TITLE PAGE

STATISTICAL ANALYSIS PLAN

Version Number: 2.0

Protocol Title: ARTEMIS: R**A**vulizumab to P**R**otect Pa**T**ients with Chronic Kidney Dis**E**ase (CKD) fro**M** Cardiac Surgery Associated Acute Kidney **I**njury (CSA-AKI) and **S**ubsequent Major Adverse Kidney Events (MAKE): A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study

Alexion Protocol Number: ALXN1210-CSA-AKI-318 Protocol Amendment 3

AstraZeneca D Code: D928DC00001

Compound: Ravulizumab (Sponsor code ALXN1210)

Brief Title: ARTEMIS: A Phase 3 Study of Ravulizumab to Protect Patients with CKD from CSA-AKI and MAKE

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address: 121 Seaport Boulevard, Boston, MA 02210

Regulatory Agency Identifier Number(s):

Registry	Identification
IND	160527
EU CT	2022-501802-36-00

Author: PPD

Version Date: 22 May 2025

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VERSION HISTORY

This SAP for Study ALXN1210-CSA-AKI-318 is based on PA3, dated 02 Dec 2024.

SAP Version	Version Date	Change	Rationale
1.0	03 Apr 2025	Not applicable	First version
2.0	20 May 2025	Added exploratory win ratio analysis in Section 4.4.3. Added two subgroup factors based on urine Ba in Section 4.6.6. Added analysis window in Section 6.3.1.	To specify a win ratio analysis for an exploratory hierarchical composite endpoint. To specify two additional subgroup analyses based on urine Ba. Clearly define analysis window to be applied.

More details regarding version history are provided in Section 4.8.

APPROVAL SIGNATURES

This document has been e-signed in ARISE (Veeva RIM). Please refer to the last page for signature details.

[Biostatistician Name, Title]	Date dd Mmm yyyy
[Biostatistics Functional Manager Name, Title]	Date dd Mmm yyyy
[Medical Monitor Name, Title]	Date dd Mmm yyyy

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
BLQ	below the limit of quantification
C5	complement component 5
CFB	change from baseline
CHW	Cui, Hung, and Wang
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CPB	cardiopulmonary bypass
CRF	case report form
CSA-AKI	cardiac surgery-associated acute kidney injury
CSR	clinical study report
cTTO	composite time trade-off
CV(%)	coefficient of variation (percentage)
DMC	Data Monitoring Committee
DPS	Data Point Set
eGFR	estimated glomerular filtration rate
eGFRcr	estimated glomerular filtration rate from serum creatinine
eGFRcr-cys	estimated glomerular filtration rate from serum creatinine and serum cystatin C
eGFRcys	estimated glomerular filtration rate from serum cystatin C
EQ-5D-5L	European Quality of Life Group's 5-dimension 5-level
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue (questionnaire)
IA1	Interim Analysis 1
IA2	Interim Analysis 2
IAS	Immunogenicity Analysis Set
ICU	intensive care unit
IE	intercurrent event
IQR	interquartile range
ITT	Intent-to-Treat

Abbreviation or Specialist Term	Definition
IV	intravenous
KDIGO	Kidney Disease - Improving Global Outcomes (nonprofit foundation)
KDQOL-36™	Kidney Disease Quality of Life instrument – 36 items (questionnaire)
KRT	kidney replacement therapy
LLoQ	lower limit of quantification
MAKE	major adverse kidney event
MAKE90	major adverse kidney event at Day 90 post cardiopulmonary bypass
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NAb	neutralizing antibody
NGAL	neutrophil gelatinase-associated lipocalin
NS	no sample
mITT	modified Intent-to-Treat
PA3	Protocol Amendment 3
PD	pharmacodynamic(s)
PDAS	Pharmacodynamic Analysis Set
PK	pharmacokinetic(s)
PKAS	Pharmacokinetic Analysis Set
PMDA	Pharmaceuticals and Medical Devices Agency
POS	Post-operative Set
PPS	Per Protocol Set
pRBC	packed red blood cell
PT	Preferred Term
Q1	first quartile
Q2	second quartile (i.e. median)
Q3	third quartile
QoL	quality of life
RIFLE	risk, injury, failure, loss of kidney function, and end-stage kidney disease
SAP	statistical analysis plan
SAE	serious adverse event
sCr	serum creatinine
sCysC	serum cystatin C
SF-12v2	Short Form 12-item Health Survey Version 2

Abbreviation or Specialist Term	Definition
SOC	System Organ Class
STS	Society of Thoracic Surgeons
SS	Safety Set
SSRE	sample size re-estimation
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TM	thrombomodulin
VAS	visual analog scale
WHO-Drug	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods for analyzing data for Study ALXN1210-CSA-AKI-318 Protocol Amendment 3 (dated 02 Dec 2024), a Phase 3 study of ravulizumab in adult participants with chronic kidney disease (CKD) and stable cardiac disease undergoing non-emergent cardiac surgery requiring cardiopulmonary bypass (CPB) to reduce the risk of post-operative kidney events and subsequent major adverse kidney event at Day 90 post CPB (MAKE90). Standard data presentation instructions and table, figure, and listing specifications are contained in the data presentation plan in a separate document.

1.1. Objectives, Endpoints, and Estimands

1.1.1. Objectives and Endpoints

Objectives and endpoints are listed in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ravulizumab in reducing the risk of MAKE90 following CPB	MAKE90 is defined as meeting at least 1 of the following criteria: • Decrease from Baseline in eGFR (CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] formula using sCysC) of ≥ 25% at Day 90 post CPB • Initiation of kidney replacement therapy (KRT) through Day 90 post CPB • Death from any cause through Day 90 post CPB
Key secondary efficacy	
To assess the efficacy of ravulizumab in reducing the risk of AKI (based on sCr) following CPB	(1) Occurrence of CSA-AKI without recovery at Day 90 post CPB
	(2) Occurrence of severe CSA-AKI (KDIGO Stage 2 or 3) from randomization to Day 7 post CPB
	(3) Occurrence of severe AKI (KDIGO Stage 2 or 3) from randomization to Day 30 post CPB
	(4) Occurrence of KRT or death from randomization to Day 90 post CPB
	(5) All-cause mortality from randomization to Day 90 post CPB
	(6) Length of post-operative intensive care unit (ICU) stay
Other secondary efficacy	
To assess the efficacy of ravulizumab in reducing the risk of MAKE (based on sCysC), MAKE	MAKE and its components at Days 30, 60, and 90 post CPB (excluding MAKE90 based on sCysC)
	Occurrence of KRT or death by Days 30 and 60 post CPB

Table 1: Objectives and Endpoints

Objectives	Endpoints
(based on sCr), AKI (based on sCr), and related outcomes following CPB	Occurrence of post-operative renal failure (STS metric based on RIFLE Failure creatinine criteria)
	Highest CSA-AKI stage within 3 and 7 days post CPB
	Occurrence of CSA-AKI without recovery at Days 15, 30, and 60 post CPB
	Occurrence of AKI at Days 3, 7, 15, 30, 60, and 90 post CPB
	AKI Progression on Days 15, 30, 60, and 90 post CPB for those experiencing CSA-AKI within 7 days post CPB: • Complete recovery • Partial recovery • Improvement • Stable • Worsening
Healthcare resource utilization	
To assess the effect of ravulizumab on health resource utilization in participants with CKD undergoing non-emergent CPB	Length of post-operative hospital stay
	Number of days on ventilator through Days 30 and 90 post CPB
	Hospital readmission rate (all cause or AKI related) through Days 30 and 90 post CPB
	Days on KRT through Days 30 and 90 post CPB
Health-related QoL	
To assess the effect of ravulizumab on the quality of life (QoL) in participants with CKD undergoing non-emergent CPB	Change from Baseline in KDQOL-36™ at Days 30, 60, and 90 post CPB
	Change from Baseline in EQ-5D-5L at Days 30, 60, and 90 post CPB
	Change from Baseline in FACIT-Fatigue at Days 30, 60, and 90 post CPB
PK and PD	
To evaluate the PK and PD of ravulizumab in participants with CKD undergoing non-emergent CPB	Serum concentrations of ravulizumab
	Absolute values, change from Baseline, and percent change from Baseline in serum-free C5 concentrations
Safety	
To evaluate the safety of ravulizumab IV in participants with CKD undergoing non-emergent CPB	TEAEs and TESAEs
	Change from Baseline in laboratory parameters at scheduled visits
Immunogenicity	

Table 1: Objectives and Endpoints

Objectives	Endpoints
To evaluate the immunogenicity of ravulizumab IV in participants with CKD undergoing non-emergent CPB	ADA (antidrug antibody) incidence, ADA response categories, and titer at Day 90 post CPB
Exploratory	
To assess biomarkers at baseline and change in response to treatment	Biomarker assessments may include, but are not limited to, complement pathway activation (eg, plasma and urine soluble C5b-9), renal injury (eg, urine NGAL), and endothelial damage (eg, plasma TM)
To assess the efficacy of ravulizumab in reducing the risk of CSA-AKI based on sCysC	AKI within 7 days post CPB based on sCysC: • Highest AKI stage by KDIGO criteria • Occurrence of severe AKI (KDIGO Stage 2 or 3)

1.1.2. Primary Estimand

The primary estimand of this study will use the treatment policy strategy based on the Intent-to-Treat (ITT) Analysis Set to estimate the treatment effect of ravulizumab regardless of any intercurrent events (IEs). The estimand is intended to provide a population-level estimate of the treatment effect of ravulizumab on the primary binary endpoint MAKE90 among CKD participants who meet study eligibility criteria and are randomized into the study. The primary estimand includes the following 5 attributes:

- Treatment: Ravulizumab or placebo.
- Population: Adult participants with CKD as defined by the inclusion and exclusion criteria.
- Variable: MAKE90, defined as meeting at least 1 of the following criteria:
  - Decrease from Baseline in estimated glomerular filtration rate (eGFR) (CKD-EPI formula using serum cystatin [sCysC]) of ≥ 25% at Day 90 post CPB
  - Initiation of KRT through Day 90 post CPB
  - Death from any cause through Day 90 post CPB
- IEs:
  - IE1: Iodinated contrast dye exposure after treatment is administered through Day 90 post CPB.
  - IE2: Surgery was performed without CPB or surgery with CPB was not performed within 15 days after treatment administration.
  - IE3: Use of confounding interventions prior to surgery (Protocol Section 6.5.3) or use of disallowed interventions after treatment is administered through Day 90 post CPB (Protocol Section 6.5.2).

Treatment policy strategy: The collected endpoint will be analyzed irrespective of IEs.

- Summary Measure: Difference between treatment groups in the proportion of participants experiencing MAKE90 regardless of any IEs.

1.1.3. Key Secondary Estimands

The key secondary estimands are intended to provide a population-level estimate of the treatment effect of ravulizumab on 6 key secondary endpoints regardless of any IEs. The estimand for each key secondary includes the following 5 attributes:

- Treatment: Ravulizumab or placebo.
- Population: Adult participants with CKD as defined by the inclusion and exclusion criteria.
- Variables:
  - Occurrence of CSA-AKI without recovery at Day 90 post CPB.
  - Occurrence of severe CSA-AKI (KDIGO Stage 2 or 3) from randomization to Day 7 post CPB.
  - Occurrence of severe AKI (KDIGO Stage 2 or 3) from randomization to Day 30 post CPB.
  - Occurrence of KRT or death from randomization to Day 90 post CPB.
  - All-cause mortality from randomization to Day 90 post CPB.
  - Length of post-operative ICU stay.
- IEs:
  - IE1: Iodinated contrast dye exposure after treatment is administered through Day 90 post CPB.
  - IE2: Surgery was performed without CPB or surgery with CPB was not performed within 15 days after treatment administration.
  - IE3: Use of confounding interventions prior to surgery (Protocol Section 6.5.3) or use of disallowed interventions after treatment is administered through Day 90 post CPB (Protocol Section 6.5.2).

  Treatment policy strategy: The collected endpoint will be analyzed irrespective of IEs.
- Summary measures: Difference between treatment groups in the proportions (for binary key secondary endpoints) or the median (for the length of post-operative ICU stay endpoint) regardless of any IEs.

1.2. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of ravulizumab in adult participants with CKD and stable cardiac disease undergoing non-emergent cardiac surgery requiring CPB for coronary artery bypass graft, valve replacement or repair, or combined procedure to reduce the risk of post-operative kidney events and subsequent

MAKE90. Participants considered at risk for kidney events after CPB have eGFR ≥ 20 to < 60 mL/min/1.73 m^2 with predicted renal failure risk of ≥ 2.8% using the STS Adult Cardiac Surgery Risk Models (STS Calculator).

The study consists of a Screening Period of up to 28 days with randomization and dosing within 7 days prior to surgery with CPB, a 90-day Primary Evaluation Period post CPB, and a Survival Follow-up including assessment of KRT status at 365 days post CPB (Figure 1).

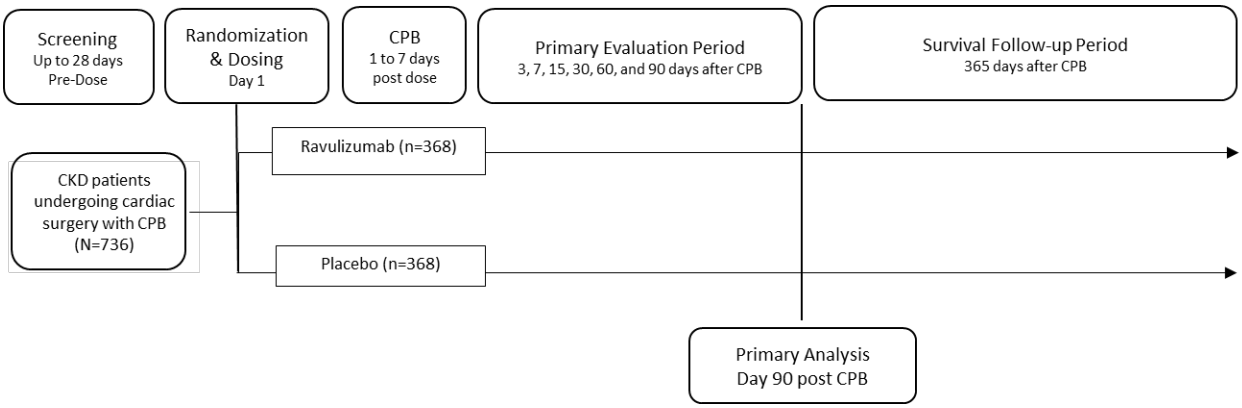
Approximately 736 participants will be randomized in a 1:1 ratio to treatment with either ravulizumab or placebo. Randomization will be stratified by baseline CKD stage (3A, 3B, and 4) and surgery type (mitral valve replacement or combined procedures versus other single procedure).

Eligible participants will be randomized and receive a single weight-based dose of ravulizumab or placebo. Randomization and dosing should occur on the same day except in cases when study intervention needs to be prepared the day before dosing. At the time of randomization, surgery must be scheduled to occur within 7 days. The infusion is required to be completed at least 1 hour prior to surgery start (ie, induction of anesthesia). The date of the dosing will be Day 1 for each participant. All treated participants will be followed for 90 days after CPB procedure during the Primary Evaluation Period, and a Survival Follow-up Visit will be completed on Day 365 post CPB.

Analysis of the Primary Evaluation Period will be conducted when all participants have completed this period. In addition, 2 interim analyses of this study will be conducted after approximately 30% and 50%, respectively, of the randomized participants have completed the Primary Evaluation Period, with the purpose of assessing early futility in Interim Analysis 1 (IA1), and assessing futility, early stop for efficacy, and sample size re-estimation (SSRE) in the Interim Analysis 2 (IA2).

An independent Data Monitoring Committee (DMC), comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion. The specific responsibilities of the DMC and a schedule of meetings will be described in the DMC Charter. Briefly, the DMC will be established for an independent review of safety and efficacy assessments throughout the duration of the study. In particular, the DMC will review unblinded study information provided by an independent Data Analysis Center during the conduct of the study for periodic safety review and 2 planned interim analyses. A DMC SAP will include details of the analysis plan for the periodic safety reviews. An interim statistical analysis plan will include technical and analysis details of the interim analyses. At each planned interim analysis, DMC will make formal recommendations based on the prespecified criterion (Section 4.7).

Figure 1: Study Design Schematic



Note: Screening and randomization or randomization and surgery can occur on the same calendar day. Screening, randomization, and surgery (ie, all 3 visits) may not occur on the same calendar day. Randomization and dosing should occur on the same day (Day 1) except in cases when study intervention needs to be prepared the day before dosing; CPB procedure should occur within 7 days after dosing. Infusion is required to be completed at least 1 hour prior to surgery start (ie, induction of anesthesia).

2. STATISTICAL HYPOTHESES

2.1. Primary Hypothesis

The primary hypothesis to be tested for this study is that ravulizumab will be superior to placebo in reducing the risk of MAKE90:

$$H_0\colon\ p_1 \geq p_0$$

$$H_1\colon\ p_1 < p_0$$

where p_1 and p_0 represent the probability of experiencing MAKE90 event in ravulizumab group and placebo group, respectively.

The treatment effect based on the MAKE90 endpoint will be estimated by the difference in the proportion of participants experiencing MAKE90 regardless of any IEs between the ravulizumab group and the placebo group. A negative difference will indicate a beneficial treatment effect for ravulizumab.

2.2. Key Secondary Hypotheses

The key secondary hypotheses will be tested sequentially in the following hierarchical order given the null hypothesis for the primary endpoint is rejected.

1. Ravulizumab is superior to placebo with a statistically significant lower proportion of participants who have CSA-AKI without recovery at Day 90 post CPB.
2. Ravulizumab is superior to placebo with a statistically significant lower proportion of participants who have severe CSA-AKI (KDIGO Stage 2 or 3) from randomization to Day 7 post CPB.
3. Ravulizumab is superior to placebo with a statistically significant lower proportion of participants who have severe AKI (KDIGO Stage 2 or 3) from randomization to Day 30 post CPB.
4. Ravulizumab is superior to placebo with a statistically significant lower proportion of participants who experience KRT or death from randomization to Day 90 post CPB.
5. Ravulizumab is superior to placebo with a statistically significant lower proportion of participants who died from any cause from randomization to Day 90 post CPB.
6. Ravulizumab is superior to placebo with a statistically significant shorter length of post-operative ICU stay.

2.3. Multiplicity Adjustment

A multiple testing procedure will include a test on the primary endpoint and then a prespecified hierarchical test on the key secondary endpoints. The primary endpoint MAKE90 will be tested following the group sequential theory as detailed in the Protocol Section 9.5. Specifically, if the 1-sided p-value for the primary endpoint analysis at the IA2 is < 0.0025, the early efficacy criterion is met. With the planned information fraction of 0.5 at the IA2, it follows from the group sequential theory (Jennison, 1999) that the 1-sided alpha spending will be 0.024 at the final analysis to control the overall 1-sided type I error rate at the level of 0.025 for the primary

endpoint. If the information fraction at the IA2 deviates from the planned 0.5, the alpha spending at the final analysis will be calibrated to control the overall 1-sided type I error rate at the level of 0.025 following the group sequential theory.

If the primary endpoint is statistically significant, the key secondary endpoints will be tested in the fixed sequence as specified in Section 2.2 following the same alpha-spending approach as that for the primary endpoint. The testing of key secondary endpoints will continue down the hierarchy, only if the test for the preceding endpoint is statistically significant.

If the study does not stop early for early futility or efficacy at the interim analyses, the CHW method (Cui, 1999) will be adopted in the final analysis of the primary and key secondary endpoints for the SSRE.

Under the above prespecified multiple testing procedure, the alpha-spending approach for the primary and the key secondary endpoints, and the CHW method for the final analysis, the overall type I error will be controlled at a 1-sided 0.025 level for multiplicity across the primary and key secondary endpoints.

The non-binding futility assessments at the 2 interim analyses have no risk of type I error inflation.

3. ANALYSIS SETS

The following participant analysis sets are defined as follows:

Participant Analysis Set	Description
Intent-to-Treat (ITT)	All participants randomized to study intervention. Participants will be analyzed as randomized.
modified Intent-to-Treat (mITT)	All randomized participants who receive their complete weight-based dose of study intervention and undergo CPB procedure within 15 days of dosing. Participants will be analyzed as randomized.
Per Protocol Set (PPS)	All participants in mITT and have no important protocol deviation. Participants will be analyzed as randomized.
Post-operative Set (POS)	All participants in mITT and who have stable preoperative kidney function (prior to CPB [Visit 3] sCr remains < 1.5× of Baseline, with no KRT). Participants will be analyzed as randomized.
Safety Set (SS)	All randomized participants who receive study intervention. Participants will be analyzed according to the study intervention they actually receive.
Pharmacokinetic Analysis Set (PKAS)	All ravulizumab-treated participants with at least 1 postbaseline PK concentration available.
Pharmacodynamic Analysis Set (PDAS)	All randomized participants who receive study intervention and at least 1 postdose PD measurement.
Immunogenicity Analysis Set (IAS)	All randomized participants who receive ravulizumab and have at least 1 reportable postdose ADA result. Participants will be analyzed according to the study intervention they actually receive.

The following data point sets are defined as follows:

Data Point Sets	Description
DPS1	All data points obtained at or after randomization until the Day 90 post CPB visit
DPS2	All data points obtained at or after randomization up to the first IE or the Day 90 post CPB visit, whichever comes earlier
DPS3	All observed data

The participant analysis sets and data point sets will be used as follows:

Objective	Endpoint/Estimand	Participant Analysis Set	Data Point Set
Primary	Primary endpoint/primary estimand (treatment policy)	ITT	DPS1
Primary	Primary endpoint/Supplementary Estimand 1 (hypothetical)	ITT	DPS2

Objective	Endpoint/Estimand	Participant Analysis Set	Data Point Set
Primary	Primary endpoint/Supplementary Estimand 2	mITT	DPS1
Primary	Primary endpoint/Supplementary Estimand 3	PPS	DPS1
Primary	Primary endpoint/Supplementary Estimand 4	POS	DPS1
Secondary	Key secondary endpoints/secondary estimands (treatment policy)	ITT	DPS1
Secondary	Key secondary endpoints/secondary supplementary estimands	mITT, PPS, and POS	DPS1
Safety	Safety endpoints	SS	DPS3

4. STATISTICAL ANALYSES

4.1. General Considerations

- Summary statistics will be computed and displayed by treatment group and overall (ie, combined treatment groups, where applicable). Graphical displays may be provided as appropriate.
- For continuous variables, descriptive statistics will include the number of participants and the number of participants with nonmissing values, minimum, maximum, mean, median, SD, first quartile (Q1), third quartile (Q3) and interquartile range (IQR). The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to 1 more decimal place than the raw data recorded in the database. The SD will be reported to 2 more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be 4 for any summary statistic.
- For categorical variables, the number of participants, frequencies, and percentages will be presented. Percentages will be presented in 1 decimal place. Percentages will be calculated using the number of participants with nonmissing values as the denominator.
- All statistical tests will be 2-sided and performed at the 5% significant level unless otherwise specified.
- PK, PD, and biomarker concentration data will be summarized using the following descriptive statistics: the number of participants in the analysis set (N), the number of participants with available data (n), n (below the limit of quantification [BLQ]) (ie, the number of participants with BLQ samples), arithmetic mean, SD, arithmetic CV%, median, minimum, and maximum. For PK analyses, geometric mean and geometric coefficient of variation (CV%) will also be presented.
- For PK analyses, BLQ concentrations will be treated as 0 for the calculation of descriptive statistics. Individual values that are BLQ will be presented as "BLQ" in the data listing.
- Baseline is defined as Day 1 randomization prior to administration of study intervention unless noted otherwise. A summary of change from Baseline (CFB) will be calculated as the visit value of interest minus the baseline value when both are not missing. If either value is missing, then CFB will not be calculated in the descriptive statistics summary.
- All confidence intervals (CIs) and statistical tests will be presented as 2 sided unless otherwise specified. p-Values that are ≥ 0.001 and ≤ 0.999 will be presented in 3 decimal places. All other p-values < 0.001 will be presented as "< 0.001," while p-values > 0.999 will be presented as "> 0.999." CIs will be presented in 1 more decimal place than the raw data.
- Except for the primary endpoint and binary key secondary endpoints, other binary secondary endpoints are planned to be analyzed using the Cochran-Mantel-Haenszel (CMH) method for risk difference to adjust for the 2 stratification variables. If certain strata are empty or extremely sparse, an exact CMH method will be applied to ensure

valid inference in such data conditions. In cases where the exact CMH method also fails or produces unstable estimates due to a large proportion of empty or near-empty strata, clinically justifiable collapsing of those strata will be considered. Any modifications, such as combining categories to achieve adequate counts, will be documented, and the final reported results will include the point estimate, corresponding CI, and p-value for each endpoint after the chosen approach.

- Summary statistics will be provided based on data from the scheduled visit. Participant-level listings will be provided based on available data from scheduled and unscheduled visits.
- SAS® statistical software Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina, USA) will be used for analyses.

4.2. Primary Endpoint(s) Analysis

4.2.1. Derivation of Endpoint(s)

MAKE90 is the primary endpoint that is defined as meeting at least 1 of the following criteria:

- Decrease from Baseline in eGFR (CKD-EPI formula using sCysC) of ≥ 25% at Day 90 post CPB
- Initiation of KRT through Day 90 post CPB
- Death from any cause through Day 90 post CPB

Baseline and postbaseline eGFRs will be calculated from sCysC using the CKD-EPI formula. Baseline eGFR will be the average of eGFR calculated from the last assessment during the Screening and Day 1 Visits prior to study intervention administration.

4.2.2. Main Analytical Approach

The main analysis will be based on the ITT Analysis Set. The primary estimand is the population-level treatment difference between ravulizumab and placebo in the proportion of participants experiencing MAKE90 based on a treatment policy strategy regardless of any IEs. The corresponding estimator is the weighted average of treatment difference in the MAKE90 rate using the Mantel-Haenszel weight for strata (Greenland, 1985) adjusting for the 2 stratification variables.

When the study does not stop early for futility or efficacy at the IA2, the CHW method (Cui, 1999) will be adopted for the testing of the primary endpoint at the final analysis if the study sample size increases after IA2 due to the SSRE. If there is no change in the study sample size after IA2, the conventional testing method will be applied for the testing of the primary endpoint at the final analysis. Regardless of the SSRE outcome at IA2, the primary estimator will be the unweighted treatment effect estimated based on all study data.

For the missing values of the MAKE90 endpoint due to partially or completely missing individual components, missing data for KRT initiation or death will be imputed as a non-event (ie, no KRT has been initiated, and death has not occurred), and missing eGFR values will be handled by multiple imputation (MI) in 2 steps assuming missing at random (MAR). The first step will impute data using Markov Chain Monte Carlo to create a monotonic missing data

pattern; the second step will use the regression method for monotone missing data to impute the remaining missing observations. The regression model for imputation will include treatment group, CKD stage, surgical type, and observed eGFR values. With a complete dataset, the eGFR component of the MAKE endpoint will be evaluated. In each imputed dataset, the CMH method adjusting for the stratification variables will be used to obtain the point estimate of the risk difference and the standard error. Rubin's rule will then be used to combine results from analyses of 100 imputed datasets. The p-value and 2-sided 95% CI of the treatment difference in MAKE90 will be reported.

4.2.3. Sensitivity Analyses

The following sensitivity analyses will be conducted based on the ITT Analysis Set to evaluate the robustness of results when the missing data assumption deviates from that in the primary analysis.

- The first sensitivity analysis for the primary endpoint will be conducted to assess the sensitivity of deviation from the non-event imputation of missing data for KRT initiation or death in the primary analysis. The missing MAKE90 endpoint data due to partially or completely missing data for individual components will be handled by MI based on a logistic regression model assuming MAR. The logistic regression model for imputation will include treatment group, CKD stage, and surgical type as covariates. The CMH method, along with Rubin's rule, will be applied in the same manner as the main analysis to yield the p-value and 95% CI.
- The second sensitivity analysis will be conducted using control-based pattern imputation (Ratitch, 2011). For participants from the ravulizumab group who withdraw early from the study, any missing MAKE90 values will be imputed under the assumption that their outcome would be similar to those in the placebo group with similar baseline characteristics using a logistic regression model. The imputation model will be constructed using the observed data from the placebo group, including CKD stage and surgery type as covariates. The model is then used to impute the missing MAKE90 data for participants in both treatment groups assuming MAR. This will be carried out 100 times and result in 100 complete datasets. The CMH method will be carried out in a similar manner to the main analysis for these 100 datasets. Rubin's rule will be applied to combine results from analyses of imputed datasets. The p-value and 2-sided 95% CI of the treatment difference in MAKE90 will be reported.
- Tipping point analyses will be conducted based on the delta adjustment method (O'Kelly, 2014) to assess the sensitivity of the primary analysis results when the missing data mechanism for eGFR has deviated from the MAR assumption. The approach assumes that participants from the ravulizumab group who discontinue at a given time point would have their unobserved eGFR worse by an amount (delta) compared to the observed eGFR from those participants who continue to the next time point. The missing data for KRT initiation or death will still be imputed as a non-event (ie, no KRT has been initiated, and death has not occurred). This methodology is expected to inform what it would take to overturn study conclusions based on varying assumptions about missing eGFR data (O'Kelly, 2014)

- If the study does not stop early for futility or efficacy at IA2 and the sample size increases after IA2, the fourth sensitivity analysis using the conventional unweighted test statistics will also be conducted for the testing of the primary endpoint at the final analysis, regardless of the SSRE outcome at IA2.

4.2.4. Supplementary Analyses

Supplementary Analysis 1

A supplementary analysis will be performed on the ITT Analysis Set based on the following hypothetical estimand framework:

- Treatment: Ravulizumab or placebo.
- Population: Adult participants with CKD as defined by the inclusion and exclusion criteria.
- Variable: MAKE90.
- IEs: The following IEs will be considered using a hypothetical strategy.
  - IE1: Iodinated contrast dye exposure after treatment is administered through Day 90 post CPB.
  - IE2: Surgery was performed without CPB or surgery with CPB was not performed within 15 days after treatment administration.
  - IE3: Use of confounding interventions prior to surgery (Protocol Section 6.5.3) or use of disallowed interventions after treatment is administered through Day 90 post CPB (Protocol Section 6.5.2).

  Hypothetical strategy: Data collected post-IE will be censored and marked as missing in the analysis.
- Summary Measure: Difference between treatment groups in the proportion of participants experiencing MAKE90 if the specified IE does not occur.

The hypothetical strategy will be applied to estimate the treatment effect in the hypothetical situation when no IE occurs. Data collected post-IE will be censored and marked as missing in the analysis. Missing data in the MAKE90 endpoint will be multiply imputed by the logistic regression model as described in the first sensitivity analysis (Section 4.2.3). The p-value from the stratified CMH method for risk difference and 2-sided 95% CI will be provided after combining results from analyses of imputed datasets using Rubin's rule.

Other Supplementary Analyses

The main analysis approach for the primary endpoint and its components will be performed in the same manner on the mITT Analysis Set, PPS, and POS. The treatment policy strategy will be applied in these supplementary analyses.

4.3. Secondary Endpoint(s) Analysis

Without further specification, the secondary analysis will be based on the ITT Analysis Set.

4.3.1. Key Secondary Endpoint(s)

The following 6 key secondary endpoints will be tested hierarchically if the null hypothesis for the primary endpoint is rejected.

1. Occurrence of CSA-AKI without recovery at Day 90 post CPB.
2. Occurrence of severe CSA-AKI (KDIGO Stage 2 or 3) from randomization to Day 7 post CPB
3. Occurrence of severe AKI (KDIGO Stage 2 or 3) from randomization to Day 30 post CPB
4. Occurrence of KRT or death from randomization to Day 90 post CPB.
5. All-cause mortality from randomization to Day 90 post CPB.
6. Length of post-operative ICU stay.

4.3.1.1. Derivation of Endpoint(s)

The baseline sCr will be the average of the central laboratory measurements of the last sCr collected during Screening and on Day 1 prior to study intervention administration. In case of central laboratory is missing for both Screening and Day 1, local laboratory sCr values will be used for the baseline. The highest observed sCr within 7 days post CPB will be determined based on both central and local laboratory measurements of the obtained sCr values. The highest observed sCr within 30 days post CPB will be determined based on all available sCr values reported from the local and central laboratories.

Derivations of the first 5 key secondary endpoints are defined below.

Key Secondary Endpoints	Definition
1. Occurrence of CSA-AKI without recovery at Day 90 post CPB	Meets both of the following criteria: • Experiencing CSA-AKI based on the highest observed sCr from randomization to Day 7 post CPB (occurrence of CSA-AKI) • Occurrence of non-recovered CSA-AKI at Day 90 post CPB
2. Occurrence of severe CSA-AKI (KDIGO Stage 2 or 3) from randomization to Day 7 post CPB	Meets modified KDIGO criteria for Stage 2 or 3 CSA-AKI (Table 2) based on the highest observed sCr from randomization to Day 7 post CPB
3. Occurrence of severe AKI (KDIGO Stage 2 or 3) from randomization to Day 30 post CPB	Meets modified KDIGO criteria for Stage 2 or 3 AKI, as outlined in Table 2, based on the highest observed sCr (confirmed by at least 1 additional measurement) from randomization to Day 30 post CPB

Key Secondary Endpoints	Definition
4. Occurrence of KRT or death from randomization to Day 90 post CPB	Meets any of the following criteria from randomization to Day 90 post CPB: • Initiation of KRT • Death
5. All-cause mortality from randomization to Day 90 post CPB	Meets the following criteria from randomization to Day 90 post CPB: • Death

Table 2: AKI Staging by Modified KDIGO Criteria

AKI Stage	Definition
1	An increase in sCr by ≥ 0.3 mg/dL in a 48-hour period, or An increase in sCr to ≥ 1.5 to < 2.0× Baseline
2	An increase in sCr to ≥ 2.0 to < 3.0× Baseline
3	An increase in sCr to ≥ 3.0× Baseline, or An increase in sCr to ≥ 4.0 mg/dL in participants meeting AKI criteria, or Initiation of KRT[a]

[a] The use of operative ultrafiltration as a standard-of-care procedure to routinely manage fluid balance during cardiac surgery is not considered as initiation of KRT.
Source: Adapted from Khwaja (Khwaja, 2012)

The length (hours) of post-operative ICU stay will be calculated based on the date/time of post-operative ICU discharge minus the date/time of post-operative ICU admission for a participant who is admitted to ICU postsurgery and is alive at ICU discharge, where the post-operative ICU stay refers to the ICU admission transferred from initial hospitalization admission for surgery. For participants who die at the surgery or during the post-operative ICU stay, the length of the post-operative ICU stay will be imputed using the worst observed values.

4.3.1.2. Main Analytical Approach

Each key secondary endpoint will be summarized and analyzed in the same manner as the main analysis for the primary endpoint. Specifically, these endpoints will be analyzed under the treatment policy estimand where observed data will be analyzed regardless of any IEs.

Similar to the primary endpoint, if the study does not stop early for futility or efficacy at IA2 and the sample size increases after IA2 due to the SSRE, the CHW method (Cui, 1999) will be adopted at the final analysis for testing each of the key secondary endpoints sequentially conditional on the significance of the primary endpoint. If there is no change in the study sample size after IA2, the conventional testing method will be applied for the hypothesis testing. Regardless of the SSRE outcome at IA2, the treatment effect estimators for each of the key secondary endpoints will be the unweighted treatment effects estimated based on all study data.

In the main analytic approach, missing data for the all-cause mortality endpoint or the death component of the composite endpoint of "KRT or death through Day 90 post CPB" will be

handled by the MI method under the MAR assumption; missing data for all other key endpoints or the KRT component of the composite endpoint of "KRT or death through Day 90 post CPB" will be imputed as not experiencing the endpoint event.

The proportion of participants meeting each of the binary key secondary endpoints will be summarized by treatment group. The point estimates and associated 2-sided 95% CIs of the treatment difference in proportions will be estimated using the CMH method adjusting for stratification factors. When MI is used to handle missing data, such as all-cause mortality endpoint or the composite endpoint of "KRT or death through Day 90 post CPB," Rubin's rule will be used for combining results from analyses of 100 imputed datasets to yield MI point estimate, standard error, and 2-sided 95% CI. The p-value of testing no difference between the 2 rates will be reported.

For ICU stay, nonparametric analysis using stratified Wilcoxon method will be used for treatment comparison. The stratified Wilcoxon test will include 2 stratification variables in the randomization. The median, IQR, minimum and maximum values of the length of post-operative ICU stay will be presented by treatment group. The median difference between treatment groups and 95% CI will be estimated using the Hodges-Lehmann method and the p-value will be calculated using the stratified Wilcoxon method adjusting for 2 stratification variables.

4.3.1.3. Sensitivity Analyses

Similar to the fourth sensitivity analysis for the primary endpoint, if the study does not stop early for futility or efficacy at IA2 and the sample size increases after IA2, a sensitivity analysis using the conventional unweighted test statistics will be conducted for the testing of key secondary endpoints.

In addition, tipping point analyses will be conducted for all key secondary binary endpoints (excluding the length of post-operative ICU stay). Use the endpoint of "occurrence of CSA-AKI without recovery at Day 90 post CPB" as an example. The imputation model will be constructed using the observed data by fitting a logistic regression model including treatment group, CKD stage, and surgery type as covariates. For participants in the ravulizumab group with missing endpoint data, a shift is applied to the estimated logits from the imputation model (ie, missing not at random imputation); for participants in the placebo group with missing endpoint data, no adjustment is made to the estimated logits from the imputation model (ie, MAR imputation). As a result, the logits are obtained for missing values in both the ravulizumab and placebo groups. For all missing endpoint values, imputed responses (event or non-event) are created using direct Bernoulli sampling based on the imputed logits of the binary endpoints. This will be carried out 100 times to result in 100 complete datasets. The CMH method will be carried out in a similar manner to the main analysis for these 100 datasets. Rubin's rule will be applied to combine results from analyses of imputed datasets. The p-value and 2-sided 95% CI of the treatment difference in "occurrence of CSA-AKI without recovery at Day 90 post CPB" will be reported. The tipping point analysis for other key secondary binary endpoints will be conducted in a similar manner.

The actual selected scenarios in the tipping point analyses for each key secondary endpoint will depend on the observed rates and the number of participants with missing endpoint values.

4.3.1.4. Supplementary Analyses

The main analysis approach for key secondary endpoints will be performed in the same manner on the mITT Analysis Set, PPS, and POS.

4.3.2. Other Secondary Endpoint(s)

For the following binary endpoints in other secondary efficacy endpoints, the proportion of participants experiencing the event will be summarized by treatment group. The treatment effect of these endpoints will be estimated as the weighted average of treatment difference using the Mantel-Haenszel weight for strata (Greenland, 1985) and the 2-sided 95% CI will be presented for each assessment visit.

- MAKE and its components at Days 30, 60, and 90 post CPB (excluding MAKE90 based on sCysC)
- Occurrence of KRT or death by Days 30 and 60 post CPB
- Occurrence of post-operative renal failure (STS metric based on RIFLE Failure creatinine criteria, Table 3)
- Highest CSA-AKI stage within 3 and 7 days post CPB
- Occurrence of CSA-AKI without recovery at Days 15, 30, and 60 post CPB
- Occurrence of AKI at Days 3, 7, 15, 30, 60, and 90 post CPB
- AKI Progression (Table 5) on Days 15, 30, 60, and 90 post CPB for those experiencing CSA-AKI within 7 days post CPB:
  - Complete recovery
  - Partial recovery
  - Improvement
  - Stable
  - Worsening

For the endpoints of MAKE and its components at Days 30, 60, and 90 post CPB (excluding MAKE90 based on sCysC), missing data handling and analytical method will be the same as MAKE90 based on sCysC, as specified in Section 4.2.2.

MAKE event based on the combined CKD-EPI equation for estimating eGFR using both sCr and sCysC will be derived and summarized at Days 30, 60, and 90 post CPB by treatment groups. If an adequate number of study participants have both sCr and sCysC values at relevant visits (including baseline), the same missing data handling and analytical method will also be applied as specified in Section 4.2.2 to compare the treatment groups.

For the following binary endpoints:

- Occurrence of KRT or death by Days 30 and 60 post CPB
- Occurrence of CSA-AKI without recovery at Days 15, 30, and 60 post CPB
- Occurrence of AKI at Days 3, 7, 15, 30, 60, and 90 post CPB

Non-event imputation will be used for participants with missing data, that is, missing data for those binary endpoints will be imputed as not experiencing the endpoint event.

The highest CSA-AKI stage (Table 2) within 3 and 7 days post CPB for each participant will be calculated, respectively. The corresponding number and proportion of participants in each CSA-AKI stage will be summarized by treatment group. The AKI progression (based on sCr or need for KRT) relative to the highest CSA-AKI within 7 days post CPB will be derived for each participant (Table 5) at specified time points. The number and proportion of participants in each AKI progression category will be summarized by treatment group and visit.

Table 3: AKI Staging by Modified RIFLE Criteria

AKI Stage	Definition
Risk	An increase in sCr to ≥ 1.5 to < 2.0× Baseline
Injury	An increase in sCr to ≥ 2.0 to < 3.0× Baseline
Failure	An increase in sCr to ≥ 3.0× Baseline, or An increase in sCr to ≥ 4.0 mg/dL with an increase of ≥ 0.5 mg/dL from Baseline, or Initiation of KRT[a]

[a] Use of operative ultrafiltration as a standard-of-care procedure to routinely manage fluid balance during cardiac surgery is not considered as initiation of KRT.
Source: Adapted from Bellomo et al (Bellomo, 2004)

Table 4: Stages of Post-CSA-AKI Kidney Function to Determine AKI Progression on Days 15 through 90 after Surgery

Post-AKI Stage	Definition
0	Complete recovery: sCr < 1.1× Baseline Partial recovery: sCr ≥ 1.1 to < 1.5× Baseline
1	sCr ≥ 1.5 to < 2.0× Baseline
2	sCr ≥ 2.0 to < 3.0× Baseline
3	sCr ≥ 3.0× Baseline, or sCr ≥ 4.0 mg/dL in participants meeting CSA-AKI criteria or KRT

Table 5: AKI Progression on Days 15 through 90 after Surgery

AKI Progression	Definition
AKI recovery (sCr based)	Complete: • sCr < 1.1× Baseline Partial: • sCr ≥ 1.1 to < 1.5× Baseline

Table 5: AKI Progression on Days 15 through 90 after Surgery

AKI Progression	Definition
AKI improvement (sCr based)	• Move down 1 or more stages from the highest CSA-AKI stage, as outlined in Table 4, or • Remain in Stage 3 but discontinue KRT
Stable AKI (sCr based)	• Unchanged AKI or KRT status
Worsening AKI (sCr based)	• Move up 1 or more stages from the highest CSA-AKI stage, or • Remain in Stage 3 but initiate KRT

4.3.3. Healthcare Resource Utilization Endpoints

The healthcare resource utilization endpoints, including the length (days) of post-operative hospital stay, the number of days on ventilator through Days 30 and 90 post CPB, the hospital readmission rate (all cause or AKI related) through Days 30 and 90 post CPB, and days on KRT through Days 30 and 90 post CPB, will be summarized by treatment group.

The length (days) of post-operative hospital stay will be calculated based on the date of discharge or the date of post-operative death (whichever is earlier) minus the completion date of the surgery with CPB plus 1, where the hospital stay refers to the hospital admission due to CPB operation. The cumulative days on KRT will be calculated based on KRT end date minus KRT start date + 1 for each occurrence of KRT. The days on ventilator will be derived by computing the difference between mechanical ventilation stop and start date/time for each initiation of ventilation, subsequently taking a sum, which is then converted into days via division by 24. The days on ventilator through Days 30 and 90 post CPB will be the cumulative days of ventilation during those periods, respectively. For the above 2 endpoints, length of post-operative hospital stay and number of days on ventilator through Days 30 and 90 post CPB, they will be summarized for each treatment group using descriptive statistics, which include the number of observations, mean, SD, median, minimum, maximum, Q1, Q3, and IQR values in each treatment group. The median difference between treatment groups and 95% CI will be estimated using the Hodges-Lehmann method.

Hospital readmission rate (analyzed by all causes and by each category as outlined in Protocol Section 8.10 and listed below) through Days 30 and 90 post CPB will be presented by treatment group and visit. The point estimates of treatment differences and associated 2-sided 95% CIs will be estimated, using the CMH method adjusting for stratification factors, if appropriate.

- Primary reason will be assessed as either
  - Re-operation, which will always be the primary reason, if present
    - Re-operation includes revision or repair of index cardiac surgeries or additional, auxiliary, or supplemental cardiac surgical procedures
  - Cardiovascular event not requiring re-operation (eg, myocardial infarction, stroke, heart failure, and arrhythmia)

- AKI
- Other reason

4.3.4. Health-Related QoL Endpoints

The summary scores or subscale scores calculated from each questionnaire will be used to measure health-related QoL. The derivation of scores within each questionnaire is discussed in the following subsections.

For each summary score, the summary statistics will be presented for observed data and CFB at specified visits by treatment group. The CFB data will be analyzed using an MMRM assuming MAR by including Baseline, CKD stage, surgery type, STS renal failure score at Screening, visit (categorical), treatment group, and treatment group by visit interaction as fixed effects based on all available data. An unstructured covariance matrix will be used. In the case that the model with an unstructured covariance matrix fails to converge, Toeplitz, heterogeneous compound symmetry, and a compound symmetry covariance structure will be applied in the order listed until the model converges. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The point estimate and two-sided 95% CI for the mean difference in these measurement scores will be presented.

4.3.4.1. Kidney Disease Quality of Life instrument – 36 Items (questionnaire)

The Kidney Disease Quality of Life instrument – 36 Items (KDQOL-36™) questionnaire given in Protocol Section 10.7 is a short form that includes 36 items: the Short-Form-12-Item Health Status Survey-Version 2 (SF-12v2) and another 24 kidney targeted items. The SF-12v2 (Items 1 through 12) yields the Physical Component Summary and Mental Component Summary. The 3 kidney targeted scales assess Burden of Kidney Disease (Items 13 through 16), Symptoms and Problems of Kidney Disease (Items 17 through 28), and Effects of Kidney Disease (Items 29 through 36).

The scores from the 5 components in KDQOL-36™ will be analyzed separately.

The 2 component scores of SF-12v2 (ie, Mental Component Summary and Physical Component Summary) will be derived with derivation rules as applicable in QualityMetric PRO CoRE Software.

The scoring for KDQOL-36™ for 3 kidney specific components, including Burden of Kidney Disease, Symptoms and Problems of Kidney Disease, and Effects of Kidney Disease, can be found at https://www.rand.org/health-care/surveys_tools/kdqol.html by RAND Health Care. The SAS code to score the 3 components (ie, Items 13 through 36) is available from the website https://www.rand.org/content/dam/rand/www/external/health/surveys_tools/kdqol/kdqol36.sas.

4.3.4.2. European Quality of Life Group's 5-Dimension 5-Level

The number and percentage of participants rating their scale for the 5 domains of the European Quality of Life Group's 5 dimension 5-level questionnaire (EQ-5D-5L) will be presented by visits. The health score and its CFB will be summarized by visits at Days 30, 60, and 90 post CPB.

EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (ie, State 11111). The collection of index values (weights) for all possible EQ-5D health states is called a value set. EQ-5D-5L index scores for this study will be obtained using the composite time trade-off (cTTO) method based on the Tobit model (Pickard, 2019). The calculation is illustrated in Table 6.

If data for some but not all dimensions are missing at a specific time point, the data for the missing dimension(s) from the last available assessment prior to the time point with missing data will be used in the US cTTO calculation. If all dimensions are missing, the last available US cTTO score prior to the time point with missing data will be used.

The visual analog scale (VAS) records the respondent's self-rated health on a vertical VAS where the endpoints are labeled "The best health you can imagine" for 100 and "The worst health you can imagine" for 0. Missing values will be coded as "999" and will be treated as missing in the analysis. The obtained VAS score and Health State Index Score will be analyzed.

Table 6: EQ-5D-5L cTTO Calculation with Example

US cTTO	Coefficient	Value for Health State 21354
Full health (11111)		Full health = 1
Mobility Level 2	-0.096	-0.096
Mobility Level 3	-0.122	
Mobility Level 4	-0.237	
Mobility Level 5	-0.322	
Self-Care Level 2	-0.089	
Self-Care Level 3	-0.107	
Self-Care Level 4	-0.220	
Self-Care Level 5	-0.261	
Usual Activity Level 2	-0.068	
Usual Activity Level 3	-0.101	-0.101
Usual Activity Level 4	-0.255	
Usual Activity Level 5	-0.255	
Pain/Discomfort Level 2	-0.060	
Pain/Discomfort Level 3	-0.098	
Pain/Discomfort Level 4	-0.318	

Table 6: EQ-5D-5L cTTO Calculation with Example

US cTTO	Coefficient	Value for Health State 21354
Pain/Discomfort Level 5	-0.414	-0.414
Anxiety/Depression Level 2	-0.057	
Anxiety/Depression Level 3	-0.123	
Anxiety/Depression Level 4	-0.299	-0.299
Anxiety/Depression Level 5	-0.321	
Health State Index Score		= 1-0.096-0.101-0.414-0.299 = 0.090

4.3.4.3. FACIT-Fatigue Scale

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire consists of 13 items scored on a 5-point Likert scale (0 = not at all, 4 = very much). The FACIT-Fatigue subscale scoring guideline (Version 4) will be used as follows (https://www.facit.org/measures/FACIT-Fatigue)

- The Likert scales for all negatively stated items (ie, all items except An5 and An7 from the electronic case report form [CRF]) are to be reversed in the direction such that a higher number reflects a more favorable health state.
- After reversing the proper items, all items are summed to obtain a score.
- The fatigue subscale score is then calculated by multiplying the sum of the item scores by 13, then dividing by the number of items answered.
- The fatigue subscale score will be summarized by treatment group and visit.

4.4. Exploratory Endpoints Analysis

4.4.1. Biomarker Assessments

Biomarkers to be measured may include, but are not limited to, assessments of complement pathway activation (eg, plasma and urine soluble C5b-9), endothelial damage and/or activation (eg, plasma thrombomodulin [TM]), vascular inflammation (eg, shed tumor necrosis factor receptor I [TNF-RI]), inducers of cell-cycle arrest (eg, tissue inhibitor of metalloproteinase-2 [TIMP-2]), and renal injury (eg, urine neutrophil gelatinase-associated lipocalin [NGAL]). Analyses of exploratory biomarker data will be described in a separate analysis plan and may be summarized after study completion.

4.4.2. AKI Based on sCysC

The highest AKI stage within 7 days post CPB based on sCysC modified KDIGO criteria (Table 2) will be computed for each participant. The number and percentage of participants in each AKI stage will be summarized by treatment group.

The number and percentage of participants who have severe AKI (KDIGO Stage 2 or 3) within 7 days post CPB based on sCysC will be summarized by treatment group.

4.4.3. Stratified Win Ratio Analysis

An exploratory analysis of the composite outcome may be conducted using the stratified win ratio method of Finkelstein and Schoenfeld (Finkelstein, 1999). Patients in the treatment group will be compared to patients in the control group on a one-to-one basis across all possible pairs within each randomization stratum. Each pairwise comparison is evaluated sequentially for the four ranked endpoint components (in order of clinical priority: death from any cause through Day 90 post CPB, initiation of KRT through Day 90 post CPB, total ICU days through Day 90 post CPB, hospital readmission through Day 30 post CPB). For each pair, if one patient has a better outcome on the highest-priority event (e.g. experiences death later or not at all) than the other, the patient is the "winner" and comparison stops at that level. If they are tied on death, the next outcome KRT is considered, and so on, until the pair is classified as a win for treatment, a win for control, or a tie. The win ratio will be calculated as the total number of winning pairs in favor of the treatment divided by the total number in favor of control. A stratified Finkelstein-Schoenfeld (F-S) test will be used to account for the stratification, yielding an estimated win ratio with two-sided 95% confidence interval and p-value for the win ratio using the Finkelstein-Schoenfeld test statistic.

This exploratory win ratio analysis may be reported separately from the CSR.

4.5. Safety Analyses

The safety will be assessed based on AEs, clinical laboratory findings, and vital sign findings. All safety analyses will be performed on the SS.

4.5.1. Extent of Exposure

Duration of exposure to study intervention, the number of participants exposed, and treatment compliance will be summarized by treatment group and overall using descriptive statistics. Participant-level listings will also be provided.

All available dosing data will be presented in a listing, and dose interruptions/modifications and reasons for dose interruptions/modifications will also be presented, if available.

The treatment compliance is defined as follows:

> Compliance (%) = (total amount of study intervention administered/total amount of study intervention specified by the protocol) × 100

4.5.2. Adverse Events

The definition of adverse events (AEs) and serious adverse events (SAEs) can be found in Protocol Section 10.3. The verbatim terms, as reported in the CRFs by Investigators to identify AEs, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 24.1 or higher) and will be summarized by System Organ Class (SOC) and Preferred Term (PT). AE intensity is determined by the Investigator using the following assessment categories: mild, moderate, and severe. The causality assessment is categorized as not related or related.

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset or existing events that worsen in severity from the initiation of dosing of study intervention through 90 days after the dose of study intervention. Technical specifications and derivations for TEAE for the missing date can be found in Section 6.1.

The endpoints to support the objective of the safety analysis include incidence of TEAEs and treatment-emergent serious adverse events (TESAEs). Participants having multiple AEs within a category (eg, overall, SOC, and PT) will be counted once in that category. For intensity tables, a participant's highest intensity within a category will be counted. Adverse events of special interest (AESIs) and infusion-related reactions will be summarized in a similar manner. For relationship tables, a participant's highest relationship to study intervention within a category will be counted.

4.5.2.1. Overall Summary of AEs

An overall summary of TEAEs will be presented by treatment group, including frequency of participants experiencing the event (n) and relative frequency (n/N × 100, where N is the number of participants in the SS). The summary will include categories indicating how many events are TEAEs and TESAEs. Within TEAEs, the following subcategories will also be summarized:

- Intensity of TEAEs (mild, moderate, or severe)
- Relationship to study intervention/ coronavirus disease 2019 (COVID-19)/CPB surgery/protocol-required vaccine/protocol-required antibiotics (not related and related)
- TEAEs leading to withdrawal from the study
- TEAEs leading to death
- AESI (Meningococcal Infections)
- Infusion-related reactions

Detailed by-participant listings of TEAEs, TESAEs, related TEAEs, and TEAEs leading to withdrawal from the study will be provided.

4.5.2.2. AEs and SAEs by SOC and PT

The number of TEAEs/TESAEs and the number and percentage of participants with events will be presented by SOC and PT sorted by descending frequency of SOC and then by descending frequency of PT within SOC based on the ALXN1210 group. Participants are counted once in each SOC and PT. Percentages will be based on the SS.

4.5.2.3. AEs by SOC

The number of TEAEs and the number and percentage of participants with events will be presented by SOC. Participants are counted once in each SOC. Percentages will be based on the SS.

4.5.2.4. AEs by PT

The number of TEAEs and the number and percentage of participants with events will be presented by PT. Participants are counted once in each PT. Percentages will be based on the SS.

4.5.2.5. AEs and SAEs by SOC, PT, and Relationship

The number of TEAEs and the number and percentage of participants with events will be presented by SOC and PT as described in Section 4.5.2.2 by relationship (related and not related). If a participant has > 1 occurrence of an AE, the highest relationship to study intervention will be used in the summary table. A similar analysis will be conducted for TESAEs.

4.5.2.6. AEs and SAEs by SOC, PT, and Intensity

The number of TEAEs/TESAEs and the number and percentage of participants with events will be presented by SOC, PTs, and intensity. If a participant has > 1 occurrence of an AE, the highest intensity reported will be used.

Additionally, a summary of related TEAEs/TESAEs by SOC, PT, and intensity using the highest intensity will be presented.

4.5.3. Physical Examination and Vital Signs

The abnormal physical examination findings will be classified as AEs and analyzed accordingly.

The actual values and CFBs in vital signs at each scheduled visit will be listed and summarized descriptively. The missing data will not be imputed, and only scheduled assessments will be summarized in tables. When multiple records exist for the same vital sign parameter within the same analysis visit, the record closest to the target date will be used in the summary. If there are multiple records with the same distance from the target date, the latest record will be used.

4.5.4. Clinical Laboratory Tests

Clinically significant changes from a participant's baseline value or previous values will be recorded as AEs and analyzed accordingly. The test results by the study central laboratory from scheduled visits will be summarized unless otherwise noted. The listings will include results from both scheduled and unscheduled visits and will be distinguished by the central or local laboratory. For the purposes of analyses, the laboratory results based on standardized units will be used.

Observed values and changes from Baseline in clinical chemistry, hematology, and urine chemistry will be listed and summarized descriptively by treatment group at Baseline and at each postbaseline time point. For laboratory results that can be classified as normal, low, or high based on normal range values, shift tables from Baseline to the final postbaseline value (eg, the last nonmissing value available) according to the reference ranges will be provided.

4.6. Other Analyses

4.6.1. Association between Key Secondary Endpoints and Clinical Outcomes

The association between the key secondary points of "occurrence of severe CSA-AKI from randomization to Day 7 post CPB" or "occurrence of severe AKI from randomization to Day 30 post CPB" and the following clinical outcomes will be examined.

- Death

- Initiation of KRT
- Readmission to hospital
- Duration (days) of KRT
- Duration (hours) of ventilation
- Duration (days) of hospitalization
- MAKE90

To assess the impact of each key secondary endpoint on the clinical outcomes, the following analyses will be conducted (Buyse, 2016).

- For each binary clinical outcome, including death, initiation of KRT, readmission to hospital, and MAKE90, a 2-by-2 contingency table of the clinical outcome and key secondary endpoint will be provided. The Chi-square test will be performed to assess the impact of the key secondary endpoint on the clinical outcome.
- For each continuous clinical outcome, including duration of KRT, ventilation, and hospitalization, the summary statistics will be provided by the key secondary endpoint category. A linear regression model will be fitted for the continuous clinical outcome with the key secondary endpoint as a covariate. As a sensitivity analysis, a rank-based regression model will also be employed for the continuous clinical outcome with the key secondary endpoint as a covariate. The test on the coefficient of the key secondary endpoint covariate will assess impact of the key secondary endpoint on the clinical outcome.

To assess the whether the relevant effects of the treatment on the clinical outcomes are captured by each key secondary endpoint, the following analyses will be performed (Buyse, 2016).

- For each binary clinical outcome, including death, initiation of KRT, readmission to hospital, and MAKE90, 2-by-2 contingency tables of clinical outcome and key secondary endpoint will be provided by treatment group. A logistic regression model will be fitted for the clinical outcome, with the key secondary endpoint and treatment group as covariates.
- For each continuous clinical outcome, including duration of KRT, ventilation, and hospitalization, the summary statistics will be provided by the key secondary endpoint category and treatment group. A linear regression model will be fitted for the continuous clinical outcome, with the key secondary endpoint and treatment group as covariates. As a sensitivity analysis, a rank-based regression model will also be employed for the continuous clinical outcome with the key secondary endpoint and treatment group as covariates.
- The test on the coefficient of the treatment group covariate will assess whether the treatment effect on the clinical outcome is captured by the key secondary endpoint.

4.6.2. PK and PD Analyses

The PK and PD analyses will include all data in the Pharmacokinetic Analysis Set (PKAS) and Pharmacodynamic Analysis Set (PDAS).

Blood samples for the measurement of serum ravulizumab concentrations and PD assessments (free complement component 5 [C5]) will be collected before and after administration of study intervention at the time points specified in the schedule of assessments. The baseline PK and PD blood samples will be collected predose on Day 1, within 120 minutes before administering study intervention. The PK/PD samples from scheduled visits and the central laboratory assessment will be summarized unless otherwise noted.

The following output will be generated from PK analyses:

- A summary table for serum ravulizumab concentrations by scheduled time point, which includes N, n (ie, number of participants with nonmissing values), n(BLQ) (ie, the number of participants with BLQ samples), arithmetic mean, SD, CV%, geometric mean, geometric CV% (calculated as gCV% = SQRT(e^{s^2}-1) × 100, where SQRT is the square root, e is Euler's number, s is the SD of the log transformed values), median, minimum, and maximum values will be presented. All BLQs will be considered 0 in the summary statistics.
- Plots for mean ± SD serum ravulizumab concentration versus time on both linear and semilogarithmic scales will be provided. The mean plot will use scheduled time; BLQ value will be set as missing.
- Data listing for individual serum ravulizumab concentrations by study day and time point and data from scheduled and unscheduled visits will be included. Serum concentrations below the LLoQ will be presented as BLQ in the listings, and the LLoQ value will be presented as a footnote. Missing PK samples will be reported as no sample (NS).

The following output will be generated for PD analyses:

- A summary table of absolute values, CFB, and percent CFB in serum-free C5 concentrations by treatment group and scheduled time point will be presented.
- Plots for mean ± SD plot in absolute values, CFB, and percent CFB versus time by treatment group will be provided. The mean plot will use scheduled time.
- Data listings for absolute values, CFB, and percent CFB in serum-free C5 concentrations by actual time will be included.

Other PK/PD analyses will be described in a separate PK/PD analysis plan.

4.6.3. Immunogenicity Analyses

All immunogenicity analyses will be performed on the Immunogenicity Analysis Set (IAS).

Baseline is defined as the last nonmissing ADA signal obtained on or before the first study intervention administration.

Immunogenicity variables, including ADA status, ADA response, ADA titer, and NAb status, will be summarized over the duration of the study.

The summaries of ADA incidence over the duration of the study will include the following response categories:

- **ADA negative:** An ADA-negative signal in the ADA assay at all time points collected for ADA analysis.
- **ADA positive:** An ADA-positive signal in the ADA assay at any time point collected for ADA analysis.

Participants who are ADA positive may be further categorized into ADA response categories as follows:

- **Pre-existing immunoreactivity:** An ADA-positive response with either of the following 2 conditions met:
  - ADA-positive response at Baseline with all post-first dose ADA results negative

    OR
  - ADA-positive response at Baseline with all post-first dose ADA responses < 4-fold over the baseline titer level
- **Treatment-emergent ADA responses:** An ADA-positive response post-first dose when baseline results are negative or missing.
- **Treatment-boosted ADA responses:** An ADA-positive response post-first dose that is ≥ 4-fold over the baseline titer level when the baseline result is positive.

The incidence of ADA status categories and ADA response categories will be summarized as absolute occurrence (n) and percentage (%) of all participants in IAS. Confirmed antibody positive samples will be further evaluated for antibody titer and the presence of NAbs. The NAb status categories are defined as follows:

- **NAb negative**: A negative signal in the NAb assay collected at all time point
- **NAb positive**: A positive signal in the NAb assay collected at any time points

Participant-level listing of ADA results, including ADA status category, ADA response category, ADA titer, and NAb status, will be provided and sorted by visit and sampling time.

In addition, the following exploratory analyses may be considered. The details of these exploratory analyses are out of the scope of SAP and will be documented in a standalone report (if applicable).

- Impact of immunogenicity on exposure. Associations between ADA/NAb status and systemic exposure to the ravulizumab may be explored to assess the potential impact of immunogenicity on drug concentration-time (PK) profiles.
- Impact of immunogenicity on safety. Associations between ADA/NAb status and serious and severe AEs, such as systemic hypersensitivity, anaphylaxis, injection/infusion site reactions lasting > 24 hours, and other immune-related SAEs, may be explored to assess the potential impact of immunogenicity on drug safety.
- Impact of immunogenicity on efficacy. Associations between ADA/Nab status and key efficacy endpoints or variables may be explored to assess the potential impact of immunogenicity on drug efficacy.

4.6.4. Study Specific Analyses

4.6.4.1. Surgical Information

The number of participants will be summarized by the type of surgery performed and treatment group.

The participant status at the time of surgery (elective, urgent, emergent, and salvage) and surgical parameters, including whether surgery was performed with CPB, whether deep hypothermic arrest was performed, lowest intraoperative hemoglobin, lowest intraoperative hematocrit, and highest intraoperative glucose, will be summarized by treatment group.

Other intraoperative procedures information, including whether an intraoperative intra-aortic balloon pump was used, whether intraoperative extracorporeal membrane oxygenation was performed, whether an intraoperative temporary assist device was used, whether any ultrafiltration was used during surgery, intraoperative fluid input/output total, and net intraoperative fluid balance, will be summarized by treatment group.

4.6.4.2. Kidney Replacement Therapy

The number and percentage of participants who receive KRT from randomization and prior to surgery, from randomization through 90 days CPB will be summarized by treatment group. The details of KRT, such as types used and reasons for starting and stopping, will also be summarized.

4.6.4.3. Packed Red Blood Cells and Whole Blood Transfusion

The number and percentage of participants receiving packed red blood cells (pRBC) or whole blood transfusion through 90 days post CPB will be summarized by treatment group and the blood product administered. The number of units for whole blood transfusions and worst hemoglobin level prior to transfusion (defined as the value numerically farthest outside of the normal range) for each participant will be identified and summarized by treatment groups. The participant-level listing will be provided.

4.6.5. All-Cause Mortality from Long-term Follow-up

The all-cause mortality rate at the end of the Long-term Follow-up Period will be summarized by treatment groups. The point estimate and 95% CI of the treatment difference will be presented. The number of missing values will be presented.

4.6.6. Subgroup Analyses

Subgroup analyses of the primary endpoint and key secondary endpoints will be performed for the following subset of participants:

- Race (White, Black or African American, American Indian or Alaska Native, Asian [including subcategories of Japanese and Chinese], Native Hawaiian or other Pacific Islander, and Other)
- Sex (male, female)
- Ethnicity (Hispanic or Latino and not Hispanic or Latino)

- CKD stage at Screening (3A, 3B, and 4)
- Surgery types
- CPB procedure time (≤ Q1, > Q1 to ≤ Q2, > Q2 to ≤ Q3, > Q3)
- Age groups (≥ 18 to ≤ 65 years, > 65 to ≤ 75 years, and > 75 years)
- Body weight groups at Baseline (≥ 30 to < 60 kg, ≥ 60 to < 100 kg, and ≥ 100 kg)
- Levels of albuminuria (measured as albumin to creatinine ratio) at baseline (KDIGO, 2012)
  - < 30 mg albumin/g creatinine
  - ≥ 30 to < 300 mg albumin/g creatinine
  - ≥ 300 mg albumin/g creatinine
- Participants with and without diabetes mellitus at Baseline
- STS predicted post-operative renal failure risk score at Screening (≤ Q1, > Q1 to ≤ Q2, > Q2 to ≤ Q3, > Q3)
- STS predicted mortality risk score at Screening (≤ Q1, > Q1 to ≤ Q2, > Q2 to ≤ Q3, > Q3)
- Participant status at the time of surgery (elective, urgent, emergent, and salvage)
- Geographic region (Europe, US, Japan, China, and the rest of the world)
- Duration from dosing through surgery (≥ 1 and ≤ 3 days, > 3 and ≤ 15 days, > 15 days)
- Urine Ba at Baseline (≤ median, > median)
- Urine Ba at Day 3 post CPB (≤ median, > median)

Missing data will be multiply imputed for eGFR, and non-event will be imputed for missing data in the KRT initiation or death. Subgroup analyses use the same multiply imputed datasets for analyses of primary and key secondary endpoints. The number of participants and frequencies for observed data will be presented for each subgroup. The point estimate and 95% CIs of the difference of proportions from the conventional Wald test on primary and key secondary endpoints will be provided in each subgroup and corresponding forest plots will be generated. If certain subgroup(s) are empty or extremely sparse, collapsing of those subgroups will be considered. Any modifications, such as combining subgroups to achieve adequate counts, will be documented.

The biomarker (urine Ba) data may not be available at the time of database lock. Under such circumstance, the subgroup analyses based on the urine Ba will be performed when the relevant data become available. Results of these analyses will be reported in either an addendum to the CSR or in a separate report.

4.7. Interim Analyses

Two interim analyses are planned after 30% (approximately 220 participants) and 50% (approximately 368 participants) of the randomized participants have completed the Primary Evaluation Period (ie, Day 90 Visit post CPB).

The purpose of IA1 is to assess early stopping for futility using the conditional power evaluated for the primary endpoint under the assumption of the observed effect size at the interim analysis. If the conditional power at IA1 is < 20%, the study will be considered for early stopping for futility. However, the futility criterion will be non-binding. In other words, if the primary endpoint meets the prespecified futility criterion at IA1, Alexion may continue the study without stopping the study for futility.

The IA2 includes futility, early stop for efficacy, and SSRE assessments. For the futility and SSRE assessments, the conditional power for the primary endpoint analysis will be evaluated under the assumption of the observed effect size at the IA2.

- If the conditional power at the IA2 is < 20%, the study will be considered for early futility stopping. Similar to the futility analysis at IA1, a DMC recommendation to stop, based on the IA2 results, will also be non-binding.
- If the conditional power at the IA2 falls in the promising zone (Mehta, 2011), defined by a conditional power in the range [0.4 – 0.9), the study sample size will be increased by 20%, that is, from approximately 736 to 884 participants.
- For the early efficacy assessment at the IA2, the 1-sided alpha spending is set at 0.0025. More precisely, if the p-value for the primary endpoint analysis at the IA2 is < 0.0025, the early efficacy criterion is met.

With the planned information fraction of 0.5 at the IA2, it follows from the group sequential theory (Jennison, 1999) that the 1-sided alpha spending will be 0.024 at the final analysis to control the overall type I error rate at the level of 0.025 for the primary endpoint. If the information fraction at the IA2 deviates from the planned 0.5, the alpha spending at the final analysis will be calibrated to control the overall type I error rate at the level of 0.025 following the group sequential theory. The same alpha-spending allocation used for the primary endpoint will be applied to the key secondary endpoints sequentially conditional on a significant primary endpoint result.

These interim analyses will be performed by an independent DMC that is not involved with study conduct or the final analysis of study data. The study team will remain blinded during the study. Alexion may additionally assess the PK and PD response.

If the study does not stop early for early futility or efficacy, the CHW method (Cui, 1999) will be adopted in the final analysis, in the event that the sample size is increased at the IA2. Technical and analysis details for each planned interim analysis is documented in an interim statistical analysis plan prior to the interim analysis.

4.8. Changes to Protocol-Planned Analyses

The alpha-spending function used for the key secondary endpoints is changed to be the same as the alpha-spending function applied for the primary endpoint MAKE90. This is changed from

the Pocock boundary as originally specified in the PA3 for testing at IA2 and the final analysis (if applicable).

Specifically, for the early efficacy assessment at IA2, the 1-sided alpha spending is set at 0.0025 for testing key secondary endpoints hierarchically if the primary endpoint is statistically significant at the level of 0.0025. More precisely, if the 1-sided p-value for the primary endpoint analysis at IA2 is < 0.0025, then the key secondary endpoints will also be tested at the level of 0.0025 hierarchically until the sequential testing stops at a nonsignificant key secondary endpoint in the hierarchy or all 6 key secondary endpoints are tested.

If the primary endpoint does not meet the early efficacy criteria at IA2, then the primary endpoint and key secondary endpoints will be tested at the final analysis in a similar manner as IA2 but under a different significance level. With the planned information fraction of 0.5 at IA2, it follows from the group sequential theory that the 1-sided alpha spending will be 0.024 at the final analysis to control the overall type I error rate at the level of 0.025 for the primary endpoint and key secondary endpoints. If the information fraction at IA2 deviates from the planned 0.5, the alpha spending at the final analysis will be calibrated to control the overall 1-sided type I error rate at the level of 0.025 following the group sequential theory.

This change is to align the testing procedure with the FDA's comments on PA3 to keep a consistent alpha-spending function between the primary endpoint, MAKE90, and the key secondary endpoints. If the protocol is amended later, then this change will be incorporated accordingly in the protocol amendment; if no new protocol amendment is made prior to the study completion, the change in the alpha-spending function for the key secondary endpoints documented in this approved SAP will serve as a prespecified testing method for the key secondary endpoints.

5. SAMPLE SIZE DETERMINATION

The sample size estimation was based on a 2-proportion difference using a normal approximation method to compare the treatment difference in the proportion of participants experiencing MAKE90 between the ravulizumab and the placebo groups. A sample size of 736 (368 participants per treatment group) has 90% power to detect a statistically significant treatment difference of 10% in the proportion of participants with MAKE90 under a 2-sided significance level of 0.05, assuming the proportion of MAKE is 25% for the placebo group and 15% for the ravulizumab group with an approximately 10% dropout rate. The assumption of 25% MAKE90 rate in the placebo group was derived based on recent interventional and observational studies and are described in Protocol Section 9.2.

6. SUPPORTING DOCUMENTATION

6.1. Technical Specifications for Derived Variables

The following derived data will be calculated.

6.1.1. Treatment-Emergent AEs

The analysis of TEAEs is described in detail in Section 4.5.2.

TEAEs are defined as those AEs with onset or existing events that worsen in severity from the initiation of dosing of study intervention through 90 days after the dose of study intervention. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE do not indicate that it occurred prior to the first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study intervention dose, then the AE is treatment emergent; else,
- If the start year is the same as the year of the first study intervention dose and
  - The start month is missing, then the AE is treatment emergent; else if
  - The start month is present and is the same or after the month of the first study intervention dose, then the AE is treatment emergent; else,
- If the start date is completely missing, then the AE is treatment emergent.

All other AEs are considered pretreatment AEs.

Percentages are based on the total number of treated participants in the particular treatment group in SS.

6.1.2. eGFR Based on sCr

The estimated glomerular filtration rate from serum creatinine (eGFRcr) will be calculated based on sCr using the CKD-EPI equation in participants ≥ 18 years of age as follows (Inker, 2021):

$eGFR_{cr} = 142 \times \min(sCr/\kappa, 1)^{\alpha} \times \max(sCr/\kappa, 1)^{-1.200} \times 0.9938^{Age}$ [× 1.012 (females)], where sCr is serum creatinine (mg/dL), κ = 0.7 (females) or 0.9 (males), and α is -0.241 (females) or -0.302 (males).

6.1.3. eGFR Based on sCysC

The estimated glomerular filtration rate from serum cystatin C (eGFRcys) will be calculated using the CKD-EPI cystatin C equation as follows:

$eGFR_{cys} = 133 \times \min(sCys/0.8, 1)^{-0.499} \times \max(sCys/0.8, 1)^{-1.328} \times 0.9962^{Age}$ [× 0.932 (females)], where sCys is serum cystatin.

6.1.4. eGFR Based on sCr and sCysC

The estimated glomerular filtration rate from serum creatinine and serum cystatin C (eGFRcr-cys) will be calculated using the CKD-EPI creatinine-cystatin equation as follows (Inker, 2021):

$eGFR_{cr\text{-}cys} = 135 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(sCr/\kappa, 1)^{-0.544} \times \min(sCys/0.8, 1)^{-0.323} \times \max(sCys/0.8, 1)^{-0.778} \times 0.9961^{Age}$ [× 0.963 if female], where sCr is serum creatinine (mg/dL), sCys is serum cystatin C (mg/L), $\kappa = 0.7$ (females) or 0.9 (males), and α is -0.219 (females) or -0.144 (males).

6.2. Study and Participant Characteristics

6.2.1. Participant Disposition

A summary of disposition will include the number and percentage of screened, randomized, and treated participants. The screen failure participants will be summarized in number and percentage by reason.

The number and percentage of participants in each analysis set defined in Section 3 will be summarized for all randomized participants, with the number and percentage of excluded participants and the reason for exclusion. A listing will be provided for all enrolled participants, indicating their inclusion/exclusion to each analysis set and the reason for exclusion.

The number and percentage of participants who complete or prematurely discontinue the Primary Evaluation Period and the primary reason for premature discontinuation (including COVID-19-related reasons) will be summarized for all randomized participants by treatment group and overall. Study duration (calculated as the difference between the first dose and the last visit date + 1) will be summarized and listed for each participant. The date of using the study intervention and the study termination date will be listed.

The number and percentage of enrolled participants will be summarized by country and site for each treatment group and overall.

6.2.2. Baseline Characteristics and Demographics

All demographics, baseline characteristics, and disease characteristics will be summarized using the ITT and SS. Summary statistics will be presented by treatment group and overall. By-participant listings of these data will be provided.

6.2.2.1. Demographics and Baseline Characteristics

The following demographic variables will be summarized by treatment group and overall:

- Sex (female and male)
- Race (White, Black or African American, American Indian or Alaska Native, Asian [including subcategories of Japanese and Chinese], Native Hawaiian or other Pacific Islander, Not reported, Unknown, and Other)
- Ethnicity (Hispanic or Latino and not Hispanic or Latino)
- Age at Screening (years)
- Age groups (≥ 18 to ≤ 65 years, > 65 to ≤ 75 years, and > 75 years)
- Baseline weight (kilograms)
- Baseline weight frequency of participants in the following categories: (≥ 30 to < 60 kg, ≥ 60 to < 100 kg, and ≥ 100 kg)

- Baseline height (centimeters)
- Body mass index (BMI, kilograms per square meter [kg/m^2])
- Geographic region (Europe, US, Japan, China, and the rest of the world)

6.2.2.2. Disease Characteristics

The following disease characteristics will be summarized by treatment group and overall:

- CKD stage at Screening (3A, 3B, and 4)
- Anticipated surgery type at Screening
- STS predicted post-operative renal failure risk score at Screening
- STS predicted mortality risk score at Screening
- EuroScore mortality risk score at Screening
- STS risk variables
- Levels of albuminuria (measured as albumin to creatinine ratio) at baseline (KDIGO, 2012)
  - < 30 mg albumin/g creatinine
  - ≥ 30 to < 300 mg albumin/g creatinine
  - ≥ 300 mg albumin/g creatinine
- Participants with or without diabetes mellitus at Baseline
- Baseline eGFR (sCysC based, sCr based, and based on both sCysC and sCr)

6.2.3. Medical History

All medical history from 2 years prior to Screening will be documented in the CRF. Any changes to medical history occurring during the Screening Period and prior to dosing of study intervention on Day 1 will be documented prior to study intervention administration.

Medical history will be classified by SOC and PT using the MedDRA (Version 24.1 or higher) and will be reported by treatment group and overall for the SS. By-participant listings of medical/surgical history and physical examinations will be presented.

6.2.4. Prior and Concomitant Medications

Prior medications or procedures are defined as medications or procedures taken within 3 months prior to Screening. Concomitant medications or procedures are defined as medications or procedures received by the participants on or after the first dose of study intervention, including those started before the first dose of study intervention and continued after the first dose of study intervention. Medications with partial dates are considered as both prior and concomitant if either type cannot be determined with certainty.

Prior and concomitant medications (including over-the-counter or prescription medicines, vaccines, vitamins, and/or herbal supplements) and nonpharmacologic therapies and procedures,

will be summarized using the SS. Medications will be coded using the World Health Organization (WHO) Drug Dictionary version in use by Alexion at the time of the analysis while nonpharmacologic therapies and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) will be coded using the MedDRA (Version 24.1 or higher).

Medication summaries by treatment group (ie, number and percentage) of participants using prior and concomitant medications will be presented by WHO-Drug Anatomical Therapeutic Chemical Level 3 and by WHO-Drug generic name. Procedures will be summarized similarly by the MedDRA (Version 24.1 or higher) SOC and PT. Protocol-required vaccinations will be summarized similarly and will also be presented.

By-participant listings of these data will be provided.

6.2.5. Protocol Deviations

Protocol deviations will be determined per the standard operating procedure "Identifying, Documenting, Reviewing, Determining the Impact and Reporting of Protocol Deviations" (ALXN-SOP-0004743 and ALXN-WI-0004204) and will be documented in the protocol deviation plan. The number and percentage of participants with specific protocol deviations will be summarized for all enrolled participants by important and non-important deviations. To ensure completeness of the list of protocol deviations, the following will be verified programmatically from the database:

1. Participants from whom informed consent was not obtained
2. Participants who violated any inclusion or exclusion criteria
3. Participants who received any disallowed medication or underwent any disallowed therapeutic procedure
4. Participants randomized who did not receive the planned dosing
5. Participants who did not undergo surgery, who underwent surgery without CPB, or who underwent surgery with CPB not within 15 days after treatment administration

For the purpose of defining the PPS, participants having the following important protocol deviation criteria will be considered for exclusion from the PPS.

- Participants randomized who did not receive the planned dosing
- Participants who did not undergo surgery or who underwent surgery without CPB or who underwent surgery with CPB not within 15 days after treatment administration
- Participants with deviation from the following inclusion criteria:
  - Known or apparent CKD (by history, diagnostic results, or reasonable medical assessment made by the Investigator and recorded in the medical record) and eGFR ≥ 20 to < 60 mL/min/1.73 m^2 using CKD-EPI equation by sCr or sCysC measurement, obtained by local or central laboratory during the 28 days prior to randomization
  - At risk for postsurgical kidney events as defined by a minimum STS Calculator Renal Failure Risk Score of $\geq 2.8\%$ assessed at time of Screening

- Participants with deviation from the following exclusion criteria:
  - Off-pump surgery is planned (eg, surgery without CPB)
- Participants who took any of the protocol-prohibited medications/procedures during the study:
  - Other agents that act on the complement pathway
  - Intravenous gamma globulin
  - Plasmapheresis or plasma exchange
  - Use of any pharmacologic agents specifically for prevention or treatment of AKI other than their approved indication (eg, experimental or investigational, fenoldopam, levosimendan, and nesiritide)

Protocol deviations from monitoring reports and other relevant sources will also be reviewed, and any important deviations will be included in the list that is summarized and reported. Summary statistics will be presented by treatment group and overall. The PD plan will be finalized prior to the clinical database lock.

6.3. Specifications for Analysis Windows and Instrument Scoring Details

6.3.1. Analysis Windows

The analysis window is derived using the target days from the protocol. For any scheduled or unscheduled records, analysis visit is derived using the analysis windows. Except for surgery with CPB, which is defined as the study day X. All other visits are partitioned as consecutive intervals using the mid points of scheduled visits. The following table describes the algorithm for the visit window.

Analysis Visit	Target Day	Analysis Windows	
		Low	High
Dosing Day/Day 1[a]	1	0	1
Surgery [b]	X	2	X
3 days post-CPB	X + 3	X + 1	X + 5
7 days post-CPB	X + 7	X + 6	X + 11
15 days post-CPB	X + 15	X + 12	X + 22
30 days post-CPB	X + 30	X + 23	X + 45
60 days post-CPB	X + 60	X + 46	X + 75
90 days post-CPB	X + 90	X + 76	X + 105
365 days post-CPB	365	X + 106	X + 380

[a] Randomization and dosing should occur on the same day except in cases when study intervention needs to be prepared the day before dosing.
[b] Participants randomized and dosed but who have a delay in the scheduled surgery and do not receive surgery within 15 days after dosing, will be scheduled for Primary Evaluation Period visits based on the day of dosing

Analysis Visit	Target Day	Analysis Windows	
		Low	High

(Day 1, Visit 2); participants who are randomized but not dosed with study intervention will have Primary Evaluation Period visits schedule based on Day 1 (Visit 2), defined as day of randomization.

6.3.2. Rules for Selecting the Analysis Records

Only 1 record per analysis visit will be selected in analysis. The following defines the rules in selecting the record.

1. Only scheduled visits of the specific endpoint will be selected and summarized in the tables, figures, and inferential analysis.
2. For example, if an unscheduled EQ-5D-5L is mapped into Visit 6, because Visit 6 is not a scheduled visit for EQ-5D-5L, this record will not be flagged for descriptive and inferential analysis. Please refer to the protocol for the schedule of assessments.
3. If there are multiple records within the same AVISIT window, the record closest to the target day will be selected.

If there are records with equal distance from the target day, the later record will be selected.

6.4. Prespecified Analyses on Japanese Population

The Japanese population consists of study participants from all Japanese sites. To support the PMDA submission to assess the consistency in efficacy, PK/PD, and safety between the entire population (or non-Japanese only for PK/PD) and the Japanese population if feasible, the following outputs will be produced in addition to the subgroup analyses described in Section 4.6.6. Additional subgroup analyses may be conducted if related subgroup analysis is deemed necessary for PMDA submission. Unless otherwise specified, the endpoints, variables definitions, and methods used for these outputs will be the same as described in Section 4. These outputs will be used to support PMDA submission only and will not be included in the CSR.

- Summaries of study disposition, protocol deviation, demographic and baseline characteristics, disease characteristics, medical history, and surgical information.
- Summaries of primary and key secondary endpoints in the primary analysis population(s).
- Summaries of ravulizumab PK concentrations and PD biomarkers over time as described in Section 4.6.2 for the Japanese population and non-Japanese population.
- Summary of study drug compliance.
- Summaries of AE overview; TEAE and SAEs by SOC and PT; TEAE by highest severity; TEAE by relationship to study treatment; TEAE leading to death; TEAE leading to study discontinuation; TEAEs of special interest (meningococcal infections).
- Analyses for other selected endpoints may be performed if deemed necessary. All analyses will be performed descriptively without formal statistical testing (ie, without a

p-value). If there are very few Japanese participants, tables and figures may not be generated.

6.5. Prespecified Analyses on Chinese Population

The analyses for the China cohort and Asian subgroup (or East Asian if applicable) will be conducted to support the registration in China.

China cohort will include all participants enrolled at the sites in China, and (East) Asian subgroup will include all participants who came from sites from regional (East) Asian countries. These analyses will not be included in the global CSR but will be included in separate reports for filing in China.

The following summary outputs will be generated for the China cohort and (East) Asian subgroup as mentioned above. Unless otherwise specified, the endpoint and variable definitions and methods used for these outputs will be the same as described for the overall population.

- Summaries of study disposition, demographics and baseline characteristics, disease characteristics, and prior and concomitant medications.
- Summaries of primary and key secondary endpoints.
- Summaries of PK concentration and PD.
- Summaries for ADA incidence, response categories, and titer, as well as NAb incidence.
- Summary of study drug exposure and duration.
- Summaries of TEAE overview, TEAEs and SAEs by SOC and PT, TEAEs by severity, TEAEs by relationship to study intervention, TEAEs leading to study intervention discontinuation, and AESIs.

Analyses for other selected endpoints may be performed if deemed necessary. All analyses will be performed descriptively without formal statistical testing. If there are very few participants, tables and figures may not be generated.

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