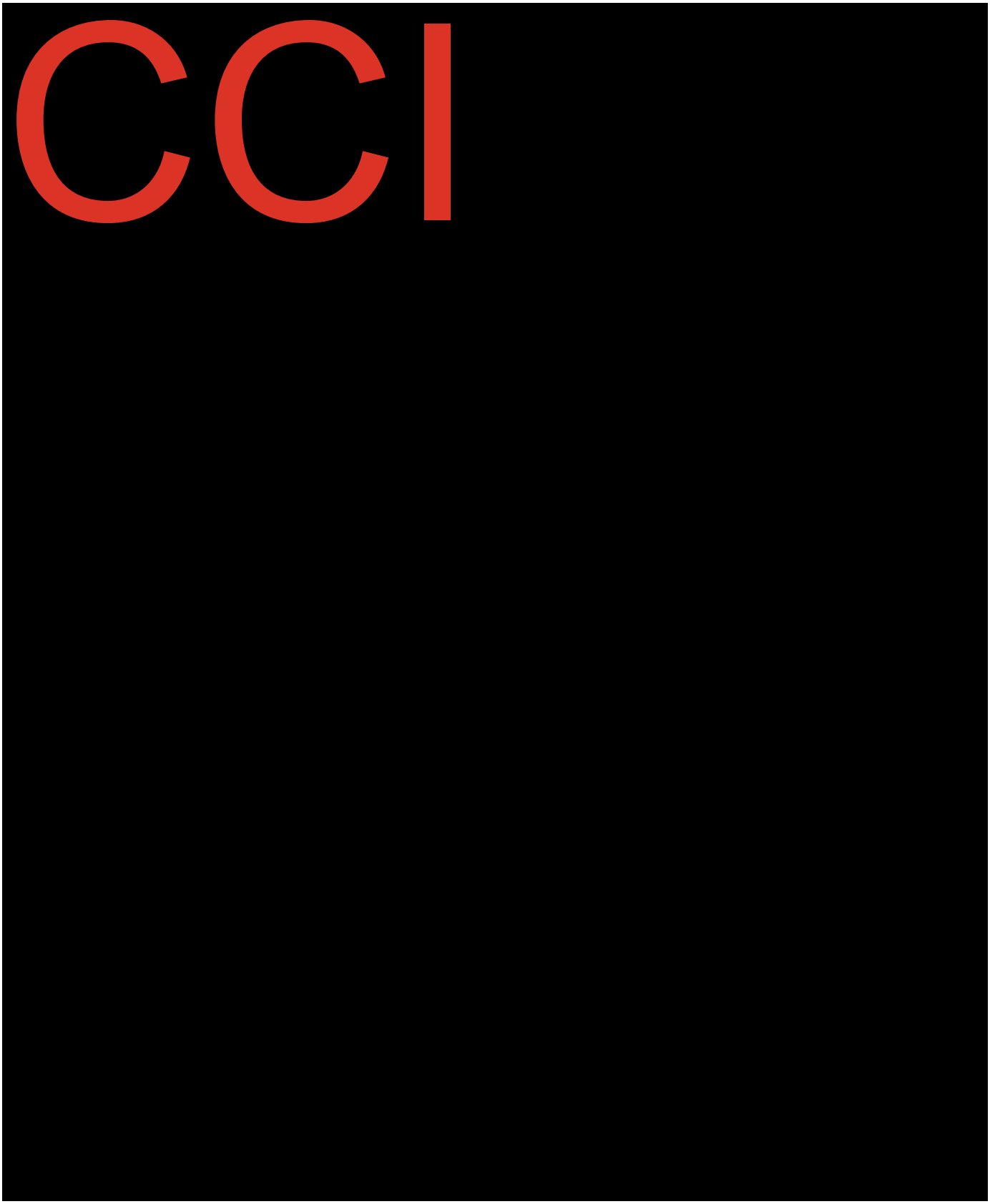
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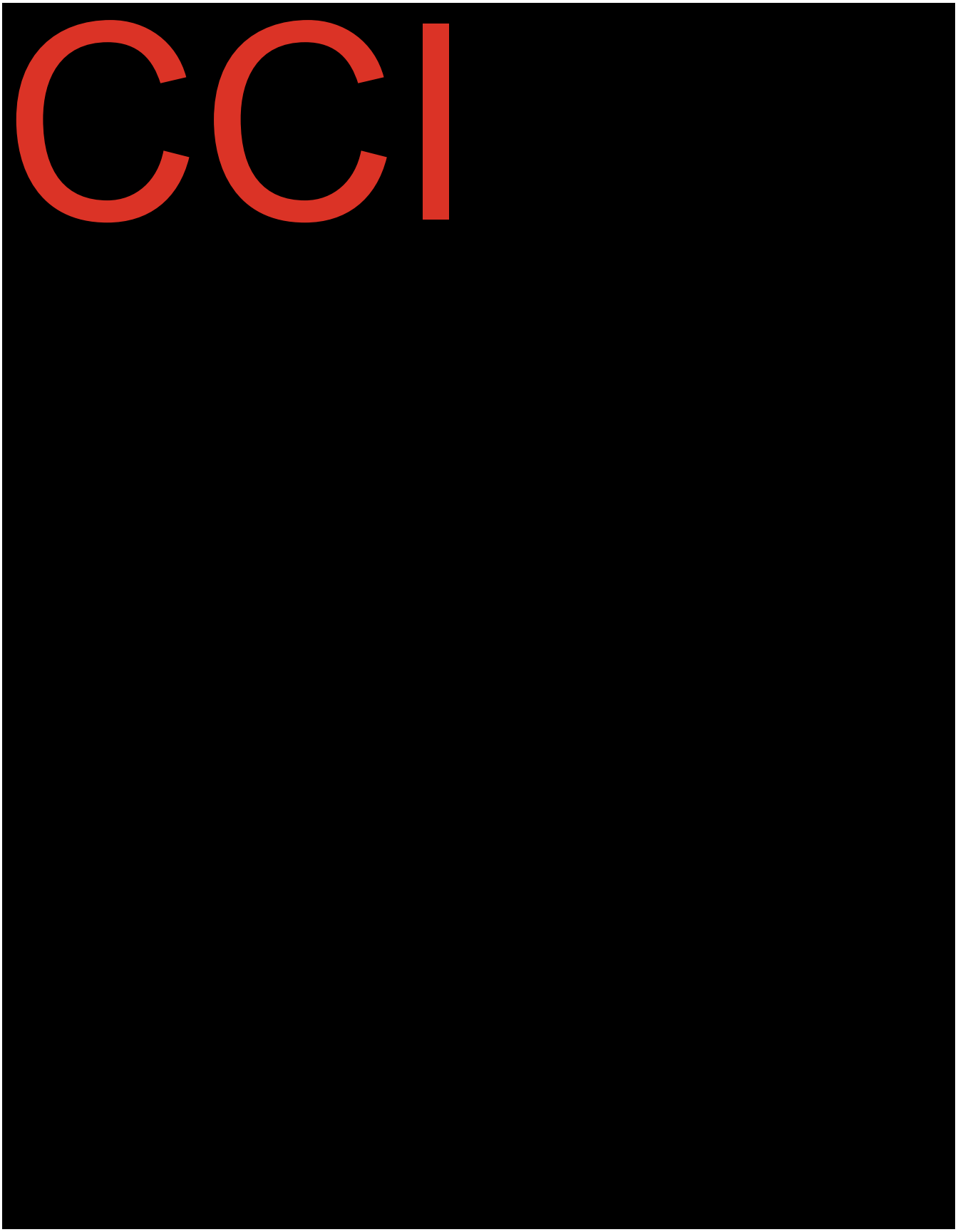
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