STATISTICAL ANALYSIS PLAN FOR INTERIM ANALYSES (SAP FOR IA #1 & IA #2)

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
Study Product:	Clazakizumab
Development Phase:	Phase 3
Sponsor:	CSL Behring, LLC 1020 First Avenue King of Prussia, PA 19406
Version:	1.0
Version Date:	16 August 2023
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonization) and all applicable national and local regulations.

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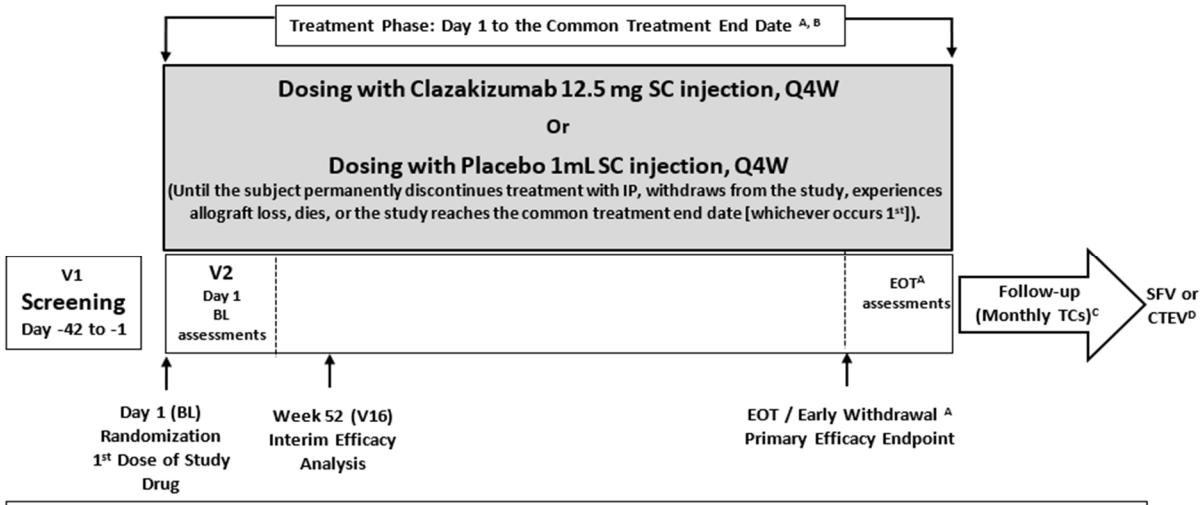


BL = Baseline; CTEV = common treatment end visit; EOT = End of Treatment; Q4W = once every 4 weeks; SC = subcutaneous; SFV = safety follow-up visit; TCs = telephone calls; V = visit.

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

1. MODIFICATION HISTORY

Version	Effective Date	Author of Modification	Summary of Change
1.0	16 August 2023		First Version

2. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
CABMR	chronic active antibody mediated rejection
CP	Conditional power
CSR	Clinical study report
DSA	Donor-specific antibodies
DSMB	Data Safety Monitoring Board
EOS	End of study
eCRF	Electronic case report form
GBM	Glomerular basement membrane
IP	Investigational product
ITT	Intention-to-Treat
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean fluorescence intensity
MI	Multiple imputations
MMRM	Mixed model repeated measures
MNAR	Missing not at random
SAE	Serious adverse event
SAP	Statistical analysis plan
SAP for IA	Statistical Analysis Plan for interim analyses
SAS	Statistical Analysis System
SD	Standard deviation
SE	Standard error
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

3. PURPOSE

This Statistical Analysis Plan for interim analyses (SAP for IA) provides a detailed description of the statistical methods to be used for the efficacy data and data derivations to be conducted at the first and the second interim analyses (IA #1 and IA #2) for study CSL300_3001 for review by DSMB. The analyses to be performed in case of regulatory submission based on IA #2 are also described here.

This SAP for IA complies with the International Council for Harmonization (ICH) E9 'Statistical Principles for Clinical Trials' and E9(R1) 'Statistical Principles for Clinical Trials: Addendum on Estimands and Sensitivity Analysis in Clinical Trials', and is based upon the following study documents:

- Clinical Study Protocol Amendment 9 dated **3 July 2023**
- electronic Case Report Form (eCRF), Version 12 dated 26 April 2023

A separate statistical analysis plan (SAP) will be prepared for the final analysis.

4. STUDY DESIGN

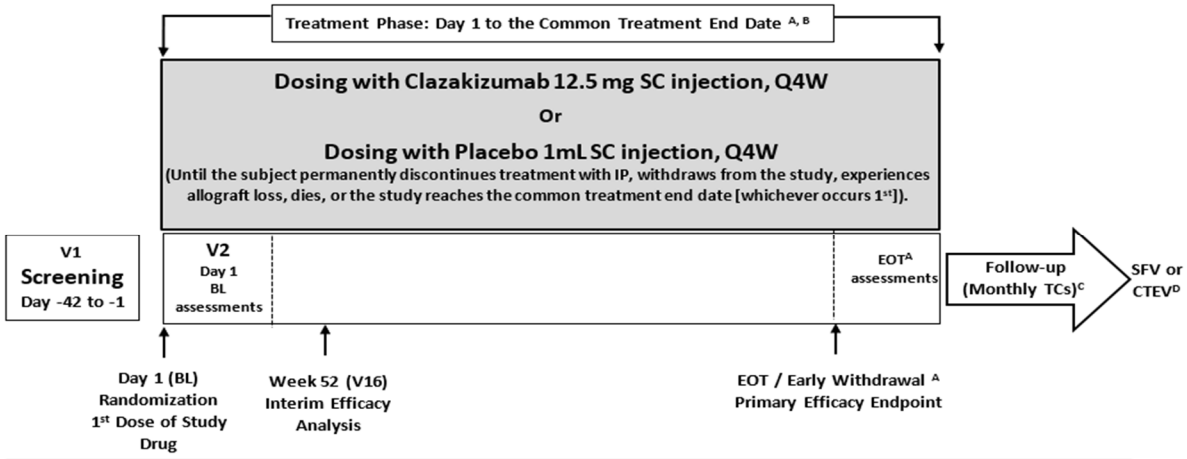
This study is a Phase 3, interventional, multi-site, randomized, double-blind, placebo-controlled, parallel-group study, consisting of 3 periods:

- Screening period (up to 6 weeks; Day -42 to Day -1)
- Double-blind treatment period (approximately 5 years on average; from Day 1 until the subject permanently discontinues treatment with IP, withdraws from the study, experiences allograft loss, dies, or reaches the common treatment end date, whichever occurs first). The common treatment end date is the date when the primary efficacy endpoint (all-cause composite allograft loss) is achieved, ie, the date the prescribed target number of primary allograft loss events (221) has been reached.
- Follow-up period for safety (monthly telephone calls for 5 months after last dose of investigational drug)

The average study duration for an individual subject will not be expected to be more than 5.5 years.

Adult kidney transplant recipients with chronic active antibody mediated rejection (CABMR) will be enrolled in this study. Across sites in North America, South America, Europe, Asia and Australia, approximately 350 subjects (175 per treatment group) will be randomized into the double-blind treatment period.

The Study Flow Chart



BL = Baseline; 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 (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 common treatment end date will occur when the pre-specified target number of allograft loss events (221) has been reached. The common treatment end date will be communicated to study sites in advance to enable study sites to plan their subject's 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.

Figure 1: Study Flow Chart

4.1. Objectives and Endpoints

The objective of IA #1 is:

1. To re-estimate the sample size for IA #2 based on the observed effect size for the change from baseline to Week 52 in eGFR

The objectives of IA #2 are:

1. 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)
2. To summarize the incidence of all-cause allograft loss or irreversible loss of allograft function due to chronic active antibody-mediated rejection (CABMR, defined as return to dialysis*, allograft nephrectomy, re-transplantation, estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2*, 40% decline in eGFR from Baseline that is sustained for at least 60 days, or death from any cause [*total cumulative duration of eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days])

Table 1: Interim Analyses Efficacy Endpoints

Interim Analysis	Endpoints	Summary Measure(s)
IA #1 and IA# 2	Change from Baseline to Week 52 in eGFR (in mL/min/1.73 m^2)	Mean change from Baseline to Week 52 in eGFR (in mL/min/1.73 m^2) Effect size for the change from Baseline to Week 52 in eGFR
IA #2 only	All-cause allograft loss or irreversible loss of allograft function (defined as return to dialysis*, allograft nephrectomy, re-transplantation, estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2*,40% decline in eGFR from Baseline that is sustained for at least 60 days, or death from any cause [*total cumulative duration of eGFR < 15 mL/min/1.73 m^2 AND / OR dialysis ≥ 60 days])	Proportion of subjects who met the primary composite endpoint of All-cause Allograft Loss or irreversible loss of allograft function. Proportion of subjects with 40% decline in eGFR from Baseline sustained for at least 60 days. Proportion of subjects with 40% decline in eGFR from Baseline that is sustained for at least 60 days and accompanied by investigator's decision to supplement the therapy by additional treatment. Proportion of subjects who returned to dialysis. Proportion of subjects with allograft nephrectomy

Interim Analysis	Endpoints	Summary Measure(s)
		Proportion of subjects who had re-transplantation. Proportion of subjects with eGFR <15 mL/min/1.73 m^2 Proportion of subjects who died

Table 2: Safety Endpoints for DSMB Safety Reviews

Endpoints	Summary Measure(s)
Treatment-emergent adverse events (TEAEs), serious TEAEs	Proportion of subjects with TEAEs and serious TEAEs and the number of events
Adverse Events of Special Interest (AESIs)	Proportion of subjects with Adverse Events of Special Interest (AESIs) and the number of events
Viral infection monitoring (BKV, CMV, and EBV by PCR)	Proportion of subjects tested positive for BKV, CMV, and EBV
Clinical laboratory data (serum chemistry, urine chemistry, lipids and hematology)	Mean change from baseline in laboratory parameters by visit

4.1.1. Hypothesis for Efficacy Analysis at IA #2

The study is designed to test the null (H_0) versus the alternative (H_A) hypothesis for the mean change from baseline in eGFR at week 52.

$$H_0: \mu_{claza} - \mu_{placebo} = 0$$

$$H_A: \mu_{claza} - \mu_{placebo} \neq 0$$

Where μ_{claza} is the mean change from baseline to week 52 in eGFR (in mL/min/1.73 m^2) in the clazakizumab group and $\mu_{placebo}$ is the mean change from baseline to week 52 in eGFR (in mL/min/1.73 m^2) in the placebo group.

4.2. Study Treatments

All subjects eligible for study participation will be randomized to treatment with either 1 mL (12.5 mg) clazakizumab or 1 mL placebo administered by SC injection, Q4W.

4.3. Randomization Procedures and Blinding

Eligible subjects will be randomized by means of Interactive Response Technology (IRT). The IRT will assign the investigational product (IP) to each subject. Randomization will be done centrally. Randomization will be stratified by

- dichotomized screening eGFR (25–45 mL/min/1.73 m2 versus >45–65 mL/min/1.73 m2)
- baseline proteinuria (urine albumin creatinine ratio (UACR) <300 mg/g (<30 mg/mmol) or UACR ≥300 mg/g (≥30 mg/mmol))
- treatment for early (within 6 months of transplant) antibody-mediated rejection (ABMR) rejection episodes (yes/no)
- treatment for late (greater than 6 months post-transplant) ABMR rejection episodes (yes/no).

Two formal unblinded interim analyses (IA #1 and IA #2) will be performed by the Unblinded Independent Statistician for the Data Safety Monitoring Board (DSMB) review. DSMB charter describes the roles and responsibilities of the Unblinded Independent Statistician and the DSMB.

Unless there is a medical emergency, study unblinding for the final composite primary endpoint (all-cause allograft loss) analysis will be done after the final database lock. The study blind may only be broken for an individual patient in the case of an emergency and when the knowledge of the investigational product is essential for the clinical management of the patient. A record will be kept at each study center (and in the electronic case report form [eCRF]) of all broken treatment codes, of the person who broke the treatment code, and of the reasons for breaking the treatment code.

4.4. Planned Sample Size

IA #1

The IA #1 is planned to be performed when 100 subjects have been randomized and completed 52 weeks of study participation (refer to Section 4.5.1 for subject trigger for interim analysis).

The planned sample size for IA#1 maybe higher than 100 randomized subjects to allow for withdrawals such that approximately 100 randomized subjects with 52 weeks of follow-up are included in the analysis.

IA #2

The fixed sample size for IA #2 was determined to be 180 randomized subjects (90 per group) based on a fixed design with 90% power, a two-sided alpha of 0.05, a common standard deviation (SD) of 9.252 mL/min/1.73 m^2 for the mean eGFR change from Baseline to Week 52, a minimum difference of 4.515 mL/min/1.73 m^2 between the treatment groups (assuming eGFR declines at a rate of 0.753 mL/min/1.73 m^2/month in the placebo group and that clazakizumab reduces the rate of decline by 50%; effect size = 4.515/9.252 = 0.488).

The planned sample size has been increased to approximately 200 randomized subjects to allow for 10% withdrawals such that at least 180 randomized subjects with 52 weeks of follow-up are included in the analysis.

4.5. Planned Interim Analyses and Reviews

The trigger for the two interim analyses (IA #1 and IA #2) is defined in the section below.

The results from IA #2 may be used for a regulatory submission. At the IA #2, the DSMB will, following a review of the interim data, make recommendations for continuing or stopping the study based on the observed risk-benefit of clazakizumab, and for increasing the sample size if required.

Detailed procedures for maintaining the blind will be specified in the Data Access Plan (DAP) to ensure that the interim data remain blinded to maintain clinical trial integrity until trial completion.

4.5.1. Subject Trigger for Interim Analyses

IA #1 will be based on 100 randomized subjects completing 52 weeks of study participation and IA #2 will be based on at least 180 randomized subjects (or more as per the re-estimated sample size determined at IA #1) completing 52 weeks of study participation. Additional subjects may be included in IA #1 and IA #2 to account for the discontinuations prior to week 52.

Randomization will continue until the target number of subjects are randomized in the study. At IA#1 and IA#2, subjects randomized beyond the required number of subjects (i.e., 100 for IA#1, 180 for IA#2) will not be included with an exception for BLA submission package and confirmation from regulatory agencies at pre-submission meetings following IA#2 (details are in Section 8.1).

4.5.2. Sample size Re-estimation in IA #1

The primary analysis of change from baseline to week 52 in eGFR has been based on a 2-stage design where the subjects included in the 2 stages are defined as follows:

- Stage 1 consists of randomized subjects who are included in IA#1
- Stage 2 consists of randomized subjects who are randomized post the randomization of the subjects included in IA#1.

Sample size re-estimation has been planned to estimate the number of additional subjects to be randomized and followed up for 52 weeks (stage 2) for IA#2.

Sample size re-estimation will be conducted using the inverse normal method for a 2-stage design with pre-specified cumulative information fractions of [0.5556, 1] to control the type I error rate where 0.5556 = 100/180 is the ratio of the planned size of stage 1 to the total planned sample size. Following steps will be implemented to re-estimate the sample size for IA #2:

Set a pair of weights to the square root of the information fraction at each stage. In this case, $w\_1 = \sqrt{(100/180)} = 0.7454$ is based on the number of subjects planned for stage 1 and $w\_2 = \sqrt{(80/180)} = 0.6667$ is based on the number of subjects planned for stage 2. These weights are based on the originally planned design.

The estimate of sample size at stage 2 ($\tilde{n}\_2$) is derived as per equation (1), derivation is based on Bauer and Koenig (2006). For a general discussion on conditional power and sample size re-estimation, see Lan and Wittes (1988), Proschan et al. (2006, Chapters 3, 11), and Wassmer and Brannath (2016, Chapter 7). Estimate of sample size at stage 2 ($\tilde{n}\_2$) is,

$$\tilde{n}_2 = \frac{4}{\Delta_2^2}\left(\frac{z_{\alpha/2}\sqrt{n} - z_1\sqrt{n_1}}{\sqrt{n_2}} + z_{CP}\right)^2 \quad (1)$$

where,

Z_1 = Estimated treatment difference at Week 52 divided by its standard error

Δ_1 = observed effect size at Stage 1

Δ_2 = assumed effect size at Stage 2

n_1= planned total sample size at Stage 1 i.e. 100

n_2= planned total increment in sample size at Stage 2 i.e. 80

n = planned total sample size at IA #2 i.e. 180 ($n\_1 + n\_2$)

$\mathrm{CP} = \text{target conditional power}$

- Total sample size for IA #2 will be selected as follows:
  - If $n\_1 + \tilde{n}\_2 \leq 180$ then sample size for IA #2 will remain as planned sample size of 180 randomized subjects with 52 weeks of study participation. DSMB is expected to recommend that the IA #2 should be conducted with 180 randomized subjects with 52 weeks of study participation as planned.
  - If $180 < n\_1 + \tilde{n}\_2 \leq 250$ then sample size for IA #2 should be close to $n\_1 + \tilde{n}\_2$ such that the sample size of IA #2 could be a maximum of 250 randomized subjects with 52 weeks of study participation. DSMB is expected to make a recommendation about the number of randomized subjects with 52 weeks of study participation required for IA #2 (a maximum of 250 randomized subjects with 52 weeks of follow-up).
  - If $n\_1 + \tilde{n}\_2 > 250$ then sample size for IA #2 could increase to a maximum of 250 randomized subjects with 52 weeks of study participation. DSMB is expected to make a recommendation about IA #2 based on the review of the data package.
  - The sample size for the interim efficacy analysis surrogate endpoint (IA #2) will not exceed a total of 250 subjects with 52 weeks of study participation (approximately 280 subjects will be randomized to account for 10% withdrawal before week 52).

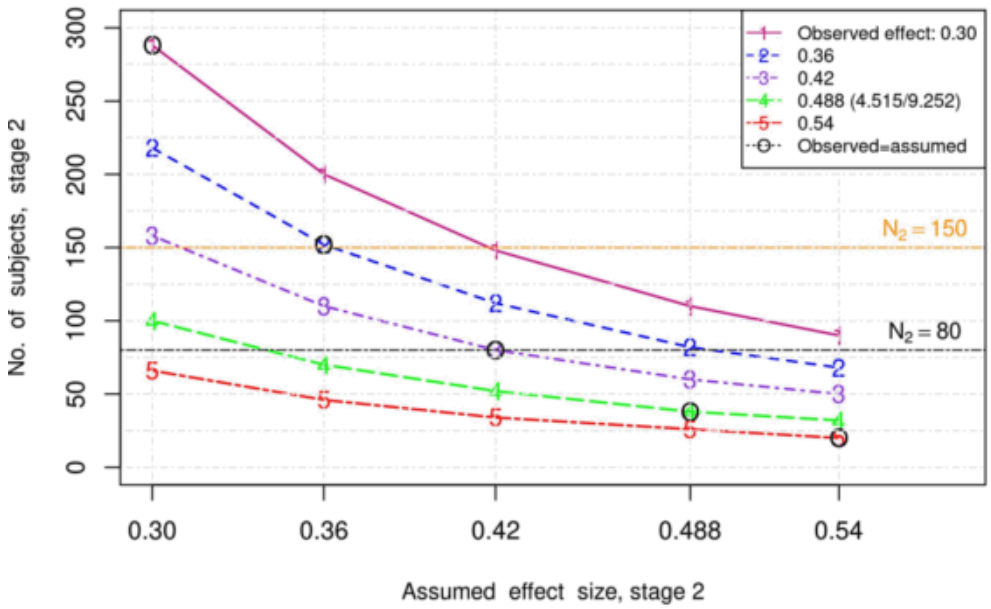
4.5.2.1. Operating Characteristics of Sample Size Re-Estimation at IA#1

Effect Size at Stage 1 and Stage 2

The following figure is an example that shows the number of subjects needed at stage 2 to ensure 90% conditional power for five different scenarios of observed effect size at IA #1 and various assumed effect size for the stage 2.

The black open circles in each line represents the number of subjects needed at stage 2 when the assumed effect size at stage 2 is identical to the observed effect size at stage 1.

Figure 2: Number of Additional Subjects Needed



The green line represents the observed effect size of 0.488 at IA #1 (effect size assumed in study design). Fewer than 50 subjects would need to be randomized in stage 2 to ensure 90% conditional power for analysis at IA #2 (black open circle on the green line) assuming effect size of 0.488 at stage 1 will remain unchanged in stage 2. In this case, the sample size at IA #2 would remain at the planned sample size of 180 randomized subjects as it cannot decrease below 180 randomized subjects with 52 weeks of study participation.

If the observed effect size at IA #1 is 0.36 (represented by blue line) then the sample size at IA #2 would need to be at the maximum of 250 randomized subjects (150 additional subjects required at stage 2) to ensure 90% conditional power (black open circle on the blue line) assuming same effect size will be seen at stage 2.

If the observed effect size at IA #1 is 0.30 (represented by solid purple line) then the total sample size at IA #2 would need to be close to 400 randomized subjects (approximately 300 additional randomized subjects at IA #2 if the same effect size is assumed for stage 2). In this case, as the maximum sample size cannot exceed 250 randomized subjects, the DSMB recommendation to continue the study at IA #2 implies DSMB assumes an increase of effect size of at least 0.42 at stage 2 at 90% conditional power.

Overall Power at IA #2

Overall power for the IA #2 is summarized in Table 3 for a range of hypothetical scenarios of effect size, conditional power and maximum total sample size at IA #2. Overall power is obtained from simulations with 100 randomized subjects in Stage 1 and information rates [0.5556, 1]. Simulations were performed using rpact R package (rpact 2021). The R codes are provided in the Appendix 0 including the seed used for simulation.

Table 3: Operating Characteristics for Overall Power at IA #2

eGFR Effect Size	Conditional Power	Maximum Total Sample Size at IA #2	Expected Total Sample Size at IA #2	Overall Power
0.488	90%	180	180	90%
		250	202	96%
0.46	90%	180	180	87%
		250	205	93%
0.43	90%	250	209	90%
0.40	85%	250	210	85%
	90%	250	213	85%
0.37	85%	250	214	79%
	90%	250	218	80%
0.33	85%	250	220	70%
	90%	250	223	71%
0.30	85%	250	224	62%
	90%	250	227	63%

If the effect size is 0.488 (the assumed effect size used for the original study design), then there is no increase in sample size required for IA #2, (ie, the maximum sample size for IA #2 was specified as 180 randomized subjects). In this case, the expected total sample size of 180 randomized subjects will ensure overall 90% power. When simulation is performed with the maximum allowed samples size of 250 randomized, overall power increased to 96% with the expected total sample size of 202 randomized subjects.

Overall power is around 85% when the effect size is 0.40, with expected total sample size of 210 randomized subjects for conditional power of 85% and expected total sample size of 213

randomized subjects for conditional power of 90%. These simulations were done with the maximum allowed samples size of 250 randomized subjects at IA #2.

Overall power drops below 80% with the maximum allowed samples size of 250 randomized subjects when the effect size is less than 0.37.

Simulation results show that the study design with the sample size re-estimation procedure provides 80% or higher overall power for various plausible scenarios.

4.5.2.2. Efficacy Results Presentation to DSMB at IA #1

The observed effect size (Δ_1) based on the 100 randomized subjects with 52 weeks of study participation will be presented to the DSMB. The effect size is calculated as the ratio of the difference in mean change from baseline to Week 52 in eGFR between clazakizumab and placebo to the SD. The difference in mean change from baseline to Week 52 in eGFR between clazakizumab and placebo and the SD will be estimated from the MMRM model (refer to Section 10.1.1).

Estimates of sample sizes at stage 2 ($\tilde{n}_2$) will be calculated based on the observed effect size at IA #1 using equation (1) for a range of assumed effect sizes at stage 2 (Δ_2), for e.g. Δ_2 could be five values ranging approximately from $\Delta_1 - 0.12$ to $\Delta_1 + 0.12$, with one value same as Δ_1.

A figure of $\tilde{n}_2$ vs Δ_2 for the above range will be also presented to DSMB. This figure will include lines corresponding to conditional power of 90%, 85% and 80% (refer to Appendix 14.1 for sample figures). A table may also be created to present the numbers in the figure along with the conditional power for the minimum and the maximum allowed sample size increase at stage 2 i.e. 80 and 150, respectively.

Any decision to stop the study in the event of unacceptable effect size of eGFR or to increase the sample size for the IA #2 beyond the protocol specified maximum of 280 randomized subjects would be made by CSL Behring based on the recommendation of the DSMB.

4.5.3. Efficacy Results Presentation to DSMB at IA #2

The number of subjects required for IA#2 is approximately 180 randomized subjects with 52 weeks of study participation (if the sample size re-estimation at IA #1 remains at this planned number). If the sample size re-estimation at IA #2 increases the sample size for IA #2 then the IA # will be done when the re-estimated number of subjects are randomized and followed for 52 weeks. Since the re-estimated sample size for IA #2 is unknown, this document will refer to IA #2 to be based on 200 randomized subjects (to have approximately 180 randomized subjects with 52 weeks of study participation).

Change from baseline to Week 52 in eGFR will be analyzed at IA #2. The details of efficacy analyses of change from baseline in eGFR is described in Section 10.

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 all-cause composite allograft loss or irreversible loss of allograft function) would be made by CSL Behring based on the recommendation of the DSMB after review of the totality of the data, ie, observed effect on eGFR, updated predicted all-cause allograft survival based on the model using data observed in the study, and safety data.

4.5.4. DSMB Safety Reviews

DSMB will receive the safety outputs outlined in the charter which are delivered to DSMB for each safety review (approximately every 9 months as specified in the DSMB Charter) including those during IA #1 and IA #2. The DSMB can recommend stopping the study for safety reasons at any time.

5. CHANGES FROM THE PROTOCOL PLANNED ANALYSES

There are no changes to the analyses planned in the study protocol.

6. STUDY ANALYSIS SETS

6.1. Screened Analysis Set

The Screened analysis set consists of all subjects who provided written informed consent.

6.2. Intention-to-Treat (ITT) Analysis Set

The ITT set will consist of all randomized subjects who took at least one dose of investigational drug and who had a baseline assessment and at least one post-baseline assessment of eGFR. Refer to Section 8.1.1 for details on data to be included in the analysis.

Subjects will be analyzed according to the treatment to which they were randomized.

6.2.1. Efficacy Analysis Set

Efficacy analysis set for IA #1: This will be a subset of ITT analysis set. This subset will include first 100 randomized subjects who meet the subject trigger definition (refer to Section 4.5.1).

Subjects who discontinue the study prior to the subject trigger will also be included in this analysis set.

Efficacy analysis set for IA #2: This will be a subset of ITT analysis set. This subset will include number of subjects as per the re-estimated sample size who meet the trigger definition (refer to Section 4.5.1).

Subjects who discontinue the study prior to the subject trigger will also be included in this analysis set.

Efficacy analysis set for Stage 2: This set will include subjects in the Efficacy analysis set for IA #2 but not in the Efficacy analysis set for IA #1.

6.3. Per-protocol (PP) Analysis Set

The PP set will consist of all randomized subjects who satisfy the ITT analysis set criteria and who complied with the protocol requirements (i.e., no major protocol deviations that impact the primary efficacy endpoint for the interim or the final analysis). PP analysis set will be used for IA #2 only. Protocol deviations resulting in exclusion from the PP set will be documented in the data review meeting (DRM) minutes before the study data unblinding for IA #2.

Subjects will be analyzed according to the treatment to which they were randomized.

6.4. Safety Analysis Set

The Safety set will consist of all randomized subjects who took at least one dose of investigational drug.

Refer to Section 8.1.1 for details on data to be included in the IA#1 and IA#2 interim analysis.

Subjects will be included in the analysis according to the actual treatment received ie, in cases where information is available indicating that a subject received a different treatment for the entire course of his/her participation in the study, the subject will be analyzed according to the treatment actually received rather than the treatment to which he/she was randomized. If a subject receives

both clazakizumab and placebo, the safety information of the subject will be summarized under the clazakizumab arm.

6.5. Pharmacokinetic (PK) Analysis Set

The pharmacokinetic analysis set consists of all subjects in the safety analysis set with at least one quantifiable PK concentration after investigational drug administration.

6.6. Pharmacodynamic (PD) Analysis Set

The pharmacodynamic analysis set consists of all subjects in the Safety Analysis Set with at least one PD measurement obtained after investigational drug administration.

6.7. PK/PD Sub-study Analysis Set

The PK/PD sub-study analysis set consists of all subjects in the Safety Analysis Set who consented to be part of the PK/PD Sub-study and have at least 1 quantifiable PK concentration of investigational drug after administration.

7. GENERAL CONSIDERATIONS

Datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards. Study data will be provided in Study Data Tabulation Model (SDTM) format. Analysis data will be provided in Analysis Data Model (ADaM) format.

SAS version 9.4 or higher will be used to perform all data analyses.

Summaries of continuous variables will be in terms of the number of observations, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum. Other descriptive statistics (eg, standard error, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics identified with the analysis in the applicable SAP for IA section.

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.

8. DATA HANDLING CONVENTIONS

8.1. Database Lock (DBL)

There will be a DBL for each interim analysis. BLA submission following IA#2 will be based on the analysis datasets generated from the locked database for IA#2. The analysis datasets will include the target number of subjects in IA#2.

DBL for IA #1 will occur when the 100 randomized subjects meet the subject trigger definition (see Section 4.5.1 Subjects randomized beyond the last randomized subject required for IA#1 will not be included in the IA#1 analysis.

DBL for IA #2 will occur when 180 randomized subjects or more (as re-estimated during IA #1) meet the subject trigger definition (see Section 4.5.1).

The trigger definition (see Section 4.5.1) will be used to include data for all additional subjects randomized beyond the target number of subjects required for IA#2.

8.1.1. Data Included in the Analysis

The study will continue to randomize subjects after the DBLs for IA #1 and IA #2 until the target number of subjects required in the study are randomized. Randomization will continue during the interim analyses. Therefore, number of subjects required for each IA will be selected programmatically from the source data as per the subject trigger defined in Section 4.5.1.

At the time of IA #1, subjects who discontinue the study prior to the subject trigger will also be included in the respective IA. These subjects will have less than 52 weeks of follow-up.

All available data from the DBLs will be included in the regular DSMB safety reviews (Section 4.5.4).

Table 4: Data to be included for each interim analysis and DSMB Safety Reviews

Analysis	Study Milestones			
	IA #1	IA #2	DSMB Safety Reviews	BLA Submission
Primary analysis of eGFR using MMRM	Subjects in Efficacy analysis set for IA #1 with data up to 52 weeks. Visits beyond 52 weeks will be excluded	Subjects in Efficacy analysis set for IA #2 with data up to 52 weeks. Visits beyond 52 weeks will be excluded	NA	Same as IA #2
Sensitivity analysis of eGFR	NA	Subjects in Efficacy analysis set for IA #2 with data up to 52 weeks. Visits beyond 52 weeks will be excluded	NA	Same as IA #2
Supplementary analysis of eGFR using ANCOVA and MMRM	NA	Subjects in Efficacy analysis set for IA #2 with data up to 52 weeks. Visits beyond 52 weeks will be excluded	NA	Same as IA #2 Summary of eGFR over time based on all subjects included in the DBL for IA #2
Summary statistics of eGFR	Subjects in Efficacy analysis set for IA #1 with visits up to 52 weeks	Subjects in Efficacy analysis set for IA #2 with all visits	All subjects and all visits from the DSMB data cut	Same as IA #2
Summary of proportions of subjects with all-cause allograft loss or irreversible loss of allograft function	NA	Subjects in Efficacy analysis set for IA#2	All subjects from the DSMB data cut	Subjects in Efficacy analysis set for IA#2 All randomized subjects from the DBL for IA#2
Safety analyses	NA	Subjects in Efficacy analysis set for IA #2 with all visits	All subjects and all visits from the DSMB data cut	Same as IA #2 Safety package based on all randomized subjects included in the DBL for IA#2
HRQoL	NA	NA	NA	Subjects in Efficacy analysis set for IA #2 with all visits
PK and PD	NA	NA	NA	Subjects in respective PK or PD or PK/PD analysis sets

8.2. Missing Data

Missing data occurs when any requested data are not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a "blank" (empty field) in subject listing displays. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

The details of handling missing data are presented in the corresponding sections of this SAP for IA for respective analyses (eg, primary and secondary efficacy analyses, safety analyses).

8.3. General Derived Variables

8.3.1. Reference Dates and Study Days

Reference dates are used to assign study periods relative to treatment.

- The safety reference date is the treatment start date and will be used to calculate study day for safety measures.

- The efficacy reference date is the date of randomization and will be used to calculate study day for efficacy measures.

The respective study day will be calculated as (date of interest - reference date) + 1 if the date of interest occurs on or after the reference date. If the date of interest occurs before the reference date, then the study day will be calculated as (date of interest – reference date). There will be no study day zero. Study week will be calculated by dividing study day by 7.

8.3.2. Durations and Time to Event Data

Durations (eg, the duration of an adverse event [AE]) are calculated in days as:

- event end date – event start date + 1; if end time or start time not available.
- event end date / time – event start date / time; if both end time and start time available.

Thus, there will be no duration of 0 if end time or start time are not available. If an AE has missing or partially missing start or end date, no duration will be calculated.

For elapsed time (eg, the time to event), use:

- event date / time – reference date /time, (if time available).

Thus, an event which happens on the same date as the reference date will have an elapsed time of 0, if event time or reference time are not available.

To transform durations or elapsed times, which are calculated in days into weeks, divide the number of days by 7; to report in months, divide the number of days by 30.4375; to report in years, divide the number of days by 365.25. These algorithms return decimal numbers and ignore the actual numbers of days in the months or years (the calendar days) between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

8.3.3. Baseline Definition

Baseline is defined as the most recent, non-missing value before the first IP administration (including unscheduled visits) for all assessments unless otherwise stated.

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

8.3.4. Change from Baseline

Change from baseline is calculated as:

- visit value – baseline value.

If either the baseline or visit value is missing which, will result in missing change from baseline.

8.3.5. Multiple Assessments

All data will be reported according to the nominal visit date for which they were reported. If the actual visit date deviates from the planned date according to the visit schedule in the protocol (i.e., outside the visit window) then no visit re-allocation will be done. Unscheduled data will not be

included in by-visit summaries but may contribute to the End of Study (EOS) value, or best/worst case value (eg, shift tables) and will appear in listings.

If multiple assessments are reported on the same date for the same scheduled time, then the worst-case result will be analyzed.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

8.3.6. Actual Treatment

The subjects' actual treatment will be derived by reconciling the kit numbers. The actual treatment may be different from the randomized treatment assigned to the subject.

9. STUDY POPULATION

Unless otherwise stated, all tables and listings in this section will be based on the Efficacy or Safety analysis set. Analysis sets to be used for each analysis are summarized in Section 14.5.

9.1. Subject Disposition

The following summaries will be provided by treatment group and total population using the Screened Analysis Set:

- Subjects in each of the analysis sets are described in Section 6.
- Subject study status, including subjects screened, screen failures, subjects randomized, completed the study, completed Week 52 visit, and discontinuation from the study by primary reasons for study discontinuation.
- Study treatment status, including completed study treatment, ongoing study treatment, treatment withheld, or dose reduced, discontinued subjects by primary reasons for discontinuation.
- Completed study treatment and discontinued subjects at each dosing visit.

Reasons for study withdrawal and study treatment discontinuation will be presented in the order they are displayed in the eCRF. The number of subjects randomized will be used as the denominator for the percentage calculation.

The following listings will be provided:

- Reasons for study withdrawal including the date of withdrawal.
- Reasons for study treatment discontinuation. The listing will include last dose date, and reasons for study treatment discontinuation.

9.2. Demographic and Baseline Characteristics

The following summaries will be provided by treatment group and total population using the Efficacy Analysis Sets:

- Demographic characteristics (age, race, ethnicity, sex, baseline height, baseline body weight and Body Mass Index (BMI)). In addition to summarization as a continuous variable, age will also be categorized and summarized by 18-64 and > 64.
- Randomization stratification factors (dichotomized screening eGFR [25–45 mL/min/1.73 m^2 versus >45–65 mL/min/1.73 m^2], baseline proteinuria (UACR <300 mg/g [<30 mg/mmol] or UACR ≥300 mg/g [≥30 mg/mmol]), treatment for early ABMR rejection episodes [yes/no], and treatment for late ABMR rejection episodes [yes/no]).
- Baseline disease characteristics (time since kidney transplant in months, eGFR, eGFR categories UACR, DSA titers and DSA MFI scores and Renal Biopsy parameters).

9.3. Prior/Concomitant Medications

Prior/concomitant medications will not be summarized at the time of interim analyses (IA #1 and IA #2).

9.4. Study Population - Derived Variables

Derivation of Body Mass Index (BMI)

BMI will be calculated using the following formula:

BMI (kg/m^2) = Weight (kg) / [Height (m)]^2

using the height measured at Screening and the weight measured at Day 1 (if available). If weight at Day 1 is not available, the assessment at Screening will be used.

10. INTERIM EFFICACY ANALYSES

All efficacy analyses will be based on Efficacy Analysis Sets as defined in Section 6.2.1.

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

For IA #1and IA #2, data beyond nominal Week 52 visit will be excluded from the primary and sensitivity analyses of change from baseline in eGFR, unless specified otherwise. However, eGFR data beyond 52 weeks of follow-up will be included in the descriptive summary statistics.

The randomized treatment will be used for the interim efficacy analyses described in this section.

10.1. Primary Estimand

The estimand quantifies the treatment effect of clazakizumab vs placebo in adult patients with CABMR on the difference in mean change from baseline to Week 52 in eGFR (in mL/min/1.73 m^2) regardless of the missed doses or discontinuation of study treatment, as if the allograft loss events did not occur.

Specific elements of the estimand are as follows:

Population: adult patients with CABMR

Variable: change from baseline to Week 52 in eGFR (in mL/min/1.73 m^2)

Intercurrent events: eGFR data collected after the following allograft loss events is not relevant to the clinical question of interest:

- Onset of allograft nephrectomy or re-transplantation
- Date of confirmed eGFR < 15 ml/min/1.73m^2
- Onset of permanent return to dialysis

Population level summary: Difference in mean change from baseline

10.1.1. Primary Analysis of the Primary Estimand

A Mixed Model for Repeated Measures (MMRM) will be used to test the difference between clazakizumab and placebo for change from baseline to week 52 in eGFR. eGFR data collected after the occurrence of the intercurrent events will be excluded from the analysis. The SAS procedure PROC MIXED will be used. Missing data will not be imputed. Under the assumption of missing at random (MAR), the missing data will be accounted for through correlation of repeated measures in the model. The model will include a response variable of change from baseline in eGFR (in mL/min/1.73 m2) with the following terms:

- Treatment (categorical variable for clazakizumab or placebo)
- Visit (nominal visits through Week 52, categorical variable)
- Treatment by visit interaction term
- baseline eGFR
- Randomization stratification factor of dichotomized baseline eGFR (25–45 mL/min/1.73 m^2 versus >45–65 mL/min/1.73 m^2)

- Randomization stratification factor of baseline proteinuria (UACR <300 mg/g [<30 mg/mmol] or UACR ≥300 mg/g [≥30 mg/mmol])
- Randomization stratification factor of treatment for early (within 6 months of transplant) ABMR rejection episodes (yes/no)
- Randomization stratification factor of treatment for late (within 6 months of transplant) ABMR rejection episodes (yes/no)

An unstructured covariance structure will be used to model the within-subject errors. If this analysis fails to converge, the following covariance structures will be tested and the one converging to the best fit, as determined by Akaike's information criterion (AIC), will be used as the primary analysis:

- compound symmetry
- Toeplitz,

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom if the unstructured covariance structure is used; otherwise, the default method of the between-within (in SAS Proc Mixed) will be used to estimate denominator degrees of freedom.

Analysis for IA #1

Primary analysis of change from baseline in eGFR at IA #1 will be based on the Efficacy Analysis Set for IA #1 and will only include nominal visits up to 52 weeks. Treatment effect size will be estimated from the MMRM model.

Details of sample size re-estimation for IA #2 are included in Section 4.5.2 .

Also, the guidance for the outputs for DSMB are provided in Section 14.1.

Analysis for IA #2

At IA #2, primary analysis of change from baseline in eGFR is based on the combination statistics from stage 1 and stage 2 and will only include nominal visits up to 52 weeks. Therefore, MMRM analysis will be performed separately for change from baseline in eGFR for stage 1 subjects (ie, Efficacy Analysis Set for IA #1) and stage 2 subjects (ie, Efficacy Analysis Set for Stage 2). The number of subjects in the Efficacy Analysis Set for Stage 2 will be,

- at least 80 randomized subjects if the sample size re-estimation at IA #1 does not require any increase in sample size for IA #2, or
- if the sample size re-estimation increases the sample size for IA #2 then the number of subjects for stage 2 will include all the subjects eligible for IA #2 except those who were already included in IA #1.

The effect size and test statistics will be obtained from MMRM. The inverse normal combination test will be used for testing the hypothesis at IA #2 as follows:

- Z_1 and Z_2 are z-statistics, at stage 1 (based on Efficacy Analysis Set for IA #1) and at stage 2 (based on Efficacy Analysis Set for Stage 2), respectively and corresponding one-sided p-values P_1 and P_2 will be estimated from the MMRM. The Z statistic for

the primary analysis for change from baseline to week 52 in eGFR is a combination test-statistic based on the test statistics at stage 1 and stage 2:

$$Z\_1 = \Phi\hat{}(-1)\ (1 - P\_1\ ) \text{ and } Z\_2 = \Phi\hat{}(-1)\ (1 - P\_2\ )$$

- The overall combination test statistic (Z) will be:

$$Z = \ \vdash w\_1\ Z\_1 + w\_2\ Z\_2 \dashv$$

Note that $w\_1 = \sqrt{(100/180)} = 0.7454$ and $w\_2 = \sqrt{(80/180)} = 0.6667$ have been specified in the design of the study.

- Two-sided p-value for the combination test will be: $P = 2 * (1 - \Phi(Z))$
- Reject H_0 at a 2-sided level α if $P < \alpha$

P-value for the combination test will be provided to the DSMB, along with the effect size at stage 1 and stage 2.

The details of SAS codes are provided in the Section 14.3.

10.2. Sensitivity Analyses for IA #2

To assess the robustness of the analysis of change from baseline to week 52 in eGFR, the primary analysis will be repeated using the PP Analysis Set.

Additional sensitivity analyses will be conducted as described in the following subsections. All sensitivity analyses described below will be based on the Efficacy Analysis Set for IA #2.

10.2.1. Analysis Based on Imputation of Missing Data

Missing data will be imputed using following approaches:

Single Imputation will be performed as follows and analyzed using the MMRM model specified in Section 10.1.1:

1. Missing values at all visits through week 52 that are not preceded by an all-cause composite allograft event will be imputed by the mean of the observed values at that time point within the same treatment group.
2. Missing values at all visits through week 52 following an all-cause composite allograft event will be imputed by an eGFR value of 15 mL/min/1.73m^2.

Multiple Imputation:

The delta adjustment method, assuming missingness not at random (MNAR), will be used to estimate the tipping point beyond which the active treatment would have an unfavorable effect.

The delta adjustment method, based on multiple imputations (MI) under the MNAR assumption assumes that subjects from the active treatment group who discontinue at a given time point would have, on average, an eGFR value that is worse by a specific amount δ compared with the observed values from subjects in the active treatment group who continue to the next time point. This general model can be estimated with a progression of values of δ until the treatment difference moves to a

significantly worse outcome for active subjects than for controls. This analysis is conducted to show the value of delta that would reverse the study conclusion in favor of the control arm. The values of δ that lead to a negative study conclusion can then be evaluated from a clinical perspective as to their plausibility.

Regression imputation for monotone missing data patterns will be implemented using SAS PROC MI. Analysis results from the multiple imputed datasets will be combined using SAS PROC MIANALYZE. A forest plot will be provided to summarize the point estimates and confidence intervals for the treatment effect under each value of δ.

The details of SAS codes including number of imputations and seed are provided in Appendix 14.4.

10.2.2. Nonparametric Analysis

A nonparametric rank-based analysis will be conducted based on the Efficacy Analysis Set for IA #2 without complex multiple imputation methodology. Wilcoxon rank sum test will be used for the treatment comparison (Ouyang et al., 2017) using the change from baseline eGFR value at Week 52 or at last visit prior to Week 52 if subject discontinued.

In the rank-based analysis, subjects will first be ranked on the time point when they last provided data and then by the value of eGFR change from baseline at that visit (with lower ranks for larger eGFR decline). The ranking of change from baseline in eGFR will be from smallest to largest, so that the smallest change from baseline in eGFR values will appear first within the subset of subjects with the same discontinuation visit.

Once all the rankings are assigned, the change from baseline in eGFR data are converted to a set of ranks in which the lower the rank is, the worse the outcome is. In this approach, subjects completing Week 52 will be assigned higher ranking than subjects who discontinued the study at earlier visit. For example, a subject with a change from baseline at Week 44 visit (last visit before discontinuation) which shows improvement in eGFR from baseline will be assigned lower rank than subjects who completed Week 52 with a decline in eGFR.

A Wilcoxon rank sum test will then be applied to compare treatment groups using the ranks. If the treatment comparison in this rank-based analysis supports the results obtained based on the primary analysis of the surrogate efficacy endpoint described in Section 10.1.1, then the interpretation is that earlier discontinuation did not introduce substantial bias into the primary analysis of the efficacy surrogate endpoint of change from baseline to week 52 in eGFR.

10.3. Supplementary Analyses for IA #2

The Analysis of covariance (ANCOVA) approach will be used to explore a model with linear decline in the slope of eGFR over time as a fixed effect, rather than a categorical mean at each visit. This model will replace the categorical nominal visit with the continuous numeric study week as defined in Section 8.3.1. Response variable in the model will be eGFR (instead of change from baseline in eGFR as in the primary analysis). This analysis will be based on the Efficacy Analysis Set for IA #2 and will only include nominal visits up to 52 weeks. In addition to study week, following other terms will be included in the model:

- Treatment (categorical variable for clazakizumab or placebo)

- Treatment by study week interaction term
- baseline eGFR
- Randomization stratification factor of dichotomized baseline eGFR (25–45 mL/min/1.73 m^2 versus >45–65 mL/min/1.73 m^2)
- Randomization stratification factor of baseline proteinuria (UACR <300 mg/g [<30 mg/mmol] or UACR ≥300 mg/g [≥30 mg/mmol])
- Randomization stratification factor of treatment for early (within 6 months of transplant) ABMR rejection episodes (yes/no)
- Randomization stratification factor of treatment for late (within 6 months of transplant) ABMR rejection episodes (yes/no)

The estimated slopes for each treatment, difference of slopes between the treatments and corresponding CIs will be presented.

In addition, an analysis will also be conducted using the MMRM (model specified in Section 10.1.1) based on the Efficacy Analysis Set for IA #2 (combination of subjects from stage 1 and stage 2) and will only include nominal visits up to 52 weeks. Missing data will not be imputed.

Summary statistics for the mean difference between the treatment groups for change from baseline to Week 52 based on the mixed model will be presented along with two-sided 95% confidence intervals. Estimated effect size from the model will be also presented.

10.4. Exploratory analysis of Primary Endpoint of All-Cause Allograft Loss or Irreversible loss of allograft function at IA #2

The relationship between eGFR and long-term allograft survival will be further explored by extending the results of the joint modelling study to data from the current study. These data will be provided to the DSMB at the time of the IA #2 and help inform recommendations for continuing or stopping the study and increasing the sample size for the final analysis of all-cause composite allograft loss.

Parameter estimates from the joint modeling study will be applied to predict the hazard function for all-cause composite allograft loss or irreversible loss of allograft function based on the serial eGFR measurements and other independent variables collected during the present study. To reflect the uncertainty inherent in the modeling process, several sets of predictions can be generated and combined to create an empirical distribution of the hazard ratio.

For a given patient, the survival sub-model from the joint modeling study has the following form:

$$h\_i\,(t) = h\_0\,(t)\ \exp[\boldsymbol{X\beta} + \boldsymbol{Y\alpha}]$$

where $\boldsymbol{X\beta}$ and $\boldsymbol{Y\alpha}$ are linear predictors based on baseline characteristics and eGFR trajectory features, respectively, and $h\_0\,(t)$ is a piecewise constant baseline hazard function as described by Rizopoulos (2012).

For each prediction set, a random draw from the distribution of parameter estimates in $\boldsymbol{\beta}$ and $\boldsymbol{\alpha}$ from the joint modeling study will be taken. The randomly drawn parameter vector will be used to calculate the projected hazard rate for each subject as a function of their baseline characteristics and observed trajectory of eGFR values. Survival times based on the parameters from the joint modeling study can then be compared to the observed time to all-cause composite allograft loss in an exploratory manner.

Using the actual treatment group assignments, the estimates of the log hazard rate will be averaged across subjects within a treatment group. Then an estimate of the hazard ratio for clazakizumab versus controls will be computed as

$$\hat{h}(t) = h\_0\,(t)\ \exp[\bar{\boldsymbol{X}}\_\mathbf{2}\,\hat{\boldsymbol{\beta}} + \bar{\boldsymbol{Y}}\_\mathbf{2}\,\hat{\boldsymbol{\alpha}} - (\bar{\boldsymbol{X}}\_\mathbf{1}\,\hat{\boldsymbol{\beta}} + \bar{\boldsymbol{Y}}\_\mathbf{1}\,\hat{\boldsymbol{\alpha}})]$$

where $\bar{\boldsymbol{X}}\_\mathbf{2}$ and $\bar{\boldsymbol{Y}}\_\mathbf{2}$ are averages for the clazakizumab group and $\bar{\boldsymbol{X}}\_\mathbf{1}$ and $\bar{\boldsymbol{Y}}\_\mathbf{1}$ are means from the control group. An estimated confidence interval for the hazard ratio using this method can be constructed from the empirical distribution of hazard ratios across the set of predictions.

10.5. Additional Efficacy Analyses

Analysis of eGFR beyond week 52:

Change from baseline to week 52 and week 104 in eGFR, will be conducted using the available data at the time of the IA # 2.

A Mixed Model for Repeated Measures (MMRM) analysis will be conducted based on the subjects who completed 2 years (104 weeks) in the study. Change from baseline in eGFR through week 104 will be included. The difference between clazakizumab and placebo for change from baseline to week 52 in eGFR will be estimated. The MMRM will include terms specified in Section 10.1.1.

All available eGFR data (through week 52 and beyond) from the subjects in the Efficacy Analysis Sets will be summarized by using descriptive statistics at IA #1 and IA #2

Additional Analyses:

In addition, proportion of subjects for individual components of the all-cause composite allograft loss will be presented for IA #2 based on all data from Efficacy Analysis Set for IA #2,

- 40% decline in eGFR from Baseline that is sustained for at least 60 days.
- 40% decline in eGFR from Baseline that is sustained for at least 60 days and accompanied by investigator's decision to supplement the therapy by additional treatment.
- Proportion of subjects who returned to dialysis for at least 60 days.
- Proportion of subjects with allograft nephrectomy.
- Proportion of subjects who had re-transplantation.
- Proportion of subjects with eGFR <15 mL/min/1.73 m^2 for at least 60 days.
- Proportion of subjects who died.

Proportion of subjects who received any prohibited therapy and medications (Protocol section 7.6.1) will also be presented.

10.5.1. Subgroup Analysis for IA #2

Additional subgroup analyses will be performed for Change from Baseline to Week 52 in eGFR to determine whether significant differences exist between subgroups.

These subgroup analyses will be carried out using the subjects from the Efficacy Analysis Set for IA #2.

Summary of observed change from Baseline to Week 52 in eGFR will be presented for the subgroups. The list of potential subgroups (with applicable definitions in parentheses) includes, but is not necessarily limited to, the following:

- Age (<65 years vs. ≥65 years)
- Sex (Female vs. Male)
- Race (white vs. non-white)
- Geographic region (North America vs. rest of the world)
- eGFR category at Baseline (low [<45 mL/min/1.73 m2] vs. high [≥45 mL/min/1.73 m2])
- 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)
- Treatment for late (greater than 6 months post-transplant) ABMR rejection episodes (yes/no)
- Biopsy score categories and DSA will be summarized if the data is available at the time of IA # 1 and IA # 2

10.6. Multiple Comparisons and Multiplicity

The overall type 1 error of 5% for hypothesis testing of change from baseline to week 52 is preserved by the two-stage weighted inverse normal test. Test statistics will be calculated from the subjects in each of the two stages and combined using the weighted inverse normal method in a prespecified way for the testing at IA #2 (refer to Section 4.5 for details on combination test).

11. SAFETY ANALYSES

All safety analyses will be based on the safety analysis set as defined in Section 6.4 and summaries will include safety assessments specified below.

For by-visit summaries of events, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each visit. For worst post baseline summaries of events, the denominator in percentage calculation will be based on the number of subjects with at least one non-missing value post baseline.

No formal statistical test on the treatment difference will be performed for any safety analyses.

11.1. Adverse Events (AEs)

AEs will be coded using the MedDRA dictionary version 25.0 or higher and will be presented according to SOC and PT. Treatment-emergent AEs (TEAEs), defined as AEs starting on or after the date of the first dose of IP, will be summarized. All AEs regardless of whether they were treatment-emergent or not will be listed.

Where AE start dates are missing or partially missing, AEs will be assumed to be treatment-emergent, except if the partial start dates or the AE end date indicate that the AE started before the first administration of IP (Table 5).

Table 5: TEAE Assignment in Case of Missing AE Start Date Elements

Missing elements of AE start	**Rule**	
Regardless of any missing information for AE start: AE end date < IP start date		non-TEAE
Otherwise (ie, if AE end date ≥ IP start date)		
All		TEAE
day and month	AE start year ≥ IP start year	TEAE
	AE start year < IP start year	non-TEAE
Day	AE start month / year ≥ IP start month / year	TEAE
	AE start month / year < IP start month / year	non-TEAE

If AE start dates or end dates are missing or partially missing for an AE, no duration will be calculated. If for a TEAE the relationship to study treatment is missing the worst case will be assumed for summarizing analysis (ie, the relationship to study treatment will be assumed to be "Yes"). No imputation will be done in case of missing study treatment relationship for non-treatment emergent AEs. No other imputations for missing AE information will be done.

The Adverse events of special interest (AESIs) are defined in section 10.1.4 of the protocol.

An overview summary of all AEs, including number and percentages of subjects as well as the number of events will be provided including the following:

- Any AE
- SAE
- Fatal AEs
- AEs leading to discontinuation of study treatment

Similarly, an overview summary of TEAEs, including number and percentages of subjects as well as the number of events will be provided including the following:

- Any TEAE
- TEAEs related to study treatment
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to dose interruptions
- TEAEs leading to modification to background immunosuppression
- TEAE of Severity Grade 3 or Higher
- Serious TEAEs
- Fatal TEAEs

Following descriptive tables will be generated for AEs including number and percentages of subjects and the number of events:

- TEAEs by PT
- TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- AESIs by SOC and PT
- Serious TEAEs by PT
- Serious TEAEs by SOC and PT
- SAEs by SOC and PT

Additionally, number of subjects, exposure-adjusted subject incidence rate per 100 subject-years and the number of events will be summarized for TEAEs by PT and Serious TEAEs by PT.

The exposure-adjusted subject incidence rate per 100 subject-years is calculated as

$$(\text{Total number of subjects with AE})/(\text{Total treatment exposure in years}) * 100$$

Total treatment exposure in years is the sum of treatment exposure for all subjects where treatment exposure is the difference between last dose date and first dose date + 1.

The following listings will be provided:

- All AEs
- SAEs
- AESIs

11.2. OVERVIEW OF COVID-19 IMPACT

Number and percentages of subjects with at least one of the following due to COVID-19 will be summarized in an overview table:

- Subjects with Any COVID-19 Impact,
- Protocol Deviations,
- Missing Visit,
- Alternate Visit Modality,
- Study Treatment Discontinuation,
- Study Discontinuation,
- Any TEAEs,
- Any Serious TEAEs.

11.3. Clinical Laboratory Evaluations

Laboratory data will be presented in SI units. Laboratory values and changes from baseline will be summarized descriptively by visit using only values from scheduled visits for following laboratory tests (Table 6). Box plots will be produced for change from baseline at each scheduled visit. Definition of the baseline assessment is in Section 8.3.3.

Table 6: List of laboratory tests summarized for DSMB Safety Reviews

Hematology	• Hb • Hematocrit • White blood cell count • White blood cell differential (absolute) • Platelet count • RBC
Clinical Chemistry	• BUN • Creatinine

Hematology	• Hb • Hematocrit • White blood cell count • White blood cell differential (absolute) • Platelet count • RBC
	• Liver function tests (AST, ALT, alkaline phosphatase, total bilirubin, indirect bilirubin, direct bilirubin, GGT, INR) • Potassium • Sodium • Fasting glucose
Urinalysis	• UACR spot urine test • Albumin / Creatinine Ratio
Lipids (serum)	• Cholesterol (total, HDL, and LDL) • Triglycerides

Number and percentage of subjects with post baseline laboratory abnormalities (defined in Table 7) will be summarized.

Table 7: Laboratory Values of Potential Clinical Importance

Laboratory Parameter	Abnormality	Unit
Alanine aminotransferase (ALT)	>ULN to 3xULN >3xULN to 5xULN >5xULN	U/L
Aspartate aminotransferase (AST)	>ULN to 3xULN >3xULN to 5xULN >5xULN	U/L
Bilirubin	>ULN to 2xULN >2xULN	umol/L
Neutrophils	<2.5 to 1.5 <1.5 to 1 <1	10^9/L
Platelets	<LLN to 75 <75 to 50 <50	10^9/L

11.3.1. Analysis of Immunoglobulin G (IgG)

Number and percentage of subjects with worst post baseline IgG (400 mg/dl) levels will be summarized for following categories.

- < 4.0
- ≥ 4.0

The denominator in percentage calculation will be based on the number of subjects with at least one non-missing value post baseline.

11.4. Other Safety Measures

11.4.1. Viral PCR Assay

Subjects with post baseline viral PCR assays for BKV, CMV and EBV greater than the lower limit of quantification (LLOQ) will be considered to have an active infection and counted as "positive". The number and percentage of subjects positive for each virus by visit will be summarized.

Number and percentage of subjects with worst post baseline results for following viral load categories (

Table 8) will be summarized.

Table 8: Categories for BKV, CMV and EBV viral PCR assays

Parameter	Category
BKV (IU/mL)	>LLOQ to <320 ≥320 to <3,200 ≥3,200*
CMV (IU/mL)	>LLOQ to <1,000 ≥1,000 to <5,000 ≥5,000
EBV (IU/mL)	>LLOQ to <10,200 ≥10,200 to <20,400 ≥20,400
* This is ≥ 10,000 copies/mL	

11.4.2. Calcineurin Inhibitor (CNI) levels

CNI trough levels above detectable threshold (>=20 ng/mL for Cyclosporine and >=2 ng/mL for Tacrolimus) will be summarized for baseline and post-baseline assessments for Tacrolimus and Cyclosporine using descriptive statistics.

12. ADDITIONAL ANALYSIS TO SUPPORT REGULATORY SUBMISSION FOR EXPEDITED MARKETING APPROVAL

DSMB may recommend for submission to regulatory authorities for expedited marketing approval based on the review of results of efficacy analysis at IA #2.

In such a scenario, CSLB regulatory submission team (RST) will initiate submission related activities which includes production of planned tables, figures, listings to support regulatory submission.

Analyses based on all randomized subjects in DBL for IA #2

Only summary tables will be provided for the following analyses. No subject level listings will be provided for the following summaries.

- Summary (table and figure) of eGFR over time (and change from baseline) for all randomized subjects in the DBL for IA#2.
- Summary of proportions of subjects with all-cause allograft loss or irreversible loss of allograft function (and components) for all randomized subjects in DBL for IA#2.
- Safety package based on all randomized subjects included in the DBL for IA#2.
- Additional analysis requested by regulatory agencies at pre-submission meetings.

Following analysis will be performed to support submission based on the appropriate analysis set. Subject level listings will be provided.

- **Medical History** will be coded using MedDRA dictionary version 25.0 or higher and will be summarized by SOC and PT. Summary of medical history will be based on the Efficacy Analysis Set for IA #2.
- **Prior and Concomitant Medications** will be coded using WHO Drug Dictionary (March 2022 or later). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of IP. Concomitant medications are defined as any therapy used on or after the same day as the first dose of IP, including those that started before and continue after the first dose of IP. Prior and Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification level 4 and PT. If the ATC level 4 coding is not available for a PT, the next available lower level ATC code will be used. Summary of prior and concomitant medications will be based on the Efficacy Analysis Set for IA #2.
- **Exposure to IP** will be calculated in months as (last dose date – first dose date + 1 + 150 days)/30.4375. Exposure will be summarized by treatment group. The total actual dose and the total planned dose of IP will be calculated for each subject and summarized by treatment group. Treatment compliance will be calculated as (the total number of doses received/number of planned doses) x 100% and summarized by treatment group. Exposure summaries will be based on the Safety Analysis Set.

- **Change in Banff lesion grading score** of pre-treatment to post-treatment (Week 52) kidney biopsies will be summarized by treatment group and will be based on the Efficacy Analysis Set for IA #2.
- **AE** summaries in addition to those specified in Section 11.1 may be generated based on Safety Analysis Set.
- **Laboratory** parameters in addition to those specified in Table 6 may be summarized. Laboratory abnormalities in addition to those specified in Table 7 may be summarized. All laboratory data summaries will be based on the Safety Analysis Set.
- **Health Related Quality of Life (HRQoL)** data will be summarized for the following scales based on the Efficacy Analysis Set for IA #2:
  - EuroQol 5 dimensions questionnaire (EQ-5D-5L): Number and proportion of subjects at each response level for each of the 5 domains will be presented by treatment group and visit. Mean visual analogue scale (VAS) scores at each time point and change from baseline will be summarized by treatment group and visit. A comparison of change from baseline in mean VAS scores will be conducted using mixed model repeated measures as described in Section 10.1.1 with contrasts for the mean change from baseline to Week 24 and from baseline to Week 52. A graph should also be provided with a frequency distribution of the percent improvement in VAS scores to week 24 and week 52. Health states in the EQ-5D-5L will be converted into a single index value using EQ-5D-5L values based on the crosswalk [van Hout, 2012] for the UK value set. Index values can also be converted to e country specific utility scores using other value sets. The same analyses conducted for the VAS scores should also be conducted for the mean utility scores. Mean utility scores at each time point and change from baseline will be summarized by treatment group and visit. A comparison of change from baseline in mean Index scores will be conducted using mixed model repeated measures as described in Section 10.1.1 with contrasts for the mean change from baseline to Week 24 and from baseline to Week 52. A graph should also be provided with a frequency distribution of the percent improvement in Index scores to week 24 and week 52.
  - Kidney Disease Quality of Life 36 (KDQoL-36): Change from baseline in KDQoL-36 subscale scores at all visits will be summarized descriptively by treatment group and visit. KDQoL-36 Summary Score (KSS), which is a composite of items from the KDQoL-36's kidney targeted scales will also be derived and summarized descriptively by treatment group and visit (Peipert et al. 2019). A comparison of change from baseline in mean KSS and domain scores will be conducted using mixed model repeated measures as described in Section 10.1.1 with contrasts for the mean change from baseline to Week 24 and from baseline to Week 52. A graph should also be provided with a frequency distribution of the percent improvement in KSS and domain scores to week 24 and week 52. The domain scores for the KDQoL-36 include the physical component score, the mental health component score, the burden of kidney disease, symptoms/problems of kidney disease, and effects of kidney disease.

- Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue Scale: Change from baseline in FACIT Fatigue score at all visits will be summarized descriptively by treatment group and visit. Number and proportion of subjects achieving a minimum clinically important difference (MCID) of 3 will be presented by treatment group and visit (Cella D. et al 2002) Subject achieves MCID of 3 if the change from baseline in the FACIT Fatigue score is ≥ 3. A comparison of change from baseline in mean FACIT Fatigue scores as well as a comparison of the proportion of subjects achieving an improvement of at least 3 points will be conducted using mixed model repeated measures as described in Section 10.1.1 with contrasts for the mean change from baseline to Week 24 and from baseline to Week 52.In addition, please provide the number of subjects with any HRQoL data and the mean as well as the range of EQ-5D-5L VAS scores, EQ-5D-5L Index scores, FACIT Fatigue scores, KSS and KDQoL-36 domain scores at baseline for each of the following GFR categories G2 (60-89), G3a (45-59), and G3b (30-44).
- **PK Concentrations** of clazakizumab in serum will be listed and summarized by treatment group and nominal timepoints. Standard summary statistics will be calculated, including n, arithmetic mean, SD, CV%, median, geometric mean, minimum, and maximum. The lower limit of quantification of the clazakizumab PK assay is 20 ng/mL. Any pre-dose BLQ and/ or BLQ occurring post-dose but before the first quantifiable value will be set to zero. Any BLQ present in the profile or at the end of the profile will be treated as missing. If two or more BLQs occur in succession, then the profile will be considered to have been terminated at the previous quantifiable concentration and all further values will be treated as missing. The mean concentrations at any individual time point will be calculated if at least 50% of the individual values are available (i.e. are quantifiable and not missing) at given time point otherwise the mean value will be reported as 'not calculated (NC). All PK concentration analysis will be based on the PK Analysis Set.
- **PK Parameters** will be determined for subjects in the clazakizumab treatment group participating in the PK/PD Substudy. For all derived parameters, except T_{max}, the following summary statistics will be calculated for the clazakizumab treatment group: n, mean, standard deviation [SD], coefficient of variation (CV) defined as STD / mean*100%, median, minimum, and maximum, along with geometric mean, geometric mean SD, geometric percent coefficient of variation [%CV], and 95% CIs around the geometric mean. For T_{max}, only n, median, minimum and maximum will be presented. All PK parameter analysis will be based on the PK/PD Sub-study Analysis Set. The PK parameters will be calculated by standard noncompartmental analysis, using WinNonlin® versions 5.2 or higher.
- **PD** markers to be evaluated include IL-6 (both total and free levels) and hsCRP. These parameters will be summarized by treatment group and visit based on the Pharmacodynamic Analysis Set. Additional Biomarkers may be evaluated and reported separately.
- **PK/PD** modelling will be explored, as feasible, for further time-dependent characterization of PK versus PD endpoints and/or safety/efficacy and reported

separately. Additional information on PK/PD analyses will be provided separately in a modeling and simulation analysis plan.

- **Immunogenicity** data will be summarized and listed based on the PK analysis set. Anti-drug antibody incidence will be calculated and summarized.

13. REFERENCES

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14. APPENDICES

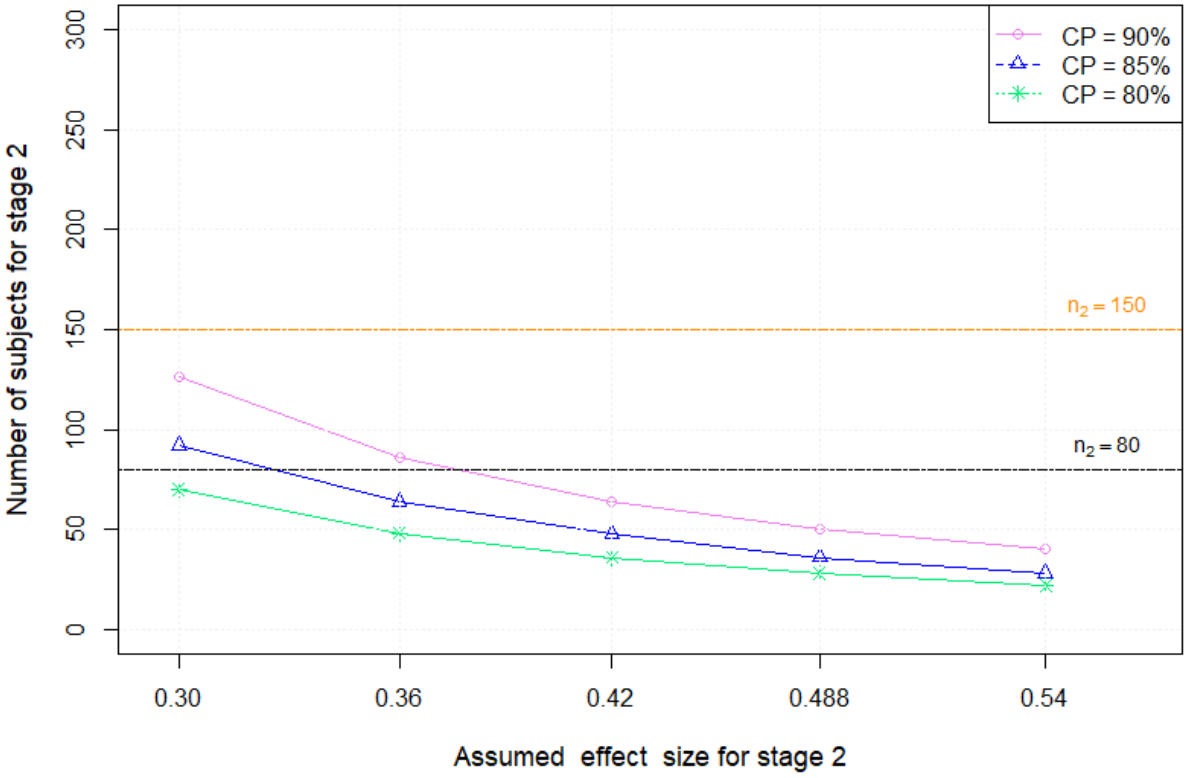
14.1. Figures for DSMB at IA #1

The following figures show examples of figures for DSMB review based on observed effect size at stage 1 (IA #1) and a range of possible effect size at stage 2. The two horizontal reference lines have been provided corresponding to the planned (N_2 = 80) and the maximum number of randomized subjects (N_2 = 250, as stated in protocol) required from stage 2

Example 1:

Figure 3 shows the proposed figure if the observed effect size estimated from the MMRM at IA #1 is 0.45. The following figure has been generated using this observed effect size at stage 1 and assumed effect size in stage 2 (range 0.30 to 0.54). The three lines represent additional subjects to be randomized at stage 2 for conditional powers 90%, 85% and 80% for testing the efficacy endpoint at IA #2.

Figure 3: Sample figure for DSMB based on hypothetical observed effect size 0.45 at IA #1

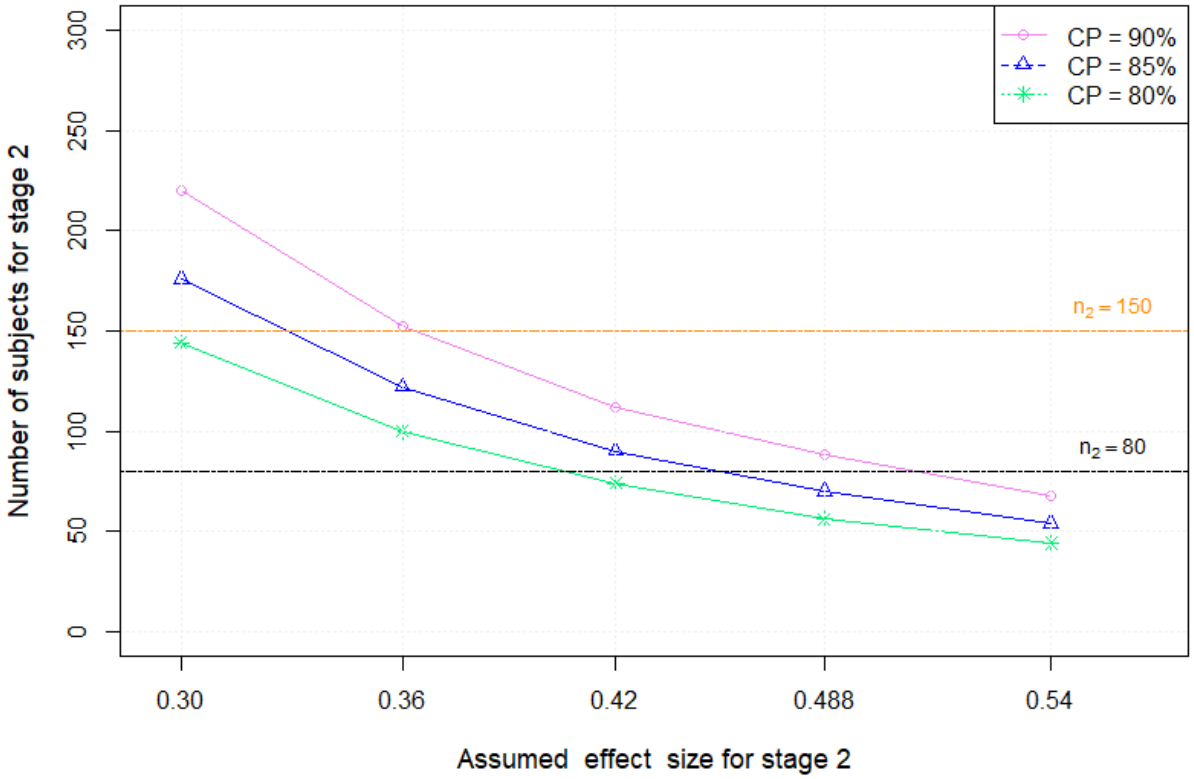


Please note that if effect size at stage 2 is similar to the effect size observed at stage 1 (0.45), then there is no need to increase from planned sample size of 180 randomized subjects with 52 weeks of follow-up at IA #2. All three curves corresponding to the conditional powers are below the horizontal line of N_2 = 80 around the effect size of 0.45.

In this case, DSMB is expected to recommend continuing the study as planned without increasing the sample size for IA #2.

Example 2:

Figure 4: Sample figure for DSMB based on hypothetical observed effect size 0.35 at stage 1 (IA #1) and assumed effect size of 0.30 to 0.54 in stage 2



In this case, it appears from the figure that more than 150 additional randomized subjects will be needed at stage 2 if the effect size at stage 2 remains similar to the observed effect size at stage 1 with conditional power of 90%. DSMB recommendation of whether to continue the study is based on the review of totality of information presented at IA #1. It appears from the figure that the study could continue with the planned maximum number of randomizations (150) at stage 2, assuming

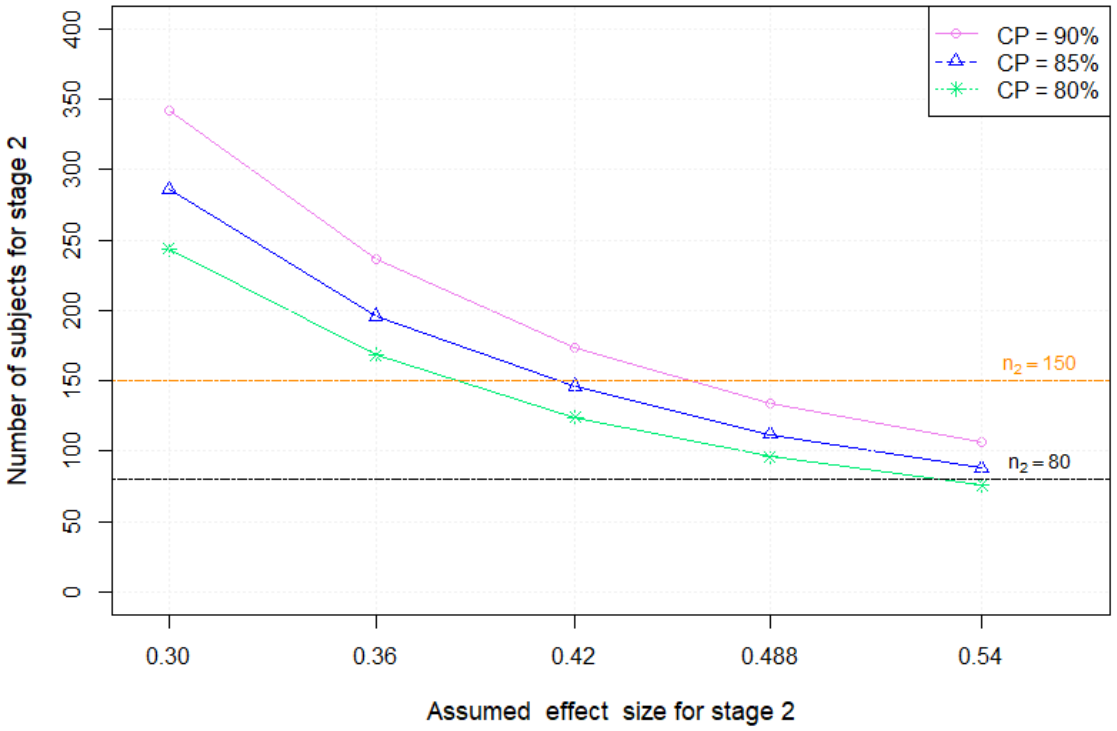
similar effect size at stage 1 and stage 2 and conditional power is approximately 85%

more optimistic effect size from the subjects at stage 2 and conditional power remains at 90%.

In this case, if DSMB is making a recommendation to continue the study based on the totality of data then a recommendation about the sample size for IA #2 is also needed. The recommended sample size for IA #2 could be the maximum allowed sample size of 250 randomized subjects or lower.

Example 3:

Figure 5: Sample figure for DSMB based on hypothetical observed effect size 0.25 at stage 1 (IA #1) and assumed effect size of 0.30 to 0.54 in stage 2



In this case, it appears that IA #2 with the planned maximum sample size of 250 randomized subjects with 52 weeks of follow-up is not adequate with reasonable conditional power or assumption of effect size at stage 2 (all the curves corresponding to conditional power are above the reference line of $N_2 = 150$, even for the assumed effect size of 0.35 for IA #2). DSMB is expected to recommend stopping further randomization. The final decision to stop the study will be confirmed by CSLB senior management.

14.2. R Code for Simulated Overall Power at IA #2 Using rpact R Package

Specify inverse normal design

```
designIN <- getDesignInverseNormal(typeOfDesign = "asUser", beta=0.1,
informationRates = c(0.5556, 1), userAlphaSpending = c(0.00, 0.025))
```

Simulation for overall power

```
n1 = 100    # Size of Stage 1, both arms
n2 = 80     # Size of Stage 2, planned, both arms
N = n1 + n2 # Total planned sample size
Nmax = 250  # Total maximum sample size
simCpower <- getSimulationMeans(designIN, thetaH0 = 0,
             alternative = 0.488, # "True" value used for simulating data
             plannedSubjects = c(n1, N), # Cumulative overall sample size
             conditionalPower = 0.9,
             minNumberOfSubjectsPerStage = c(n1, n2), #stage-wise min overall
sample size
             maxNumberOfSubjectsPerStage = c(n1, Nmax-n1), # stage-wise max
overall sample size
                maxNumberOfIterations = 10000,    # Number of simulations
                                seed = 12347)     # Random seed
```

14.3. SAS Code for MMRM Analysis Using PROC MIXED

```
proc mixed data=egfr2 order=data;
  where visit ne 'Visit 2'; *remove baseline visit;
  class subjid treatdesc visit randbegfr randbprot randearlytrt
  randlatetrt;
  model change = treatdesc visit randbegfr randbprot randearlytrt
  randlatetrt treatdesc*visit base/s DDFM=KR;
  repeated visit / type= UN subject=subjid;
  lsmeans treatdesc*visit / diff cl ;
  ods output Estimates=est;
run;
```

Where, response variable ‘change’ is change from baseline in eGFR; treatdesc = Clazakizumab or Placebo; visit=nominal post baseline visits; ‘randbegfr’, ‘randbprot’, ‘randearlytrt’, ‘randlatetrt’ are the stratification factors; DDFM=KR requests the Kenward-Roger method for the covariance matrix if unstructured covariance structure is used.

DDFM option should not be specified if other covariance structure is used.

14.4. Tipping Point Analysis Using Delta Adjustment Method

The delta adjustment method described by Ratitch et al (2013) will be implemented using the following steps:

1. Create a dataset with one record per subject, containing values of AVAL for all weeks (Baseline and Weeks 4–52) on one record, where AVALx represents the analysis value of eGFR at month X (where month = week/4, ranging from 1 to 13).
2. Run 25 Markov Chain Monte Carlo (MCMC) imputations to make the missing values in the dataset have a monotone missingness pattern. This will produce a dataset with an index

variable _Imputation_ and otherwise the same variables as the input dataset. It will have one record per imputation per subject.

3. Run a pattern mixture model regression imputation using MNAR statement in SAS on each imputed dataset from step 2. Apply delta penalty (by subtracting eGFR values) using SHIFT option to all post baseline visits in clazakizumab arm. This will generate a dataset with the same structure as the input dataset for each delta but will have the missing values filled in and delta penalty applied.
4. Transpose data in longitudinal format.
5. Run the primary MMRM analysis on the imputed datasets, once for each imputation. This will create 25 estimates of the output statistics.
6. Combine the 25 estimates to generate the test statistic and p-value.
7. Repeat steps 1–6 for a range of eGFR values. eGFR values will start from 0 in the increment of -0.5 until the p-value is >=0.05. For example, from 0 to –4 by –0.5.

Steps 2–7 may be implemented using SAS code similar to the following.

```
%macro miparms( data=, smin=, smax=, sinc=, outparms=);

data &outparms;
  set _null_;
run;

/*# of shift values*/
%let ncase= %sysevalf( (&smax-&smin)/&sinc, ceil );

/*Multiple imputation analysis for each shift*/
%do jc=0 %to &ncase;
%let sj= %sysevalf( &smin + &jc * &sinc);

/* step 2: Impute intermitent missing variables to create monotone
missingness with MCMC */

proc mi data=&data seed=81431864 nimpute=25 out=outdata1;
  by trtp;
  mcmc impute=monotone;
  var AVAL1- AVAL4;
run;

proc sort data=outdata1;
  by _Imputation_;
run;

/* step 3: Impute all visits under MNAR first, then apply delta adjustments
at each visit */

proc mi data=outdata1 seed=74358221 nimpute=1 out=outdata2;
  by _Imputation_;
  class treatdesc;
```

```
  monotone reg(AVAL2-AVAL4 / details);
  mnar ADJUST(AVAL2 / SHIFT=-&sj ADJUSTOBS=(TREATDESC =' Clazakizumab '));
  mnar ADJUST(AVAL3 / SHIFT=-&sj ADJUSTOBS=(TREATDESC =' Clazakizumab '));
  mnar ADJUST(AVAL4 / SHIFT=-&sj ADJUSTOBS=(TREATDESC =' Clazakizumab '));
  var treatdesc AVAL2-AVAL4;
run;

/* step 4: convert data in log and skinny format, calculate change from
baseline */

proc sort data=outdata2;
  by _Imputation_ subjid treatdesc;
run;

proc transpose data=outdata2 out=outdata3;
  by _Imputation_ subjid treatdesc;
  var AVAL1-AVAL4;
run;

data outdata4;
  set outdata3;
  visit=input(compress(_name_, "y"),best.);
  aval=col1;
  drop _name_ col1;
run;

data base;
 set outdata4;
 where visit=1;
 base=aval;
 keep _Imputation_ subjid base;
run;

proc sort data=base;
 by _Imputation_ subjid;
proc sort data=outdata4;
 by _Imputation_ subjid;
run;

data outdata5;
 merge outdata4 base;
 by _Imputation_ subjid;
 change=aval-base;
run;

proc sort data=outdata5;
  by _Imputation treatdesc visit subjid;
run;

/* step 4: Analyze data for imputation using MMRM */

proc mixed data=outdata5 order=data;
  by _Imputation_;
  where visit ne 'Visit 2'; *remove baseline visit;
  class subjid treatdesc visit randbegfr randbprot randearlytrt
  randlatetrt;
```

```
  model change = treatdesc visit randbegfr randbprot randearlytrt
  randlatetrt treatdesc*visit base/s DDFM=KR;
  repeated visit / type= UN subject=subjid;
  lsmeans treatdesc*visit / diff cl ;
  estimate 'Visit 6 (Claza-pbo)' treatdesc -1 1 treatdesc*visit 0 0 -1 0 0
  1/cl;
  ods output Estimates=est;
run;

/* step 5: Combine estimates for inference */

proc mianalyze data=est;
  modeleffects estimate;
  stderr;
  ods output parameterestimates=miparm;
run;

data miparm;
  set miparm;
  shift= -&sj;
run;

/*Output multiple imputation results*/

data &outparms;
  set &outparms miparm;
run;

%end;
%mend miparms;

/*Assume that the tipping point for the shift parameter that reverses the
study conclusion is between 0 and 4. The following statement performs
multiple imputation analysis for each of the shift parameters 0,-0.5, -1,  -
1.5,…,-4*/

ods listing close;
%miparms(data=pr_trans, smin=0, smax=4, sinc=0.5, outparms=parms1);
```

14.5. Analysis Under Each Analysis Set

Analysis Set	Baseline and Demography	All Interim Effiacy	Safety Analyses	PK Concentration	PK Parameters	PD
Efficacy	X	X				
Per-protocol		X*				
Safety			X			
PK				X		
PD						X
PK/PD Sub-study					X	X

*Sensitivity analysis only

Signature Page

CSL300_3001 - Statistical Analysis Plan - Statistical Analysis Plan for Interim Analysis

Signed By	Date (GMT)
PPD	16-Aug-2023 18:16:03
Approved-PPD Approval	
PPD	17-Aug-2023 10:44:59
Approved-PPD Approval	

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