TITLE PAGE

Protocol Title:

ARTEMIS: RAvulizumab to Protect PaTients with Chronic Kidney DisEase (CKD) froM Cardiac Surgery Associated Acute Kidney Injury (CSA-AKI) and Subsequent Major Adverse Kidney Events (MAKE): A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study

Alexion Protocol Number: ALXN1210-CSA-AKI-318

AstraZeneca Protocol Number: D928DC00001

Amendment Number: 3.0

Compound: Ravulizumab (Sponsor code ALXN1210)

Study Phase: 3

Short 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, USA

Regulatory Agency Identifier Number(s)

IND: 160527

EU CT: 2022-501802-36-00

Release Date: 02 Dec 2024

Sponsor Signatory:

This document has been e-signed in Alexion's electronic document management system. Please refer to last page for e-signature details.

PPD	**Date**
PPD	**Date**

Medical Monitor Name and Contact Information can be found in the Study Contact List distributed to study sites.

The 24-hour Emergency Contact Phone Number can be found on the informed consent form.

INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Primary Site Address of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

This summary indicates the major changes made to Protocol ALXN1210-CSA-AKI-318.

Amendment 3.0 (02 Dec 2024)

This modification is considered to be substantial based on the criteria set forth in the European Union Clinical Trials Regulation (EU CTR) 536/2014 Article 2, 2 (13) because it affects the conduct or management of the study.

Overall Rationale for the Amendment:

The primary reason for this amendment is to update the purpose of the second interim analysis. The purpose of the second interim analysis is to assess futility, early efficacy, and sample size re-estimation to be able to stop the study early if the superiority of the study intervention under study is clearly established. Additional updates include changes to key secondary efficacy endpoints, analyses of key secondary endpoints and disallowed medicine and therapy.

Additional minor clarifications and corrections were made.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis; Section 4.1 – Overall Design; Section 4.2 – Scientific Rationale for Study Design; Section 9.4.1 – Efficacy Analyses; Section 9.5 – Interim Analyses; Section 9.6 – Data Monitoring Committee	Modification of the purpose of the second interim analysis by adding the purpose of assessing futility and early efficacy, in addition to sample size re-estimation. As a consequence, the role of the DMC is clarified and the evaluation of conditional power is adjusted.	To stop the study early if the superiority of the study intervention under study is clearly established.
Section 9.6 – Data Monitoring Committee	Modified to include a DMC SAP and to align to the wording changes in Section 9.5 – Interim Analysis.	For clarification

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis; Section 3 – Objectives, Estimands and Endpoints; Section 3.2 – Secondary Estimands; Section 9.1.2 – Key Secondary Hypotheses; Section 9.4.1.2 – Analysis of Key Secondary Efficacy Endpoints	Modification of the key secondary efficacy endpoints: • Move of "Occurrence of STS Renal Failure (RIFLE Failure criteria) within 30 days post CPB" to other secondary efficacy endpoints and slightly rewritten for clarification • Move of "Length of post-operative ICU stay" from healthcare resource utilization endpoints to key secondary efficacy endpoints Subsequently, modification of secondary estimands, the key secondary hypotheses, and the analysis of key secondary efficacy endpoints. Minor typographical updates were also made for clarity.	For streamlining the hierarchical testing approach to minimize redundancies. The secondary endpoint using RIFLE Failure criteria is very similar to key secondary endpoint "Occurrence of severe AKI (KDIGO Stage 2 or 3) from randomization to Day 30 post CPB", and therefore moved to "other secondary endpoints". Addition of a clinically meaningful endpoint based on clinical stakeholder input/feedback.
Section 8.1.2 - Inclusion/Exclusion Criteria; Section 10.2 – Clinical Laboratory tests; Section 10.6.1 - Definitions	Modification of instructions to confirm postmenopausal status.	For clarification
Section 8.1.2.1 - Guidance for the Assessment of CKD and Calculation of eGFR (Inclusion Criterion #5)	Addition of the guidance for calculation of eligible eGFR.	For clarification
Section 8.1.2.2 - Guidance for Evaluation of AKI Risk (Inclusion Criterion #6)	Addition of the guidance for AKI risk.	For clarification
Section 8.2 – Efficacy Assessments	Modification of language with respect to creatinine tests.	For clarification
Section 8.4.1 - Time Period and Frequency for Collecting AE and SAE Information	Modification by adding language regarding SAE reporting.	For clarification
Section 1.3 – Schedule of Activities; Section 8.6 - Pharmacokinetics and Pharmacodynamics	Modification of predose sampling window for PK/PD sampling on Day 1 from within 30 minutes to 120 minutes of study intervention administration	For practical reasons

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis; Section 4.1 – Overall Design; Section 4.4 – End of Study Definition; Section 8.4.1 - Time Period and Frequency for Collecting AE and SAE Information	Updating end of study definition by replacing last visit by last Survival Follow-up Visit.	For clarification
Section 1.3 – Schedule of Activities; Section 8.1.3 - Demographics	Modification of the collection of age/sex/race and ethnicity by adding "as allowable by local regulation".	For clarification
Section 1.1 – Synopsis; Section 1.2 – Schema; Section 1.3 – Schedule of Activities; Section 4.1 – Overall Design; Section 6.1 – Study Intervention(s) Administered; Section 8.1.6 – Visits on the Same Day	Modification by adding that Screening and Randomization or Randomization and Surgery may occur on the same calendar day and that infusion is required to be completed at least 1 hour prior to surgery start.	For clarification
Section 2.3.1 – Risk Assessment; Section 8.1.4 – Vaccination and Antibiotic Prophylaxis	Modification to update the vaccination language with respect to the *N meningitidis* vaccination series.	For clarification
Section 5.2 – Exclusion Criteria	Modification of exclusion criterion #4 by adding "Presence of AKI must be assessed within 72 hours prior to randomization."	For clarification
Section 5.2 – Exclusion Criteria	Modification of exclusion criterion #14 by adding "or indolent disease not being treated."	For clarification
Section 6.3.1 - Randomization	Addition of "AVR/r + aorta procedure" in Table 10 and addition of clarifying footnotes.	For clarification
Section 6.3.2 - Blind	Modification of language regarding emergency unblinding to align with Alexion template.	For clarification
Section 5.2 – Exclusion Criteria; Section 6.5.2 – Disallowed Medicine and Therapy	Addition of intravenous gamma globulin (IVIg)	To address known effect on PK/PD

Section # and Name	Description of Change	Brief Rationale
Section 8.4.1 – Time Period and Frequency for Collecting AE and SAE Information	Modification to clarify AE collection period	For clarification
Section 9.4.1.2 – Analyses of Key Secondary Efficacy Endpoints	Addition of the statistical analysis of key secondary endpoint "Length of post-operative ICU stay".	To align with changes in key secondary endpoints
Section 9.4.1.2.1 - Association Between Key Secondary Endpoint and Clinical Outcomes	Modification to specify that the association between the key secondary point of "occurrence of severe AKI from randomization to Day 30 post CPB" and the clinical outcome will be examined.	To align with changes in key secondary endpoints
Section 9.4.1.7 - Multiplicity Adjustment	Modification to update the multiple testing procedure of the efficacy endpoints.	To align with the changes in the second IA

Abbreviations: AE = adverse event; AKI = acute kidney injury; AVR/r = aortic valve repair or replacement; CPB = cardiopulmonary bypass; DMC = Data Monitoring Committee; eGFR = estimated glomerular filtration rate; IA = interim analysis; ICU = intensive care unit; KDIGO = Kidney Disease: Improving Global Outcomes (nonprofit foundation); PD = pharmacodynamic; PK = pharmacokinetic; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; SAE = serious adverse event; SAP = statistical analysis plan; STS = Society of Thoracic Surgeons

TABLE OF CONTENTS

TITLE PAGE 1
INVESTIGATOR'S AGREEMENT 2
PROTOCOL AMENDMENT SUMMARY OF CHANGES 3
TABLE OF CONTENTS 7
LIST OF TABLES 13
LIST OF FIGURES 13
1. PROTOCOL SUMMARY 14
1.1. Synopsis 14
1.2. Schema 19
1.3. Schedule of Activities 20
2. INTRODUCTION 29
2.1. Study Rationale 29
2.2. Background 29
2.2.1. Unmet Medical Need 29
2.3. Benefit/Risk Assessment 30
2.3.1. Risk Assessment 30
2.3.1.1. Coronavirus Disease 2019 32
2.3.2. Benefit Assessment 32
2.3.3. Overall Benefit: Risk Conclusion 33
3. OBJECTIVES, ESTIMANDS AND ENDPOINTS 34
3.1. Primary Estimand 38
3.2. Secondary Estimands 39
4. STUDY DESIGN 40
4.1. Overall Design 40
4.2. Scientific Rationale for Study Design 41
4.2.1. Participant Input into Design 44
4.3. Justification for Dose 44
4.4. End of Study Definition 45
5. STUDY POPULATION 46
5.1. Inclusion Criteria 46
5.2. Exclusion Criteria 47

5.3. Lifestyle Considerations 48
5.4. Screen Failures....48
6. STUDY INTERVENTION 49
6.1. Study Intervention(s) Administered 49
6.1.1. Study Intervention(s) Packaging and Labeling....49
6.1.2. Preparation/Handling/Storage/Accountability....50
6.2. Standard of Care 51
6.3. Measures to Minimize Bias: Randomization and Blinding....51
6.3.1. Randomization....51
6.3.2. Blind 52
6.4. Study Intervention Compliance 52
6.5. Concomitant Therapy 53
6.5.1. Allowed Medicine and Therapy 53
6.5.2. Disallowed Medicine and Therapy....53
6.5.3. Confounding Procedures Prior to Surgery....53
6.6. Dose Modification 54
6.7. Intervention after the End of the Study....54
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 55
7.1. Discontinuation of Study Intervention....55
7.2. Participant Discontinuation/Withdrawal from the Study 55
7.3. Lost to Follow-up 55
8. STUDY ASSESSMENTS AND PROCEDURES....57
8.1. General Assessments and Procedures....57
8.1.1. Informed Consent 57
8.1.2. Inclusion/Exclusion Criteria 57
8.1.2.1. Guidance for the Assessment of CKD and Calculation of eGFR (Inclusion Criterion #5)....58
8.1.2.2. Guidance for Evaluation of AKI Risk (Inclusion Criterion #6) 58
8.1.2.3. Guidance for the Evaluation of Cardiac Surgery Type (Exclusion Criteria #6 and #17) 59
8.1.3. Demographics....60
8.1.4. Vaccination and Antibiotic Prophylaxis....60

8.1.5. Medical History and Baseline Characteristics 61
8.1.6. Visits on the Same Day 61
8.1.7. Hospital Discharge 62
8.1.8. Visits at Home 62
8.2. Efficacy Assessments 62
8.3. Safety Assessments 63
8.3.1. Physical Examinations 63
8.3.2. Vital Signs 64
8.3.3. Electrocardiograms 64
8.3.4. Clinical Laboratory Assessments: Safety and Efficacy 64
8.3.5. Pregnancy 65
8.3.6. Participant Safety Card 66
8.3.7. Vital Status 66
8.4. Adverse Events and Serious Adverse Events 66
8.4.1. Time Period and Frequency for Collecting AE and SAE Information 67
8.4.2. Method of Detecting AEs and SAEs 67
8.4.3. Follow-up of AEs and SAEs 67
8.4.4. Regulatory Reporting Requirements for SAEs and Other Events 67
8.4.5. Medication Error, Drug Abuse, and Drug Misuse 68
8.4.5.1. Timelines 68
8.4.5.2. Medication Error 68
8.4.5.3. Drug Abuse 68
8.4.5.4. Drug Misuse 68
8.4.6. Adverse Events of Special Interest 68
8.5. Treatment of Overdose 68
8.6. Pharmacokinetics and Pharmacodynamics 69
8.7. Genetics 70
8.8. Biomarkers 70
8.8.1. Blood Exploratory Biomarkers 70
8.8.2. Urine Exploratory Biomarkers 70
8.8.3. Additional Biomarker Assessments 70
8.9. Participant-Reported Outcome Measures 70
8.10. Healthcare Resource Utilization 71

8.11. Other Exploratory Assessments and Procedures 72
8.12. Post-treatment Follow-up Period 72
8.13. Immunogenicity Assessments 72
8.13.1. ADA Variables 73
9. STATISTICAL CONSIDERATIONS 74
9.1. Statistical Hypotheses 74
9.1.1. Primary Hypothesis 74
9.1.2. Key Secondary Hypotheses 74
9.2. Sample Size Determination 74
9.3. Populations for Analyses 76
9.4. Statistical Analyses 77
9.4.1. Efficacy Analyses 77
9.4.1.1. Analyses of Primary Efficacy Endpoint(s) 77
9.4.1.2. Analyses of Key Secondary Efficacy Endpoints 78
9.4.1.3. Other Secondary Efficacy Analyses 80
9.4.1.4. Healthcare Resource Utilization 81
9.4.1.5. Health-related QoL 81
9.4.1.6. Analyses of Exploratory Endpoints 82
9.4.1.7. Multiplicity Adjustment 82
9.4.2. Safety Analyses 82
9.4.2.1. Adverse Events 82
9.4.2.2. Physical Examination and Vital Signs 83
9.4.2.3. Clinical Laboratory Tests 83
9.4.3. Pharmacokinetic/Pharmacodynamic Analyses 83
9.4.4. Immunogenicity Analyses 83
9.4.5. Subgroup Analyses 83
9.5. Interim Analyses 84
9.6. Data Monitoring Committee 85
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 86
10.1. Regulatory, Ethical, and Study Oversight Considerations 86
10.1.1. Regulatory and Ethical Considerations 86
10.1.2. Financial Disclosure 88

10.1.3. Informed Consent Process 88
10.1.4. Recruitment Strategy 89
10.1.5. Data Protection 89
10.1.6. Committees Structure 91
10.1.7. Dissemination of Clinical Study Data 91
10.1.8. Data Quality Assurance 91
10.1.9. Source Documents 92
10.1.10. Study and Site Start and Closure 92
10.1.11. Publication Policy 93
10.1.12. Good Clinical Practice Compliance 94
10.2. Clinical Laboratory Tests 96
10.3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 99
10.3.1. Definition of AE 99
10.3.2. Definition of SAE 100
10.3.3. Recording and Follow-up of AE and/or SAE 101
10.3.4. Reporting of SAEs 103
10.3.5. Unexpected Events 104
10.4. Management of Potential Infusion-related Adverse Events During Ravulizumab Administration 105
10.5. Medication Error, Drug Abuse, and Drug Misuse 106
10.6. Contraceptive Guidance and Collection of Pregnancy Information 109
10.6.1. Definitions 109
10.6.2. Contraception Guidance 109
10.6.2.1. Guidance for Female Participants 110
10.6.2.2. Guidance for Male Participants 111
10.6.3. Collection of Pregnancy Information 111
10.6.3.1. Male Participants with Partners Who Become Pregnant 112
10.6.3.2. Female Participants Who Become Pregnant 112
10.7. Exploratory Biomarkers 114
10.8. Participant-Reported Outcome Instruments 115
10.9. COVID-19 Risk Assessment 125
10.10. COVID-19 Vaccine Risk Assessment 127

10.11. Abbreviations....128
10.12. Protocol Amendment History....132
11. REFERENCES....133

LIST OF TABLES

Table 1: Schedule of Activities 20
Table 2: Ravulizumab Important Identified and Potential Risks 31
Table 3: Mapping Objectives to Estimands/Endpoints 34
Table 4: Endpoint Definitions 37
Table 5: AKI Staging by Modified KDIGO Criteria 43
Table 6: AKI Staging by Modified RIFLE Criteria 43
Table 7: Stages of Post-CSA-AKI Kidney Function to Determine AKI Progression on Day 15 to Day 90 after Surgery 43
Table 8: Study Interventions 49
Table 9: Weight-based Single Dose of Ravulizumab or Placebo 49
Table 10: Randomization Stratification Factors 51
Table 11: Analysis Populations 76
Table 12: Protocol-Required Laboratory Assessments 96
Table 13: Clinical Criteria for Diagnosing Anaphylaxis 105
Table 14: Potential Operational Risks and Mitigation Measures due to COVID-19 125
Table 15: Potential Operational Risks and Mitigation Measures due to COVID-19 Vaccine 127
Table 16: Abbreviations and Specialist Terms 128

LIST OF FIGURES

Figure 1: Study Design Schematic 19

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

ARTEMIS RA**R**avulizumab 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

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

Regulatory Agency Identifier Numbers:

IND: 160527

EU CT: 2022-501802-36-00

Rationale:

Patients with chronic kidney disease (CKD) undergoing cardiac surgery with cardiopulmonary bypass (CPB) are at high risk for cardiac surgery-associated acute kidney injury (CSA-AKI). While CSA-AKI in the broad population having cardiac surgery with CPB occurs in 20% to 25% of patients, this risk increases to 60% to 80% in a population with CKD. Moreover, the risk of major adverse kidney events (MAKEs) is 20% to 30% in the CKD population. Inhibiting terminal complement from injuring the kidney and vasculature may reduce the incidence, severity, and duration of post-operative CSA-AKI and reduce subsequent MAKE, improving long-term survival and freedom from kidney replacement therapy (KRT), and reducing progression of CKD. Preclinical and clinical evidence suggest that early initiation of complement component 5 (C5) inhibition, especially before onset of ischemia, will confer the greatest benefit in these outcomes.

A randomized, placebo-controlled, double-blind study design is employed to minimize bias and to balance the effect of confounding factors in this complex and highly comorbid population. Placebo has been chosen as the comparator because there are no approved therapies that reduce the risk of poor clinical outcomes after cardiac surgery with CPB (ie, sustained kidney dysfunction [SKD], need for KRT, or mortality).

This study will be conducted as specified in this protocol and in accordance with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

Considering the established safety profile for ravulizumab and the measures taken to minimize risk to participants in this study, the potential risks identified in association with ravulizumab are

justified by the anticipated benefits that may be provided to participants with CKD at high risk for kidney events who are undergoing cardiac surgery with CPB.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints and/or Estimands
Primary	
To assess the efficacy of ravulizumab in reducing risk of MAKE90 following CPB	**Primary Estimand:** • Treatment: Ravulizumab or placebo • Population: Adult participants with CKD as defined by the inclusion and exclusion criteria • Endpoint/Variables: MAKE90, defined as meeting at least 1 of the following criteria: o Decrease from baseline in eGFR (CKD-EPI formula using sCysC) of ≥ 25% at Day 90 post CPB, or o Initiation of KRT through Day 90 post CPB, or o Death from any cause through Day 90 post CPB • IEs: o IE1: Iodinated contrast dye exposure after treatment is administered through Day 90 post CPB o IE2: Surgery was performed without CPB or surgery with CPB was not performed within 15 days after treatment administration o IE3: Use of confounding interventions prior to surgery or use of disallowed interventions after treatment is administered through Day 90 post CPB Treatment policy strategy: The collected endpoint will be analyzed irrespective of IEs. • Summary measures: Difference between treatment groups in proportion of participants experiencing MAKE at 90 days post CPB, regardless of any IEs
Key Secondary Efficacy	
To assess the efficacy of ravulizumab in reducing 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

Objectives	Endpoints and/or Estimands
	6) Length of post-operative ICU stay
Other Secondary Efficacy	
To assess the efficacy of ravulizumab in reducing risk of MAKE (based on sCysC), MAKE (based on sCr), AKI (based on sCr), and related outcomes following CPB	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)
	Highest CSA-AKI stage within 3 and 7 days post CPB
	Occurrence of CSA-AKI without recovery at Day 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 Day 30 and Day 90 post CPB
	Hospital readmission rate (all-cause or AKI-related) through Day 30 and Day 90 post CPB
	Days on KRT through Day 30 and Day 90 post CPB
Health-related QoL	
To assess the effect of ravulizumab on quality of life 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

Objectives	Endpoints and/or Estimands
PK and PD	
To evaluate 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 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	
To evaluate the immunogenicity of ravulizumab IV in participants with CKD undergoing non-emergent CPB	ADA status, 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 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)

Abbreviations: ADA = antidrug antibody; AKI = acute kidney injury; C5 = complement component 5; C5b-9 = terminal complement complex (membrane attack complex); CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CPB = cardiopulmonary bypass; CSA-AKI = cardiac surgery-associated acute kidney injury; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life Group's 5-dimension 5-level (questionnaire); FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue (questionnaire); ICU = intensive care unit; IE = intercurrent event; 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; MAKE = major adverse kidney event; MAKE90 = major adverse kidney event at Day 90 post cardiopulmonary bypass; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QoL = quality of life; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; sCr = serum creatinine; sCysC = serum Cystatin C; STS = Society of Thoracic Surgeons; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TM = thrombomodulin

Overall Design Synopsis:

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 (CABG), valve replacement or repair, or combined procedure, to reduce the risk of post-operative kidney events and subsequent MAKE at 90 days after surgery. Participants considered at risk for kidney events after CPB have estimated glomerular filtration rate (eGFR) ≥ 20 to < 60 mL/min/1.73 m^2 with minimum Society of Thoracic Surgeons (STS) Calculator Renal Failure Risk Score of $\geq 2.8\%$.

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.

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, 4) and surgery type (mitral valve replacement or combined procedures vs other single procedure).

Screening and Randomization or Randomization and Surgery may occur on the same calendar day due to surgical urgency or scheduling challenges. Screening and Randomization and Surgery (ie, all 3 visits) may not occur on the same calendar day. 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 no less than 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. The total study duration is up to approximately 400 days, including the Survival Follow-up Visit.

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. The purpose of the first interim analysis is to assess futility. The second interim analysis will assess futility, early stop for efficacy, and sample size re-estimation.

The end of the study is defined as the date the last participant completes the last Survival Follow-up Visit as indicated in the Schedule of Activities.

Disclosure Statement: This is a parallel group treatment study with 2 arms that is participant and Investigator blinded. Ravulizumab is being evaluated for reducing risk of death, need for KRT, and for sustained reduction in kidney function in adult patients with CKD undergoing CPB for CABG, valve replacement or repair, or combined procedure.

Number of Participants:

Approximately 736 participants will be randomly assigned to study intervention.

Study Groups and Duration:

Randomized participants will receive a single weight-based dose of ravulizumab or placebo within 7 days prior to CPB procedure. Infusion is required to be completed at least 1 hour prior to surgery start.

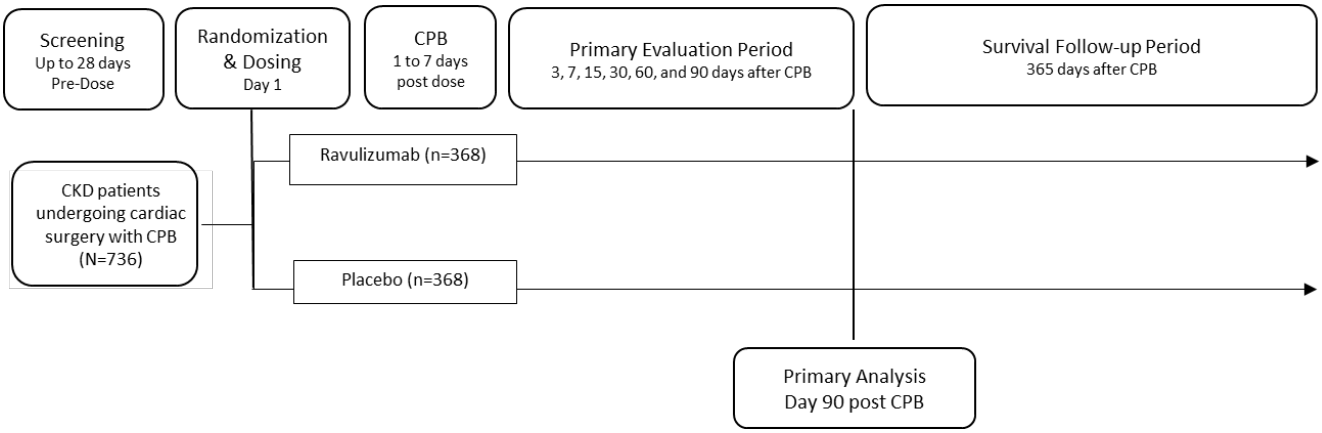
Data Monitoring Committee (DMC): Yes

An independent 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 (DAC) during the conduct of the study and make formal recommendations on early stopping for futility, early stopping for efficacy, or increasing sample size based on the pre-specified criterion.

1.2. Schema

Figure 1: Study Design Schematic



Note: Screening and Randomization or Randomization and Surgery can occur on the same calendar day. Screening and Randomization and Surgery (ie, all 3 visits) may not occur on the same calendar day. Randomization and dosing should occur on the same day (Day1) except in cases when study intervention needs to be prepared the day before dosing; CPB procedure to occur within 7 days after dosing. Infusion is required to be completed at least 1 hour prior to surgery start (ie, induction of anesthesia).
Abbreviations: CKD = chronic kidney disease; CPB = cardiopulmonary bypass

1.3. Schedule of Activities

Table 1: Schedule of Activities

Study Period	Screening	Random-ization & Dosing[a]	Primary Evaluation Period								Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Post CPB period begins at operating room exit following surgery with CPB. Home visits are allowed after discharge (where available and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities) (see Section 8.1.7). Phone or telemedicine visits are expected to occur in conjunction with home visits.
Study Day	**Day -28 to -1**	**Day 1**	**Surgery with CPB (within 7 days after Dosing)[b]**	**3 d (72 h) post CPB**	**7 d (168 h) post CPB**	**15 d post CPB**	**30 d post CPB**	**60 d post CPB**	**90 d post CPB or ED**	**Survival Follow-up 365 d post CPB[c]**	
Visit Window		**-1 d**		**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±10 d**	**±10 d**	**±15 d**	
General Assessments/Procedures											
Informed consent	X										
Confirm inclusion/exclusion	X	X									Confirm eligibility prior to randomization. See Section 5 and Section 8.1.2.
Demographics	X										Age/sex/race and ethnicity collected (variables for STS risk scores and eGFR), as allowable by local regulation.
Medical history	X										All medical history from 2 years prior to Screening and any history from any time related to cardiac or kidney disease will be recorded. See Section 8.1.5.
Baseline characteristics	X										STS risk scores and parameters to derive the risk scores will be recorded as outlined in CRF completion guidelines; EuroScore will be separately calculated, and the value recorded. See Section 8.1.5
Prior medications/ procedures	X										All procedures and medications taken within 3 months prior to Screening (see Section 8.1.5).

Table 1: Schedule of Activities

Study Period	**Screening**	**Random-ization & Dosing[a]**	**Primary Evaluation Period**								**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Post CPB period begins at operating room exit following surgery with CPB. Home visits are allowed after discharge (where available and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities) (see Section 8.1.7). Phone or telemedicine visits are expected to occur in conjunction with home visits.
Study Day	**Day -28 to -1**	**Day 1**	**Surgery with CPB (within 7 days after Dosing)[b]**	**3 d (72 h) post CPB**	**7 d (168 h) post CPB**	**15 d post CPB**	**30 d post CPB**	**60 d post CPB**	**90 d post CPB or ED**	**Survival Follow-up 365 d post CPB[c]**	
Visit Window		**-1 d**		**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±10 d**	**±10 d**	**±15 d**	
Weight and height	X	X	X	X	X	X	X	X	X		Height only at Screening; pre-operative weight at Visit 3, and **daily weights will occur Days 1 to 7 days post CPB (168 h, Visit 5)** or until hospital discharge, whichever comes first. If an accurate weight cannot be obtained in an ICU setting, total daily fluid input and output will be recorded.
Vital signs	X	X	X	X	X	X	X	X	X		Perform prior to administering study intervention on Day 1, prior to induction of anesthesia on day of surgery, and at any time on other days.
Dispense Participant Safety Card	X										Instruct participants to carry safety card at all times and bring card to scheduled visits. See Section 8.3.6.
Review Participant Safety Card		X			X	X	X	X	X		Confirm participants/caregivers carry safety card at all times.
Meningococcal vaccination	X	Completion of vaccination series according to national and local guidelines									See Section 8.1.4.

Table 1: Schedule of Activities

Study Period	Screening	Random-ization & Dosing[a]	Primary Evaluation Period								Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Post CPB period begins at operating room exit following surgery with CPB. Home visits are allowed after discharge (where available and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities) (see Section 8.1.7). Phone or telemedicine visits are expected to occur in conjunction with home visits.
Study Day	**Day -28 to -1**	**Day 1**	**Surgery with CPB (within 7 days after Dosing)[b]**	**3 d (72 h) post CPB**	**7 d (168 h) post CPB**	**15 d post CPB**	**30 d post CPB**	**60 d post CPB**	**90 d post CPB or ED**	**Survival Follow-up 365 d post CPB[c]**	
Visit Window		**-1 d**		**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±10 d**	**±10 d**	**±15 d**	
Pregnancy test (WOCBP only)	X	X					X	X	X		Female participants of childbearing potential must have a negative pregnancy test (local urine or local or central serum) within 72 hours prior to Randomization (See Section 8.1.2 and Section 8.3.5 for details). Serum test (central laboratory) at all other visits indicated.
Serum FSH, estradiol	X										Required where postmenopausal status needs to be confirmed (see Section 10.6.1).
Urine albumin to creatinine ratio and protein to creatinine ratio		X					X		X		
Study Intervention											
Randomization		X									

Table 1: Schedule of Activities

Study Period	Screening	Random-ization & Dosing[a]	Primary Evaluation Period								Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Post CPB period begins at operating room exit following surgery with CPB. Home visits are allowed after discharge (where available and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities) (see Section 8.1.7). Phone or telemedicine visits are expected to occur in conjunction with home visits.
Study Day	**Day -28 to -1**	**Day 1**	**Surgery with CPB (within 7 days after Dosing)[b]**	**3 d (72 h) post CPB**	**7 d (168 h) post CPB**	**15 d post CPB**	**30 d post CPB**	**60 d post CPB**	**90 d post CPB or ED**	**Survival Follow-up 365 d post CPB[c]**	
Visit Window		**-1 d**		**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±10 d**	**±10 d**	**±15 d**	
Study intervention administration		X									Screening and Randomization or Randomization and Surgery may occur on the same calendar day due to surgical urgency or scheduling challenges. Randomization and study intervention dosing should occur on the same day except in cases when study intervention needs to be prepared the day before dosing, randomization may then occur the day before dosing (after screening); randomization must occur prior to administration of study intervention and infusion must be completed at least 1 hour prior to surgery (ie, induction of anesthesia).
Surgical information			X								Details of surgery performed will be recorded as outlined in CRF completion guidelines.
Efficacy, Resource Utilization and Safety Assessments											
KRT requirements	X	Continuous monitoring								X	See Section 8.2

Table 1: Schedule of Activities

Study Period	**Screening**	**Random-ization & Dosing[a]**	**Primary Evaluation Period**								**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Post CPB period begins at operating room exit following surgery with CPB. Home visits are allowed after discharge (where available and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities) (see Section 8.1.7). Phone or telemedicine visits are expected to occur in conjunction with home visits.
Study Day	**Day -28 to -1**	**Day 1**	**Surgery with CPB (within 7 days after Dosing)[b]**	**3 d (72 h) post CPB**	**7 d (168 h) post CPB**	**15 d post CPB**	**30 d post CPB**	**60 d post CPB**	**90 d post CPB or ED**	**Survival Follow-up 365 d post CPB[c]**	
Visit Window		**-1 d**		**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±10 d**	**±10 d**	**±15 d**	
Vital status						X	X	X	X	X	Participant survival (yes/no) will be recorded; all attempts to collect vital status must be made on Days 15, 30, 60, and 90, including by phone contact, or indirect ascertainment from another healthcare provider or family member, or local death registries. If participant withdraws consent, survival status will be recorded at that time.
Hematology	X	X[d]	X	X	X	X	X	X	X		Collect prior to administering study intervention on Day 1, prior to induction of anesthesia on day of surgery, at any time during other visits, and within 48 hours of hospital discharge. **Daily collection of sCr and sCysC will occur Days 1 to 7 days post CPB (168 hours, Visit 5) or until hospital discharge, whichever comes first.** Full laboratory assessments will occur on Visits 4 and 5. See Section 8.3.4. Note: In addition, on Day 1 sCysC needs to be collected within 30 min after end of infusion with the PK/PD sample.
Serum chemistry & sCysC	X	X[d]	X	X	X	X	X	X	X		

Table 1: Schedule of Activities

Study Period	**Screening**	**Random-ization & Dosing[a]**	**Primary Evaluation Period**								**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Post CPB period begins at operating room exit following surgery with CPB. Home visits are allowed after discharge (where available and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities) (see Section 8.1.7). Phone or telemedicine visits are expected to occur in conjunction with home visits.
Study Day	**Day -28 to -1**	**Day 1**	**Surgery with CPB (within 7 days after Dosing)[b]**	**3 d (72 h) post CPB**	**7 d (168 h) post CPB**	**15 d post CPB**	**30 d post CPB**	**60 d post CPB**	**90 d post CPB or ED**	**Survival Follow-up 365 d post CPB[c]**	
Visit Window		**-1 d**		**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±10 d**	**±10 d**	**±15 d**	
Hospital discharge				Continuous monitoring to determine if unscheduled Hospital Discharge Visit is needed							Perform a Hospital Discharge study visit no more than 48 hours prior to the anticipated discharge if discharge does not correspond with a scheduled study visit (see Section 8.1.7) and collect vital signs, hematology, serum chemistry including sCysC, survival and KRT status; review Participant Safety Card.
Locally obtained serum creatinine				Standard of care assessments to be reported				X[e]	X[e]		All sCr tests done locally as standard of care will be reported in the first 30 days post CPB and in the first 30 days following initiation or dose modification that occur at any point post-baseline for select classes of eGFR-modifying drugs (see Section 10.2). The Investigator should regularly monitor patients with an elevated sCr > 1.5 × baseline per their local practice.
Healthcare resource utilization	X		Continuous monitoring								See Section 8.10
Concomitant medications/ procedures		Continuous monitoring									All concomitant therapies and therapeutic or diagnostic procedures (eg CT scan, angiography) will be recorded.

Table 1: Schedule of Activities

Study Period	**Screening**	**Random-ization & Dosing[a]**	**Primary Evaluation Period**								**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Post CPB period begins at operating room exit following surgery with CPB. Home visits are allowed after discharge (where available and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities) (see Section 8.1.7). Phone or telemedicine visits are expected to occur in conjunction with home visits.
Study Day	**Day -28 to -1**	**Day 1**	**Surgery with CPB (within 7 days after Dosing)[b]**	**3 d (72 h) post CPB**	**7 d (168 h) post CPB**	**15 d post CPB**	**30 d post CPB**	**60 d post CPB**	**90 d post CPB or ED**	**Survival Follow-up 365 d post CPB[c]**	
Visit Window		**-1 d**		**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±10 d**	**±10 d**	**±15 d**	
Exposure to contrast	Continuous monitoring										Details of any contrast administered from Screening, or from 7 days prior to randomization if Screening occurs less than 7 days prior to randomization, through Day 90 post CPB will be recorded as outlined in the CRF completion guidelines.
RBC transfusion			Continuous monitoring								Transfusion date, pRBC or whole blood, number of units, and pre-transfusion hemoglobin value will be recorded. Transfusions of other blood products will be recorded as concomitant procedures.
AEs	Continuous monitoring										
QoL Assessment											
FACIT-Fatigue		X					X	X	X		Participant to complete QoL scales prior to study intervention administration on Day 1.
EQ-5D-5L		X					X	X	X		
KDQOL-36		X					X	X	X		

Table 1: Schedule of Activities

Study Period	Screening	Random-ization & Dosing[a]	Primary Evaluation Period								Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Post CPB period begins at operating room exit following surgery with CPB. Home visits are allowed after discharge (where available and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities) (see Section 8.1.7). Phone or telemedicine visits are expected to occur in conjunction with home visits.
Study Day	**Day -28 to -1**	**Day 1**	**Surgery with CPB (within 7 days after Dosing)[b]**	**3 d (72 h) post CPB**	**7 d (168 h) post CPB**	**15 d post CPB**	**30 d post CPB**	**60 d post CPB**	**90 d post CPB or ED**	**Survival Follow-up 365 d post CPB[c]**	
Visit Window		**-1 d**		**±1 d**	**±1 d**	**±3 d**	**±3 d**	**±10 d**	**±10 d**	**±15 d**	
PK/PD/Immunogenicity											
Blood samples for PK/PD		X[d]	X	X	X		X		X		On Day 1, collect predose (within 120 minutes prior to the start of infusion) and at end of infusion (within 30 minutes after the end of infusion from the participant's opposite, noninfused arm). On day of surgery, collect sample prior to induction of anesthesia. Collect sample at any time on other study visits.
Blood sample for ADA		X[d]							X		On Day 1, collect sample predose. Collect sample at any time on Day 90.
Exploratory Assessments											
Blood and urine samples for exploratory biomarkers	X	X[d]	X	X	X		X		X		On Day 1, collect sample predose, prior to induction of anesthesia on day of surgery, and at any time on other days.

Note: If a participant discontinues early, Day 90/ED evaluations should be performed.

[a] Randomization and dosing should occur on the same day except in cases when study intervention needs to be prepared the day before dosing (Section 8.1.6). Screening and Randomization or Randomization and Surgery may occur on the same calendar day due to surgical urgency or scheduling challenges (Section 8.1.6). Screening and Randomization and Surgery (ie, all 3 visits) may not occur on the same calendar day.

[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 (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.

Table 1: Schedule of Activities

[c] Survival Follow-up conducted by telephone call.
[d] In order to minimize needle sticks to the participant, the predose sample may be drawn through the venous access created for the dose infusion, prior to administration of study intervention. The postdose blood samples will be drawn from the participant's opposite, noninfused arm.
[e] Only for patients with initiations or dose modifications of select classes of eGFR-modifying drugs at any point post-baseline (Section 10.2).
Abbreviations: ADA = antidrug antibody; AE = adverse event; CPB = cardiopulmonary bypass; CRF = case report form; CT = computerized tomography; d = day; ED = early discontinuation; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life Group's 5-dimension 5-level; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = follicle-stimulating hormone; ICU = intensive care unit; KDQOL-36 = Kidney Disease Quality of Life instrument -36 items; KRT = kidney replacement therapy; PD = pharmacodynamic(s); PK = pharmacokinetic(s); pRBC = packed red blood cells; QoL = quality of life; sCr = serum creatinine; sCysC = serum Cystatin C; RBC = red blood cells; STS = Society of Thoracic Surgeons; WOCBP = woman of childbearing potential

2. INTRODUCTION

Ravulizumab (ULTOMIRIS®; ALXN1210) is a humanized monoclonal antibody that binds to C5 and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin complement component 5a (C5a) and the formation of the terminal complement complex via C5b. Ravulizumab is approved in multiple global regions for treatment of adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH), adults with generalized myasthenia gravis (gMG), and adult and pediatric patients with atypical hemolytic uremic syndrome (aHUS).

2.1. Study Rationale

Patients with CKD undergoing cardiac surgery with CPB are at high risk for CSA-AKI. While CSA-AKI in the broad population having cardiac surgery with CPB occurs in 20% to 25% of patients (Corredor, 2016; Hu, 2016), this risk increases to 60% to 80% in a population with CKD (calculated from [Priyanka, 2021]). Moreover, the risk of MAKE is 20% to 30% in the CKD population (Section 9.2). Inhibiting terminal complement from injuring the kidney and vasculature may reduce the incidence, severity, and duration of post-operative CSA-AKI and reduce MAKE, improving long-term survival and freedom from KRT, and reducing progression of CKD. Preclinical and clinical evidence suggest that early initiation of C5 inhibition, especially before onset of ischemia, will confer the greatest benefit in these outcomes.

2.2. Background

2.2.1. Unmet Medical Need

The presence of CKD in patients undergoing cardiac surgery with CPB confers high risk for poor outcomes, and post-operative acute kidney injury (AKI) further enhances these risks (Meersch, 2016; Mehta, 2006; Nashef, 2012; Thakar, 2005a). AKI after CPB is characterized by an abrupt deterioration in the kidney's excretory function following cardiac surgery, typically manifesting as an increase in serum creatinine and a reduction in glomerular filtration rate (GFR).

AKI after CPB is associated with in-hospital mortality, need for KRT, permanent loss of kidney function (risking progression of CKD, including to end-stage kidney disease), high resource utilization, and poor long-term survival (Chawla, 2011; Chawla, 2014; Coca, 2009; Dasta, 2008; Ishani, 2009; Mangano, 1998; Thakar, 2009). One large meta-analysis showed that in-hospital mortality rates after cardiac surgery for patients without AKI compared to patients with AKI were 1.7% and 10.7%, respectively. The long-term (1 to 5 years) mortality rates were 11.9% and 30%, respectively (Hu, 2016). SKD after AKI increases short-and long-term mortality risk by multifold compared to transient AKI or no AKI (Brown, 2010; Corredor, 2016; Swaminathan, 2010), and increases risk of new onset CKD or accelerates progression of pre-existing CKD (Brown, 2010; Corredor, 2016; Swaminathan, 2010). The risk of developing end-stage kidney disease after AKI is substantially greater in patients with pre-existing CKD (Chawla, 2011; Chawla, 2014; Kellum, 2021).

The need for KRT due to AKI after CPB occurs in about 2% of patients undergoing cardiac surgery (Hu, 2016) but appears to be increased in those with underlying CKD, 13.3% in severe

CKD (Chawla, 2012; Mehta, 2006; Thakar, 2005a). The in-hospital mortality is extraordinarily high, 33% to > 50% (Chawla, 2012; Dasta, 2008; Landoni, 2006; Thakar, 2005b). Multiple treatment approaches have failed to demonstrate a reduction in AKI or clinical outcomes related to AKI after CPB, ie, SKD at risk of progressive CKD, need for KRT, and mortality (Schurle, 2021). There remains a high unmet medical need to develop treatments that reduce the risk of AKI and its consequences in patients with CKD undergoing cardiac surgery with CPB.

Pre-operative ravulizumab treatment of patients with CKD is intended to inhibit the participation of terminal complement in tissue injury prior to exposure to inciting events such as kidney ischemia due to hypoperfusion, atheroemboli, extracorporeal circuit exposure, and kidney and systemic ischemia/reperfusion injury (IRI) at the end of CPB (Chew, 2019; Cosio, 1985; McCullough, 2013; Wang, 2017). Terminal complement inhibition prevented or reduced the severity of tissue injury associated with ischemic AKI and IRI in multiple animal models (De Vries, 2003; Yu, 2016; Zilberman-Itskovich, 2019). Terminal complement inhibition has been shown to be protective when initiated prior to IRI onset by reducing delayed graft function (DGF; post-transplant AKI requiring KRT within 7 days) in patients with aHUS receiving kidney transplants (relative risk reduction [RRR] up to 83%) (Siedlecki, 2018). A post-hoc analysis of a DGF study excluding aHUS was conducted comparing occurrence of DGF between eculizumab and placebo by subgroups of short versus long cold ischemia times and donor types (standard versus expanded criteria donor [ECD]). Eculizumab significantly reduced incidence of DGF in those with cold ischemia times < 12 hours (RRR 52.4%) when compared to placebo, with an even greater significant reduction in DGF in ECD patients with cold ischemia times < 12 hours (RRR 79.5%). This implies treatment initiation closer to onset of ischemia was more effective, especially in patients receiving kidneys from ECDs which are directionally similar to the target population for this study (in that the donors have CKD and/or older age, etc) (data on file at Alexion). Additionally, the safety of pre-operative terminal complement inhibition (pexelizumab) in CABG patients was established in 2 Phase 3 studies (N = 7353), and promising trends in reduced mortality have been reported in the first study (PRIMO-CABG I) (Haverich, 2006; Smith, 2006; Verrier, 2004) that were not entirely confirmed in the follow-up study (PRIMO-CABG II) (Smith, 2011).

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks of ravulizumab is provided in the Investigator's Brochure (IB).

2.3.1. Risk Assessment

The safety profile for ravulizumab is well established in adults who have been treated in clinical studies for PNH and aHUS (refer to Ravulizumab IB). Ravulizumab has been well tolerated and no unexpected safety concerns have been identified based on all currently available data from clinical development programs as well as post-marketing experience. Ravulizumab functions by blocking terminal complement; therefore, participants have increased susceptibility to serious infections, in particular, *Neisseria meningitidi*s (refer to Ravulizumab IB). Specific risk mitigation measures available to support the safe use of ravulizumab in participants in this study are described in Table 2.

As with any therapeutic protein, administration of ravulizumab may lead to the development of antidrug antibodies (ADAs). Monitoring of immunogenicity is planned during this study, as described in Section 8.13. Intravenous (IV) administration of any study intervention may result in infusion-related reactions. Management of potential infusion-related reactions is described in Section 10.4.

Table 2: Ravulizumab Important Identified and Potential Risks

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Important identified risk		
Meningococcal infection	C5 inhibition is known to increase the susceptibility to infections caused by *N meningitidis*.	Participants must be vaccinated against all available serotypes of *N meningitidis* (A, C, Y, W 135, and, where available, B) per the exclusion criteria and SoA (Section 1.3). If study intervention administration occurs < 14 days after initial vaccination, participants should be administered prophylactic antibiotics for meningococcal infection beginning on day of study drug infusion through 14 days after vaccination (Section 8.1.4). Hospitalized participants may be vaccinated after study intervention administration but prior to hospital discharge. These participants will receive prophylactic treatment with appropriate antibiotics from the day of study drug dosing for at least 14 days after vaccination. Each participant will be provided with a Participant Safety Card with signs and symptoms of meningococcal infection, instructions on when to contact a healthcare provider, and relevant contact information. The Participant Safety Card will be reviewed at each visit (SoA, Section 1.3).
Important potential risk		
Serious infection	Apart from the predictable risk of infection with *Neisseria* species, which is well-known and directly related to the mechanism of action of ravulizumab, the mechanism that may lead to other serious infections in patients treated with ravulizumab remains unclear.	Increased awareness of healthcare professionals and participants about the potential risk of serious infection. Monitoring for signs and symptoms of serious infections will be conducted as part of the safety assessments for this study.

Table 2: Ravulizumab Important Identified and Potential Risks

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immunogenicity	Treatment with any therapeutic protein has the potential to induce an immune response. Potential clinical consequences may include severe hypersensitivity type reactions, decrease in efficacy. Intravenous administration has the potential risk of causing local (infusion site) and systemic (infusion-related) reactions. Only 2 treatment-emergent ADA patients have been identified across all clinical studies across all indications tested to date. There was no association of impact of immunogenicity on PK, safety or efficacy in either of these patients.	Stop infusion in the event of any drug-related severe AEs like systemic hypersensitivity or anaphylaxis. Monitoring for hypersensitivity and serious infusion-related reactions will be conducted as part of routine safety assessments for this study (Section 10.4).
Pregnancy exposure/lactation	No studies of ravulizumab have been conducted in pregnant or breastfeeding women. There are no data available on excretion of ravulizumab in breast milk.	Pregnant or nursing female participants will be excluded from the clinical study. Participants enrolled in the study, and their spouses/partners, must use a highly effective or acceptable method of contraception during treatment and for a period of 8 months following the final dose of ravulizumab. Breastfeeding should be discontinued during treatment and for up to 8 months after treatment with ravulizumab (Section 10.6).

Abbreviations: ADA = antidrug antibody; AE = adverse event; C5 = complement component 5; PK = pharmacokinetic(s); SoA = Schedule of Activities

2.3.1.1. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic was active in many countries at the time of the original protocol. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19 (Section 10.9) and vaccination against the disease (Section 10.10).

2.3.2. Benefit Assessment

Although the efficacy of ravulizumab has not been previously studied in this population, it represents an appropriate candidate for investigation due to its plausible mechanism of action and reliable pharmacokinetic (PK) and pharmacodynamic (PD) properties.

2.3.3. Overall Benefit: Risk Conclusion

Considering the established safety profile for ravulizumab and the measures taken to minimize risk to participants in this study, the potential risks identified in association with ravulizumab are justified by the anticipated benefits that may be provided to participants with CKD at high risk for kidney events who are undergoing cardiac surgery with CPB.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives and endpoints/estimands are mapped in Table 3. Definitions of endpoints are provided in Table 4.

Table 3: Mapping Objectives to Estimands/Endpoints

Objectives	Endpoints and/or Estimands
Primary	
To assess the efficacy of ravulizumab in reducing risk of MAKE90 following CPB	**Primary Estimand:** • Treatment: Ravulizumab or placebo • Population: Adult participants with CKD as defined by the inclusion and exclusion criteria • Endpoint/Variables: MAKE90, defined as meeting at least 1 of the following criteria: o Decrease from baseline in eGFR (CKD-EPI formula using sCysC) of ≥ 25% at Day 90 post CPB, or o Initiation of KRT through Day 90 post CPB, or o Death from any cause through Day 90 post CPB • IEs: o IE1: Iodinated contrast dye exposure after treatment is administered through Day 90 post CPB o IE2: Surgery was performed without CPB or surgery with CPB was not performed within 15 days after treatment administration o IE3: Use of confounding interventions prior to surgery (Section 6.5.3) or use of disallowed interventions after treatment is administered through Day 90 post CPB (Section 6.5.2) Treatment policy strategy: The collected endpoint will be analyzed irrespective of IEs. • Summary measures: Difference between treatment groups in proportion of participants experiencing MAKE at 90 days post CPB, regardless of any IEs
Key Secondary Efficacy	
To assess the efficacy of ravulizumab in reducing 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

Table 3: Mapping Objectives to Estimands/Endpoints

Objectives	Endpoints and/or Estimands
	5) All-cause mortality from randomization to Day 90 post CPB
	6) Length of post-operative ICU stay
Other Secondary Efficacy	
To assess the efficacy of ravulizumab in reducing risk of MAKE (based on sCysC), MAKE (based on sCr), AKI (based on sCr), and related outcomes following CPB	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)
	Highest CSA-AKI stage within 3 and 7 days post CPB
	Occurrence of CSA-AKI without recovery at Day 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 Day 30 and Day 90 post CPB
	Hospital readmission rate (all-cause or AKI-related) through Day 30 and Day 90 post CPB
	Days on KRT through Day 30 and Day 90 post CPB
Health-related QoL	
To assess the effect of ravulizumab on quality of life 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

Table 3: Mapping Objectives to Estimands/Endpoints

Objectives	Endpoints and/or Estimands
	Change from baseline in FACIT-Fatigue at Days 30, 60, and 90 post CPB
PK and PD	
To evaluate 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 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	
To evaluate the immunogenicity of ravulizumab IV in participants with CKD undergoing non-emergent CPB	ADA status, 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 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)

Abbreviations: ADA = antidrug antibody; AKI = acute kidney injury; C5 = complement component 5; C5b-9 = terminal complement complex (membrane attack complex); CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CPB = cardiopulmonary bypass; CSA-AKI = cardiac surgery-associated acute kidney injury; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life Group's 5-dimension 5-level (questionnaire); FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue (questionnaire); ICU = intensive care unit; IE = intercurrent event; 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; MAKE = major adverse kidney event; MAKE90 = major adverse kidney event at Day 90 post cardiopulmonary bypass; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QoL = quality of life; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; sCr = serum creatinine; sCysC = serum Cystatin C; STS = Society of Thoracic Surgeons; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TM = thrombomodulin

Table 4: Endpoint Definitions

Endpoint(s)	Definition
MAKEXX (sCysC-based), MAKEXX (sCr-based) (XX = 30, 60, or 90)	Meets at least 1 of the following criteria: • Decrease from baseline in eGFR of ≥ 25% at Day XX determined by the CKD-EPI formula using sCysC (for sCysC-based MAKEXX) or the CKD-EPI formula using sCr (for sCr-based MAKEXX) • Initiation of KRT through Day XX • Death from any cause through Day XX
AKI (sCr-based), AKI (sCysC-based)	Meets either of the following modified KDIGO criteria: • Increase in sCr (for sCr-based AKI) or sCysC (for sCysC-based AKI) by ≥ 0.3 mg/dL during any 48-hour interval • Increase in sCr or sCysC to ≥ 1.5 × baseline within 3 and 7 days, or at Day 15, 30, 60, or 90 post CPB
CSA-AKI (sCr-based), CSA-AKI (sCysC-based)	Occurrence of AKI from randomization to Day 7 post CPB
AKI Stage (KDIGO criteria; sCr-based)	Meets modified KDIGO criteria for Stage 1, 2 or 3 as outlined in Table 5
Occurrence of CSA-AKI without recovery (sCr-based) at Day XX post CPB (XX = 15, 30, 60, or 90)	Meets both of the following criteria: • Experiencing CSA-AKI based on highest observed sCr from randomization to Day 7 post CPB (Occurrence of CSA-AKI) • Occurrence of non-recovered (complete or partial) CSA-AKI at Day XX
Occurrence of severe CSA-AKI (KDIGO criteria; sCr-based)	Meets modified KDIGO criteria for Stage 2 or 3 CSA-AKI as outlined in Table 5, based on highest observed sCr from randomization to Day 7 post CPB
Occurrence of severe AKI (KDIGO criteria; sCr-based) from randomization to Day 30 post CPB	Meets modified KDIGO criteria for Stage 2 or 3 AKI as outlined in Table 5, based on highest observed sCr (confirmed by at least 1 additional measurement) from randomization to Day 30 post CPB
Occurrence of post-operative Renal Failure (STS metric based on RIFLE Failure creatinine criteria)	Meets modified RIFLE criteria for Failure as outlined in Table 6, based on highest observed sCr (confirmed by at least 1 additional measurement) or initiation of KRT from time of surgery until the latter of hospital discharge or 30 days post CPB
Occurrence of AKI (sCr-based) at Day XX post CPB (XX = 3, 7, 15, 30, 60, or 90)	sCr > 1.5 × baseline at Day XX post CPB

Table 4: Endpoint Definitions

Endpoint(s)	Definition
AKI recovery (sCr-based)	Complete: • sCr < 1.1 × baseline Partial: • sCr ≥ 1.1 - < 1.5 × baseline
AKI improvement (sCr-based)	• Move down 1 or more stages from highest CSA-AKI (except Stage 0) as outline in Table 7, 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 highest CSA-AKI stage, or • Remain in Stage 3 but initiate KRT

Abbreviations: AKI = acute kidney injury; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CPAP = continuous positive airway pressure; CPB = cardiopulmonary bypass; CSA-AKI = cardiac surgery-associated acute kidney injury; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; KDIGO = Kidney Disease: Improving Global Outcomes (nonprofit foundation); KRT = kidney replacement therapy; MAKE = major adverse kidney event; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; sCr = serum creatinine; sCysC = serum Cystatin C; STS = Society of Thoracic Surgeons

3.1. 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 regardless of any intercurrent events (IEs). The estimand is intended to provide a population level estimate of the treatment effect on a binary endpoint major adverse kidney event at Day 90 post cardiopulmonary bypass (MAKE90), amongst CKD patients 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: MAKE at Day 90 post CPB (MAKE90)
- 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 (Section 6.5.3) or use of disallowed interventions after treatment is administered through Day 90 post CPB (Section 6.5.2)

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

- Summary measures: Difference between treatment groups in proportion of participants experiencing MAKE at 90 days post CPB regardless of any IEs

3.2. Secondary Estimands

The key secondary estimands are intended to provide a population level estimate of the treatment effect, regardless of any IEs. The estimands for each key secondary will target the same estimand as for primary endpoint as follows:

- Treatment: Ravulizumab or placebo
- Population: Adult participants with CKD as defined by the inclusion and exclusion criteria
- Variable:
    - Occurrence of CSA-AKI without recovery at Day 90 post CPB
    - Occurrence of severe CSA-AKI (Kidney Disease: Improving Global Outcomes (nonprofit foundation) [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 intensive care unit (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 (Section 6.5.3) or use of disallowed interventions after treatment is administered through Day 90 post CPB (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.

Details of other secondary estimands will be included in the statistical analysis plan (SAP).

4. STUDY DESIGN

4.1. Overall 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 CABG, valve replacement or repair, or combined procedure, to reduce the risk of post-operative kidney events and subsequent MAKE at 90 days after surgery. Participants considered at risk for kidney events after CPB have eGFR $\geq$ 20 to $<$ 60 mL/min/1.73 m^2 with predicted Renal Failure Risk of $\geq$ 2.8% using the STS Adult Cardiac Surgery Risk Models (STS Calculator).

The baseline eGFR (and subsequently at Days 30, 60, and 90) will be determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum Cystatin C (sCysC). Additionally, the minimum Renal Failure Risk Score (generated by the STS Calculator) will ensure that patients are enrolled who are at risk for post-operative kidney events. Participants eligible for inclusion are detailed in Section 5. All participants will receive standard of care in addition to study intervention.

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, 4) and surgery type (mitral valve replacement or combined procedures vs other single procedure).

Screening and Randomization or Randomization and Surgery may occur on the same calendar day due to surgical urgency or scheduling challenges. Screening and Randomization and Surgery (ie, all 3 visits) may not occur on the same calendar day. 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. The total study duration is approximately 400 days, including the Survival Follow-up Visit.

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 the first interim analysis, and assessing futility, early stop for efficacy, and sample size re-estimation in the second interim analysis.

An independent 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.

4.2. Scientific Rationale for Study Design

The primary objective of this study is to assess the efficacy and safety of a single dose of ravulizumab IV in reducing the risk of the clinical consequences of AKI (MAKE) in adult participants with CKD who undergo non-emergent cardiac surgery with CPB. A randomized, placebo-controlled, double-blind study design is employed to minimize bias and to balance the effect of confounding factors in this complex and highly comorbid population. Placebo has been chosen as the comparator because there are no approved therapies that reduce the risk of poor clinical outcomes after cardiac surgery with CPB (ie, SKD, need for KRT, or mortality).

Some patients with CKD who have higher baseline GFR may be more likely to avoid developing AKI or may experience mild and transient AKI that ultimately does not result in MAKE. As such, this study focuses on the patient population with highest risk of kidney events (eGFR < 60 mL/min/1.73m^2). To ensure this study addresses the high unmet need in CKD patients undergoing CPB at risk for kidney events, a minimum risk score is required for severe AKI (based on RIFLE criteria for Failure) of $\geq 2.8\%$ as predicted by the STS risk calculator.

The risk models were developed from the STS Adult Cardiac Surgery Database (O'Brien, 2018), a large clinical outcomes registry for adult cardiac surgery. Launched in 1989, the Database contains more than 6.3 million cardiac surgery procedure records that includes 95% of all US surgeries as well as a smaller number of cases (Badhwar, 2018) occurring outside the US. Risk models are used for multiple purposes in adult cardiac surgery including quality measurement, to enable case-mix adjustment in the calculation of surgeon composite performance measures, clinical practice improvement, voluntary public reporting, and research (O'Brien, 2018). The STS "renal failure" score predicts AKI using at least 1 of the following: a) increase of serum creatinine (sCr) to ≥ 4.0 mg/dL with an increase of at least 0.5 mg/dL; or b) 3 × most recent pre-operative creatinine level; or c) a new requirement for dialysis post-operatively (STS online calculator), based on RIFLE criteria for Failure (Table 6) (Bellomo, 2004).

The robust predictiveness of the STS renal failure risk score for observed outcomes in the US population is well established (C-statistics 0.76 to 0.83 depending on surgery type) (O'Brien, 2018) and is maintained by quarterly re-calculation of annualized calibration factors to allow comparison of outcomes to contemporaneous data (Jin, 2022; O'Brien, 2018; Shahian, 2018). When applied to ex-US populations, the STS risk scores are predictive of mortality and kidney failure (Barili, 2013; Borde, 2013; Bouabdallaoui, 2018; Chang, 2016; Ikeoka, 2014; Rabbani, 2014; Singh, 2021; Wang, 2015) though most studies were conducted with older versions of the model. When observed outcomes differ from predicted, there are usually more observed events than predicted, rather than less (Borde, 2013; Bouabdallaoui, 2018; Rabbani, 2014; Wang, 2015). Permissive under-estimation of AKI risk by the calculator remains consistent with the objective of enrolling participants at high AKI risk. Alexion is unaware of a similarly robust and validated AKI risk predictor in a global population.

A single pre-operative weight-based dose of ravulizumab, given up to 7 days prior to surgery with CPB, will provide at least 18 days of complete C5 inhibition (Section 4.3). The dosing window prior to surgery provides logistical flexibility to the participant and Investigators, allowing for outpatient administration, and importantly will ensure extravascular C5 has been sequestered prior to the ischemic insult to the kidney. The complete inhibition of C5 prevents terminal complement activation from early hypoxic injury at the initiation of the procedure,

through the CPB time typically of 1 to 3 hours (Salis, 2008), ending with risk of IRI upon restoration of normal systemic perfusion. However, a second wave of complement activation may occur during post-operative inflammation response that peaks around post-operative Days 2 to 3 (Bruins, 1997). Therefore, in the event of unexpected delays (eg, a participant scheduled for elective surgery is bumped from the operating schedule due to an emergency case) the CPB procedure should occur no later than 15 days after study intervention administration to ensure complete C5 inhibition during exposure to the CPB procedure and the 3-day post-operative period characterized by heightened inflammatory response. Given the expected minimum period of complete C5 inhibition, cardiac surgeries delayed > 15 days after study intervention administration are considered IEs for the primary estimand analysis (see Table 3) and are not included in the modified Intent-to-Treat (mITT) Analysis Set definition (Section 9.3). Additionally, for cardiac surgeries delayed > 15 days after study intervention administration, Investigators will determine timing of Primary Evaluation Period visits based on Day1 (day of dosing) instead of the CPB procedure.

The primary outcome measure (MAKE) was conceived to capture the clinical outcomes after AKI and is defined as mortality, need for KRT, and SKD defined as estimated eGFR > 25% below baseline by the CKD-EPI formula (Billings, 2014; Haverich, 2006; Levey, 2009; Palevsky, 2012). SKD occurs due to AKI non-recovery, and at 90 days represents a sustained worsening of CKD. SKD is associated with multifold higher risk for long-term mortality and progression to end-stage kidney disease (ESKD) when compared to those who were AKI free, or who recovered from AKI (Cho, 2021; Ishani, 2009; Wu, 2011).

Skeletal muscle atrophy is widely recognized as a complication after cardiac surgery (van Venrooij, 2012) and can confound sCr-based assessment of eGFR. As recommended for such circumstances in the KDIGO guidelines (KDIGO, 2013), sCysC will be used for calculating SKD in the MAKE endpoint. Data from observational and randomized controlled interventional studies reporting AKI and MAKE outcomes after CPB were used to inform the MAKE 90 placebo rate assumption of 25% (Section 9.2).

The occurrence of post-operative CSA-AKI is defined as the presence of 1 of the following observations during the 7 days after surgery with CPB, based on modified KDIGO criteria:

- An increase in sCr by ≥ 0.3 mg/dL in a 48-hour period
- An increase in sCr to ≥ 1.5 times baseline within the 7 days following CPB

The highest AKI stage by modified KDIGO criteria that occurs within 3 and 7 days after surgery with CPB will be determined, as defined in Table 5. Additionally, this staging will be used to assess AKI at any time within 30 days after CPB based on the highest observed sCr; and at Days 15, 30, 60 and 90 after CPB. While the KDIGO criteria is widely adopted, in some settings (eg, STS renal failure risk calculator) there is greater familiarity with the RIFLE criteria (O'Brien, 2018). Therefore, AKI staging based on the modified RIFLE criteria will be assessed for AKI at any time within 30 days after CPB based on the highest observed sCr, and the staging criteria are outlined in Table 6. In the setting of AKI, reliable interpretation of changes in sCysC will be exploratory in this study as it is yet to be defined and is not commonly used to define or stage AKI at this time.

Table 5: 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 - < 2.0 × baseline
2	An increase in sCr to ≥ 2.0 - < 3.0 × baseline
3	An increase in sCr to ≥ 3.0 × baseline, or An increase in sCr to ≥ 4.0 mg/dL in patients meeting AKI criteria, 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 initiation of KRT.
Abbreviations: AKI = acute kidney injury; KDIGO = Kidney Disease: Improving Global Outcomes (nonprofit foundation); KRT = kidney replacement therapy; sCr = serum creatinine
Source: Adapted from (Khwaja, 2012)

Table 6: AKI Staging by Modified RIFLE Criteria

AKI Stage	Definition
Risk	An increase in sCr to ≥ 1.5 - < 2.0 × baseline
Injury	An increase in sCr to ≥ 2.0 - < 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 at least 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 initiation of KRT.
Abbreviations: AKI = acute kidney injury; KRT = kidney replacement therapy; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; sCr = serum creatinine
Source: Adapted from (Bellomo, 2004)

Changes in the post-AKI progression (based on sCr or need for KRT) relative to the highest CSA-AKI stage observed in the first 7 days following CPB will be assessed on Day 15 through Day 90 post CPB to characterize AKI progression (recovery, improvement, stable, or worsening). Stages of post-AKI progression are defined in Table 7.

Table 7: Stages of Post-CSA-AKI Kidney Function to Determine AKI Progression on Day 15 to Day 90 after Surgery

Post-AKI Stage	Definition
0	Complete recovery: sCr < 1.1 × baseline Partial recovery: sCr ≥ 1.1 - < 1.5 × baseline
1	sCr ≥1.5 - < 2.0 × baseline
2	sCr ≥2.0 - < 3.0 × baseline

Table 7: Stages of Post-CSA-AKI Kidney Function to Determine AKI Progression on Day 15 to Day 90 after Surgery

Post-AKI Stage	Definition
3	sCr ≥ 3.0 × baseline, or sCr ≥ 4.0 mg/dL in patients meeting CSA-AKI criteria, or KRT

Abbreviations: AKI = acute kidney injury; CSA-AKI = cardiac surgery-associated acute kidney injury; KRT = kidney replacement therapy; sCr = serum creatinine
Source: Adapted from (Chawla, 2017)

There are uncertainties in the underlying assumptions about the rate of MAKE in this high-risk population, as well as in the treatment effect assumption. Therefore, 2 interim analyses of this study will be conducted to determine futility, assessing early efficacy, and to evaluate the need for sample size re-estimation as described in Section 9.5.

The safety outcomes being evaluated are commonly used in clinical studies per the ICH and GCP guidelines.

4.2.1. Participant Input into Design

Not applicable.

4.3. Justification for Dose

The dose in this study will be identical to the weight-based ravulizumab maintenance dose approved for adults with aHUS, PNH or gMG and for which safety has been established.

This dose will ensure that ravulizumab serum concentration will be ≥ 175 µg/mL to achieve complete terminal complement inhibition, while maintaining maximum ravulizumab serum concentration below the highest observed value of 3000 µg/mL from all completed clinical studies, for at least 18 days in the target patient population. The 175 µg/mL threshold was previously identified as the therapeutic minimum concentration of ravulizumab required to achieve complete terminal complement inhibition.

To support this dose regimen, model-based simulations were conducted. Briefly, the population PK model used for the simulation was based on patients with aHUS together with the information of blood transfusion on ravulizumab clearance derived from patients in the 2 studies of hematopoietic stem cell transplantation–associated thrombotic microangiopathy. Factors that could potentially impact ravulizumab PK in the target patient population were integrated in the model simulation, and included impact of proteinuria, red blood cell transfusion, and post-operative hemodilution.

Other nonquantifiable factors, such as drug loss or activated complement pathway by CPB, were not included in the simulation. As such, a dose that can achieve higher than 175 µg/mL ravulizumab concentration for at least 18 days is desirable in the setting of CSA-AKI and predicted with our proposed single ravulizumab weight-based doses.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed the Primary Evaluation Period.

The end of the study is defined as the date the last participant completes the last Survival Follow-up Visit as indicated in the Schedule of Activities (SoA) (Section 1.3).

5. STUDY POPULATION

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

To be eligible to participate in the study, participants must meet all of the following criteria:

Age

1. ≥ 18 to ≤ 90 years of age at the time of signing the informed consent.

Sex

2. Male or female.
   - Female participants of childbearing potential and male participants must follow protocol-specified contraception guidance (Section 10.6).

Weight

3. Body weight ≥ 30 kg at Screening.

Disease Characteristics

4. Planned non-emergent cardiac surgery requiring CPB for the following procedures (Section 8.1.2):
   - Multi-vessel CABG
   - Valve replacement or repair; ascending aorta surgery permitted if combined with aortic valve replacement/repair
   - Combined CABG and valve surgery; inclusion of single-vessel CABG when combined with valve replacement/repair is permitted
   - Note: surgery should be scheduled to occur within 35 days after Screening (up to 28-day Screening Period with randomization and dosing within 7 days prior to CPB).
5. 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 (see Section 8.1.2.1).
6. At risk for postsurgical kidney events as defined by a minimum STS Calculator Renal Failure Risk Score of ≥ 2.8% assessed at time of Screening.

Informed Consent

7. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Emergency or salvage cardiac surgery is expected at Screening or randomization, as assessed by the Investigator (see Section 8.1.2.3).
2. Single-vessel CABG without valve surgery is planned.
3. Off-pump surgery is planned (eg, surgery without CPB).
4. Any use of KRT or presence of AKI within 30 days prior to randomization (AKI defined as 1.5× increase in sCr over baseline), except transient (≤ 5 days) Stage 1 AKI after iodinated contrast exposure. Presence of AKI must be assessed within 72 hours prior to randomization.
5. Recipient of a solid organ or bone marrow transplantation.
6. Cardiogenic shock or hemodynamic instability, including use of intra-aortic balloon pump (IABP) or other temporary cardiac output support device (see Section 8.1.2.3), extracorporeal membrane oxygenation (ECMO), or left ventricular assist device within 72 hours prior to randomization.
7. Active systemic bacterial, viral, or fungal infection within 14 days prior to randomization.
8. Participants with history of human immunodeficiency virus (HIV) who are not on anti-retroviral therapy or if on therapy have a known detectable viral load within 1 year prior to Screening.
9. Congenital immunodeficiency.
10. History of unexplained, recurrent infection.
11. Known medical or psychological condition(s), including substance abuse, or risk factor that, in the opinion of the Investigator, might interfere with the participant's full participation in the study, pose any additional risk for the participant, or confound the assessment of the participant or outcome of the study.
12. History of, or unresolved, *N meningitidis* infection.
13. Hypersensitivity to any ingredient contained in the study intervention, including hypersensitivity to murine proteins.
14. Current malignancy (excluding local or regional prostate cancer or non-melanoma skin cancer, or indolent disease not being treated) or receiving treatment for malignancy.

Prior/Concomitant Therapy

15. Use of any complement inhibitors, or plasmapheresis or plasma exchange within the year prior to Screening, or planned use during the course of the study.
16. Use of IVIg (eg, as acute therapy) within 4 weeks prior to dosing.
17. Planned use of any pharmacologic agent specifically for prevention or treatment of AKI.

18. Anticipated use of KRT, extracorporeal membrane oxygenation, or temporary cardiac support devices including left ventricular assist device (see Section 8.1.2.3) between randomization and surgery. Elective or pre-emptive insertion of temporary cardiac support devices (including IABP) is acceptable in the absence of cardiogenic shock or hemodynamic instability.

Prior/Concurrent Clinical Study Experience

19. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study intervention on Day 1 in this study or within 5 half-lives of that investigational product (IP), whichever is greater, or planned participation/use during the course of the study.

Other Exclusions

20. Presence of a do-not-resuscitate order or life expectancy of < 3 months.
21. Pregnant, breastfeeding, or intending to conceive within 8 months after the dose of study intervention.
22. Participant is not willing to be vaccinated against *N meningitidis* or is unwilling to receive prophylactic treatment with appropriate antibiotics, if needed, as described in Section 8.1.4.

5.3. Lifestyle Considerations

There are no lifestyle restrictions for this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any adverse events (AEs), including any serious adverse events (SAEs) and any related concomitant medication, occurring during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor. Participants who are rescreened outside of the Screening window (Section 1.3) are required to sign a new ICF (Section 10.1.3).

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Participants will be randomized to either ravulizumab or placebo.

Ravulizumab is formulated at pH 7.0 and is supplied in 30 mL single-use vials. Each vial of ravulizumab contains 300 mg of ravulizumab (10 mg/mL) in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80, and water for injection. The comparator product (placebo) is formulated as a matching sterile solution with the same buffer components, but without active ingredient. Additional details are presented in Table 8.

Table 8: Study Interventions

Study intervention name	Ravulizumab	Placebo
Dose formulation	Vial	Vial
Physical description	Liquid solution practically free from particles	Liquid solution practically free from particles
Unit dose strength(s)	300 mg (10 mg/mL concentrated solution)	Placebo
Route of administration	IV infusion	IV infusion
Use	Experimental	Placebo comparator

Abbreviation: IV = intravenous

Participants randomized to the ravulizumab group will receive a single weight-based dose of ravulizumab within 7 days prior to CPB procedure. Infusion is required to be completed at least 1 hour prior to surgery start (ie, induction of anesthesia). The dose will be identical to the weight-based ravulizumab maintenance dose approved for adult patients with aHUS, PNH, or gMG (Table 9).

Table 9: Weight-based Single Dose of Ravulizumab or Placebo

Body Weight	**Dose**
≥ 30 to < 40 kg	2700 mg
≥ 40 to < 60 kg	3000 mg
≥ 60 to < 100 kg	3300 mg
≥ 100 kg	3600 mg

6.1.1. Study Intervention(s) Packaging and Labeling

At a minimum, study intervention will be labeled with:

- The protocol number

- Lot number/expiry date
- Alexion name and address
- Instructions for use and storage

The study intervention will be labeled according to the country's regulatory requirements.

6.1.2. Preparation/Handling/Storage/Accountability

Upon arrival of the study intervention at the study site, the study intervention kits should be removed from the shipping container and stored in their original cartons under refrigerated conditions at 2°C to 8°C (36°F to 46°F) and protected from light. Study intervention should not be frozen. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention. Study intervention must be stored in a secure, limited-access storage area with temperature monitored daily.

Infusions of study intervention should be prepared using aseptic technique. Ravulizumab and placebo will be further diluted in a 1:1 ratio with compatible diluent. Ravulizumab and placebo will be administered with a 0.2 micron filter during infusion.

- Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
  - This responsibility includes the reporting of any temperature excursions and product complaints to AlexionIMPTE@alexion.com and productcomplaints@alexion.com within 1 business day of awareness. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.
  - The pharmacist or other designated individual will maintain records of study intervention delivered to the study site, the inventory at the study site, the distribution to and use by each patient, and the return of materials to the sponsor for storage or disposal/destruction of materials at the study site. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the study intervention and study participants.
  - Investigators will maintain records that adequately document that the participants were administered the correct study treatment kits and reconcile the products

received from the drug dispensing center. IP will not be returned to the sponsor or disposed of until accountability has been fully monitored.

- Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused study intervention is provided in the Pharmacy Manual.

6.2. Standard of Care

In this study, participants in both treatment groups will receive standard of care as concomitant therapy, which will be determined by the Investigator according to institutional practices and participant characteristics, unless prohibited in Section 6.5.2.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Eligible participants will be randomized either to the ravulizumab group or to the placebo group under a 1:1 allocation ratio. Randomization will be performed centrally using Interactive Response Technology (IRT) and the block randomization method.

To balance the effects of potential confounding factors between the ravulizumab and placebo arms, randomization will be stratified by baseline CKD stage (3A, 3B, 4) assessed during Screening based on CKD-EPI using sCr or sCysC (local or central laboratory result), and surgical type (mitral valve replacement or combined procedures vs other single procedure) (Table 10).

Table 10: Randomization Stratification Factors

Stratification Factor	Randomization Strata	Definition
Baseline CKD Stage[a]	Stage 3A	$45 \leq$ eGFR < 60 mL/min/1.73 m^2
	Stage 3B	$30 \leq$ eGFR < 45 mL/min/1.73 m^2
	Stage 4	$20 \leq$ eGFR < 30 mL/min/1.73 m^2
Surgical Type	Isolated Procedure	Isolated CABG (± TVr)
		Isolated Non-mitral valve repair or replacement (AVR/r, PVR/r or TVR/r)
		Isolated MVr
	Mitral Valve Replacement or Combined Procedure[b]	Isolated MVR (± other valve procedures)
		Multiple valve procedures (> 1 concomitant valve repair or replacement)
		CABG + Non-mitral value repair or replacement (± AVR/r, PVR/r and/or TVR); Note: TVr is included in isolated CABG
		CABG + MVr (± Other Valve Procedures)
		CABG + MVR (± Other Valve Procedures)

Table 10: Randomization Stratification Factors

Stratification Factor	Randomization Strata	Definition
		AVR/r + aorta procedure

[a] eGFR should be that which is used to determine and document eligibility. If it is a local laboratory value, the data must be entered into the CRFs.

[b] Other procedures completed during cardiac surgery (eg, MAZE, cryoablation, left atrial appendage removal or occlusion, septal defect closure, catheter-based valve procedures, device placement etc) are allowed but do not count towards "Combined Procedure"

Abbreviations: AV = aortic valve; CABG = coronary artery bypass graft; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate (mL/min/1.73m2); MV = mitral valve; PV = pulmonic valve; R = valve replacement; r = valve repair; TV = tricuspid valve

6.3.2. Blind

Participants, all investigative site personnel, and any Alexion employee, or designee, directly associated with the conduct of the study will be blinded to participant treatment assignment throughout the study. The blinding will be maintained by using identical study intervention kits and labels for ravulizumab and placebo. The placebo will have an identical appearance to that of ravulizumab. The randomization code will be maintained by the IRT provider.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator may, at the Investigator's discretion, contact Alexion to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, Alexion must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

When unblinding is the result of an AE which is unexpected or related and serious, the blind will be broken for that specific participant only. The blind with regard to treatment allocation for that specific participant will be maintained for all persons responsible for the ongoing conduct of the study (such as the management, monitors, Investigators, etc) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel.

Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Independent Ethics Committees (IECs), Institutional Review Boards (IRBs), and/or independent DMC.

6.4. Study Intervention Compliance

The infusion of study intervention into participants will be under the supervision of the Investigator or their designee to ensure that participants receive the appropriate dose at the appropriate time point during the study.

The date and time of dose administration will be recorded in the source documents and in the CRFs.

6.5. Concomitant Therapy

6.5.1. Allowed Medicine and Therapy

Any medication or therapy (including over-the-counter or prescription medicines, vaccines, vitamins, and/or herbal supplements) deemed necessary for the participant's care during the study, or for the treatment of any AE, along with any other medications, other than those listed as disallowed medications in Section 6.5.2, may be given at the discretion of the Investigator. It is the responsibility of the Investigator to record all medications in the participant's source documents and on the CRF (unless otherwise noted) along with:

- Reason for use
- Dates of administration, including start and end dates
- Route of administration
- Dosage information including dose and frequency (this information is required on the CRF for all concomitant eGFR-modifying drugs as specified in Section 10.2 and any meningococcal vaccines and antibacterial drugs used for prophylaxis against meningococcal infection. Dosing information for other concomitant medications or therapies will be recorded in the source documents but are not required in the CRF).
- IV crystalloid fluids do not need to be recorded in the participant's source documents or the CRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.2. Disallowed Medicine and Therapy

Participants are prohibited from receiving any of the following medications and therapies during study participation through collection of primary and key secondary endpoints (Day 90 post CPB):

- Eculizumab, ravulizumab (other than protocol-specified study intervention), or other agents that act on the complement pathway
- Plasmapheresis or plasma exchange
- Intravenous gamma globulin (IVIg)
- Use of any pharmacologic agent specifically for prevention or treatment of AKI (eg, experimental or investigational, fenoldopam, levosimendan, and nesiritide; if uncertain, discuss with Alexion); these therapies can be used for their approved indications

Use of a prohibited medication and/or therapy must be documented in the CRF.

6.5.3. Confounding Procedures Prior to Surgery

The use of KRT, extracorporeal membrane oxygenation, or left ventricular assist should be avoided after study intervention is administered and before surgery unless clinically indicated, at the discretion of the Investigator. Use of these procedures after study intervention is administered and before surgery are considered confounding procedures, as these procedures can trigger AKI

prior to the CPB or confound appropriate diagnosis and staging of AKI (eg, use of KRT). These procedures are considered standard of care during the operative and post-operative phases and are permitted.

6.6. Dose Modification

Dose modification of the study intervention for an individual participant is not permitted for this study.

6.7. Intervention after the End of the Study

Not applicable as each participant will receive only 1 dose of study intervention on Day 1.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Not applicable as each participant will receive only 1 dose of study intervention on Day 1.

7.2. Participant Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.
- The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and CRF.
- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This activity is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation (ED) Visit should be conducted, as shown in the SoA (Section 1.3). Refer to the SoA for data to be collected at the time of study discontinuation and follow-up, and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- If applicable locally, an optional item will be included in the ICF granting permission for the Investigator to continue contact with the participant and/or continue to have access to his/her medical chart after discontinuation from the study visits for the purpose of reporting any possible AE occurring within the Primary Evaluation Period and their vital and/or KRT status through 365 days.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to complete scheduled visits (site or home visits [Section 8.1.8]) and is unable to be directly or indirectly contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant to reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- All attempts to collect vital status (participant survival) and KRT status must be made, including by phone contact, or indirect ascertainment from another healthcare provider or family member, or from local death registries. If either death through Day 90 or survival status at Day 90 is confirmed, the patient will not be considered lost to follow-up.
- Should the participant continue to be unreachable, and indirect ascertainment of vital status and KRT status are unobtainable, they will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.10.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct. Details of study procedures are outlined in this section. Additional details may be found in the SoA and CRF completion guidelines.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- See Section 10.2 for the list of clinical laboratory tests.
- Repeat or unscheduled samples may be obtained for safety reasons or for technical issues with the samples.

8.1. General Assessments and Procedures

8.1.1. Informed Consent

The Investigator or qualified designee must obtain a signed and dated ICF for each participant prior to conducting any study-related procedures. The process for informed consent is outlined in Section 10.1.3. All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.

8.1.2. Inclusion/Exclusion Criteria

All inclusion (Section 5.1) and exclusion (Section 5.2) criteria must be reviewed by the Investigator or qualified designee to ensure the participant qualifies for study participation. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Eligibility for participation will be determined prior to randomization and dosing. Additional timing considerations are as follows:

- The eGFR value used to confirm eligibility (inclusion criterion [IC] #5) should also be used to select the CKD stage for stratification. The eGFR category designated for stratification must be based on sCr or sCysC laboratory results (local or central) obtained during the 28 days prior to randomization, and the results and calculation(s) used should be saved in source documentation.

- The STS Renal Failure Risk Score (IC #6) may be reassessed at the Investigator's discretion if the participant's clinical status has significantly changed since the Screening Visit.
- The absence of AKI (exclusion criterion [EC] #4) should be confirmed using laboratory results obtained within the 72 hours prior to randomization. For participants who completed the Screening Visit > 72 hours before randomization, creatinine should be repeated (local or central) within 72 hours of randomization to confirm the absence of AKI.
- For women of childbearing potential (WOCBPs), assessment of pregnancy (EC #20) must be confirmed within 72 hours prior to randomization. A negative local urine pregnancy test can be used for this purpose in the event that central laboratory results are not available at the time of randomization.
- Where a postmenopausal state is in question at time of screening (ie, the absence of 12 months of amenorrhea without an alternative medical cause), high follicle-stimulating hormone (FSH) and estradiol levels in the postmenopausal range must be used to confirm a postmenopausal state.

8.1.2.1. Guidance for the Assessment of CKD and Calculation of eGFR (Inclusion Criterion #5)

The study is intended to enroll participants with known or apparent CKD, as judged by the Investigator. Guidance is as follows:

At Screening, an eligible patient will have evidence of kidney disease, kidney injury, or dysfunction due to the qualifying eGFR ≥ 20 to < 60 mL/min/1.73m^2. To meet the KDIGO definition of CKD, evidence of kidney injury and/or dysfunction should be present for at least 90 days. The assessment of chronicity can be made utilizing the medical record (prior diagnosis at any time; laboratory results established greater than 90 days previously), or participant report (eg, told by their physician at least 90 days previously they have a kidney problem). Alternatively, the chronicity can be established through reasonable medical assessment made by the Investigator and recorded in the medical record. For example, a patient with the presence of kidney dysfunction based on screening eGFR ≥ 20 to < 60 mL/min/1.73m^2 who also demonstrates abnormal albuminuria or proteinuria at Screening and a has long-standing history of diabetes mellitus and/or hypertension would likely be presenting with CKD, and the Investigator would record this assessment in the source documentation.

For calculation of eligible eGFR, any of the CKD-EPI formulae may be used. The selection of which is at the Investigator's discretion, taking into account the local practice.

8.1.2.2. Guidance for Evaluation of AKI Risk (Inclusion Criterion #6)

The study is intended to enroll participants at increased risk of post-operative kidney events. The STS Renal Failure risk score is the tool for determining renal failure risk, and includes 4 laboratory values: creatinine, hematocrit, white blood count, and platelet count. The calculation can make use of any results obtained during the 28 days prior to randomization, including standard of care laboratory samples.

8.1.2.3. Guidance for the Evaluation of Cardiac Surgery Type (Exclusion Criteria #6 and #17)

The study is intended to enroll non-emergent cardiac surgery participants, as judged by the Investigator. Guidance is as follows:

1. Elective cardiac surgery is defined as (Bojar, 2020):
    a. The patient's cardiac function has been stable in the days or weeks prior to the operation.
    b. The procedure could be deferred without increased risk of compromised cardiac outcome.
2. Urgent cardiac surgery is defined as:
    a. Procedure is required during the same hospitalization in order to minimize chance of further clinical deterioration. This includes but is not limited to:
        i. Worsening or sudden chest pain
        ii. Heart failure, acute myocardial infarction (MI)
        iii. The underlying anatomy
        iv. Unstable angina with intravenous nitroglycerin
        v. Rest angina
    b. Any of these conditions that require that the patient remain in the hospital until surgery can take place, but the patient is able to wait for surgery until the next available operating room schedule time.
    c. Delay in the operation may be necessitated by attempts to improve the patient's condition, availability of a spouse or parent for informed consent, availability of blood products, or the availability of results of essential laboratory procedures or tests.
    d. The definition for urgent procedures includes use of IABP or other temporary cardiac support devices for management of cardiogenic shock or hemodynamic instability, but is separately excluded in this study.

Participants requiring emergent or salvage cardiac surgeries, as judged by the Investigator, will not be enrolled. Guidance is as follows:

3. Emergent cardiac surgery is defined as:

    Surgery is indicated without any delay for ongoing, refractory (difficult, complicated, and/or unmanageable) unrelenting cardiac compromise, with or without hemodynamic instability, and not responsive to any form of therapy except cardiac surgery. Examples include:

    a. Hemodynamic picture of shock that is being chemically or mechanically supported, such as IV inotrope or IABP (or other temporary mechanical circulatory support device) to maintain cardiac output
    b. Pulmonary edema requiring intubation and ventilation

c. An extending MI

d. Signs of ongoing ischemia, ie, electrocardiogram (ECG) changes

e. Acute native valve dysfunction (acute papillary muscle rupture or torn leaflet)

f. Prosthetic valve dysfunction with structural failure (valve-fractured or torn leaflet, thrombus formation, pannus development which impedes flow through the valve orifice, or valvular dehiscence)

g. Acute aortic dissection, rupture or dissection during cardiac catheterization; perforation, tamponade following cardiac catheterization

4. Salvage cardiac surgery is defined as:

   a. The patient is undergoing cardiopulmonary resuscitation (CPR) enroute to the operating room prior to anesthesia induction

   b. Has ongoing ECMO to maintain life

Additionally, emergent surgeries are excluded by the presence of cardiogenic shock, including the use of temporary mechanical circulatory support devices to provide support for this indication. A temporary or percutaneous assist device is a small mechanical pump that provides short-term support for the heart. Temporary assist devices may be catheter based or placed open and are exclusionary when inserted to offer short term invasive circulatory support during cardiogenic shock. The pre-emptive insertion of a temporary assist device in the absence of cardiogenic shock is allowed (eg, placed to prevent shock during the surgery).

8.1.3. Demographics

Demographic parameters, including age, sex, race, and ethnicity (for calculating STS risk score and eGFR) will be documented in the CRF, as allowable by local regulation.

8.1.4. Vaccination and Antibiotic Prophylaxis

Due to its mechanism of action, the use of ravulizumab increases a participant's susceptibility to meningococcal infection due to *N meningitidis*. To reduce the risk of infection, all participants must be vaccinated against *N meningitidis* within 3 years prior to study intervention administration. If the participant is not vaccinated within 3 years of study intervention administration, vaccination will occur during Screening or any time up to hospital discharge. If study intervention administration occurs < 14 days after initial vaccination, participants should be administered prophylactic antibiotics for meningococcal infection beginning on day of study drug infusion through 14 days after vaccination. Hospitalized participants may be vaccinated after study intervention administration but prior to hospital discharge. These participants will receive prophylactic treatment with appropriate antibiotics from the day of study drug dosing for at least 14 days after vaccination.

Vaccines against serotypes A, C, Y, W135, and where available serotype B (if recommended by local guidelines), are recommended in preventing the commonly pathogenic meningococcal serotypes. Participants must receive the vaccination series as indicated according to the current national vaccination guidelines. Vaccination may not be sufficient to prevent meningococcal infection.

Use of prophylactic antibacterial agents should follow official guidance and local practice. All participants should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of meningococcal infection experienced by the participants during the course of the study, participants will be provided a Participant Safety Card to carry with them at all times (Section 8.3.6). Additional discussion and explanation of the potential risks, signs, and symptoms will occur at specific time points as part of the review of the Participant Safety Card and throughout the study as described in the SoA (Section 1.3).

Vaccination status and administration of any vaccines and/or prophylactic antibacterial agents to reduce the risk for *N meningitidis* will be recorded in the CRFs.

8.1.5. Medical History and Baseline Characteristics

The participant's relevant medical history, including prior and concomitant conditions/disorders, treatment history, and disease status of relevant diseases will be evaluated at Screening by the Investigator and documented in the source documents and CRF. All medical history from 2 years prior to Screening and prior medications and procedures from 3 months prior to Screening, and any history from any time related to cardiac or kidney disease, including identified cause(s) of the participant's kidney disease, will be recorded. 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.

An STS risk calculator will be utilized for determining pre-operative risk for severe AKI (RIFLE Failure criteria), based on the participant's baseline characteristics as required for the risk calculator. The risk score and the participant characteristics used to determine their risk score will be captured during the 28 days prior to randomization. EuroScore will be separately calculated, and the value recorded.

8.1.6. Visits on the Same Day

- Same day Screening and Randomization (V1 and V2) may be utilized in situations of surgical urgency or scheduling challenges. Randomization in IRT and dosing has to occur on the same day in this situation. For procedures that are duplicative, these will only be required to be completed as part of V2 procedures.
- Same day Randomization and Dosing/Surgery (V2 and V3) schema may be utilized in situations of surgical urgency or scheduling challenges. Where study intervention needs to be prepared the day before dosing, randomization in IRT may occur the day prior to surgery, with dosing and other V2 and V3 study procedures occurring on the day of surgery. For procedures that are duplicative, these will only be required to be completed as part of V2 procedures. The infusion is required to be completed at least 1 hour prior to surgery start (ie, induction of anesthesia). Post-infusion samples must also be collected prior to anesthesia induction.

8.1.7. Hospital Discharge

Procedures performed at hospital discharge are noted in the SoA (Section 1.3). If the participant's hospital discharge is not anticipated to occur within the window of a scheduled study visit, a Hospital Discharge Visit should be conducted no more than 48 hours prior to the anticipated discharge. Additionally, if the hospital discharge occurs less than 48 hours before or after the window for a scheduled study visit, a separate Hospital Discharge Visit is not required. A visit conducted for hospital discharge on an unscheduled basis does not replace the need to conduct any other scheduled study visit.

8.1.8. Visits at Home

Participants should be encouraged to attend all visits in clinic. All efforts should be made to ensure the participant attends the Day 90 Visit in clinic. Home visits are allowed after discharge where available to reduce the risk of loss to follow-up. Home visits will be conducted by qualified medical professionals with the permission of the Investigator and in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. Telemedicine visits are expected to occur in conjunction with home visits in order to complete all study visit procedures.

All assessments performed at home visits must be conducted under the direction of the Investigator. Information collected must be forwarded to the Investigator's site for evaluation on the day of the visit. In case of any symptoms or signs indicating an SAE, further evaluation of the participant at the study site or an emergency care facility may be required.

8.2. Efficacy Assessments

For the primary efficacy endpoint, participants will be evaluated for MAKE90. MAKE90 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, or
- Initiation of KRT through Day 90 post CPB, or
- Death from any cause through Day 90 post CPB

Additionally, secondary endpoints will assess both AKI and MAKE endpoints at additional timepoints. To enable these efficacy evaluations, the Investigator will collect and record:

- sCr and sCysC on day of Screening, day of dosing (Day 1), day of surgery prior to induction of anesthesia, on Days 1-7, 15, 30, 60, and 90 post CPB, and upon hospital discharge:
    - Daily collection of sCr and sCysC will occur Days 1 to 7 days post CPB (168 h, Visit 5) as detailed in Section 8.3.4.
    - However, presence of AKI will be followed with daily laboratory tests through Day 7 post CPB even if discharged, or until recovered (< 1.5 × baseline), whichever comes first

- Serum or plasma creatinine tests done locally as standard of care will be reported as follows:
  - All creatinine tests done locally, ie, at the investigative site, as standard of care will be recorded as detailed in Section 8.3.4.
- Any use of KRT from randomization through Day 90 post CPB
  - Type/modality, start/stop of KRT, and reason for start/stop will be recorded
  - All attempts to collect at a minimum KRT status (yes/no) must be made and recorded on Days 15, 30, 60, and 90
  - Use of operative ultrafiltration as a standard of care procedure to routinely manage fluid balance during cardiac surgery is not considered initiation of KRT, and will be recorded as a concomitant procedure
- Any death from randomization through Day 90 post CPB
  - Date of death should be collected and recorded, and any associated AEs/SAEs including causal SAE(s) that result in the death should be reported as outlined in Section 10.3.2 and Section 10.3.4
  - All attempts to collect at a minimum vital status (survival, yes/no) must be made and recorded on Days 15, 30, 60 and 90

All efforts should be made to collect laboratory test samples, KRT status, KRT details, and survival status at all visits. However, if needed, KRT status (yes/no), KRT details, and survival can be ascertained directly by phone or telemedicine visit to prevent lost to follow-up. If attempts at direct contact with the participant fail, KRT status and survival status may be obtained indirectly from a family member, other healthcare provider, or local death registries.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- Symptom-directed examinations may occur any time after Screening as needed based on local practice/standard of care; normal findings or findings consistent with the participant's medical history will not be recorded; abnormal findings not attributable to the participant's medical history, new abnormalities, or worsening of physical findings will be reported as AEs.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Height will only be measured at Screening.
- Weight will be measured prior induction of anesthesia on the day of surgery. Daily weight will be measured in the first 7 days post CPB or until hospital discharge, whichever comes first.

- If an accurate weight cannot be obtained in an intensive care unit (ICU) setting, total daily fluid input and output will be recorded in lieu of weight measurement.

8.3.2. Vital Signs

- Temperature (°C or °F), heart rate, respiratory rate, and systolic and diastolic blood pressure (mmHg), will be assessed.
- Blood pressure and pulse measurements will be assessed with the participant in a seated position using a completely automated device. In the event the participant cannot tolerate measurements in the seated position (eg, while on mechanical ventilation in the ICU), measurements can be performed and noted as recumbent. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.
- Vital signs will be collected predose on Day 1.

8.3.3. Electrocardiograms

- Symptom-directed ECGs may occur any time after Screening as needed based on local practice/standard of care; normal findings or findings consistent with the participant's medical history will not be recorded; abnormal findings not attributable to the participant's medical history, new abnormalities, or worsening of previous ECG findings will be reported as AEs.
- Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. Clinically significant findings should be reported as an AE, when appropriate.

8.3.4. Clinical Laboratory Assessments: Safety and Efficacy

- All protocol-required laboratory assessments, as defined in Section 10.2 must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
  - Collect samples for clinical laboratory assessments as follows:
    - Prior to administering study intervention on Day 1
    - Prior to induction of anesthesia on day of surgery
    - At any time during other visits, including a Hospital Discharge Visit
  - Daily collection of samples for clinical laboratory assessments will occur on Days 1 to 7 days post CPB as follows:
    - sCr and sCysC will be collected on Days 1, 2, 4, 5, and 6 post CPB while hospitalized, along with full laboratory assessments outlined in SoA (defined in Section 1.3 and Section 10.2) on Days 3 and 7 post CPB

- sCr and sCysC on Days 4, 5 or 6 do not need to be collected if hospital discharge occurs between study visits on Day 3 and Day 7 post CPB and the participant is free of AKI
- A participant who develops any AKI within the first 7 days (at least Stage 1 by KDIGO criteria, see Table 5) will be followed with daily laboratory tests regardless of discharge status through Day 7 post CPB or until AKI recovery (sCr < 1.5 × baseline), whichever comes first

o Samples will be assessed locally as part of standard of care as follows:

- All sCr tests done locally as standard of care will be recorded in the first 30 days post CPB and in the first 30 days following initiation or dose modification that occur at any point post-baseline for select classes of eGFR-modifying drugs (see Section 10.2). The Investigators should regularly monitor patients with an elevated sCr > 1.5 × baseline per their local practice.

- The Investigator must review the safety laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All safety laboratory tests with values considered clinically significantly abnormal during participation in the study through the Day 90 Visit should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - If safety laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, AE or SAE or dose modification), then the results must be recorded in the CRF, and the corresponding AE or SAE reported.

8.3.5. Pregnancy

Pregnancy testing (serum) must be performed on all WOCBPs at protocol-specified time points in the SoA (Section 1.3). Pregnancy tests may also be performed at any time during the study at the Investigator's discretion.

A negative pregnancy test (local urine or local or central serum) is required within 72 hours prior to Randomization for WOCBP.

- Any female participant who becomes pregnant prior to randomization and dosing will be discontinued and will not receive study intervention.

- If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.6.3.
- Details of all pregnancies in female participants and female spouses/partners of male participants will be recorded and the pregnancy followed to term and Alexion notified regarding the outcome, even if the participant withdraws from the study. The corresponding infant must be followed-up with for 3 months postpartum.
- Pregnancy is not considered as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly) (Section 10.3.2). Elective abortions without complications should not be reported as AEs.

8.3.6. Participant Safety Card

Before study intervention administration, a Participant Safety Card will be provided to participants to carry with them at all times until 8 months after the final dose of study intervention. The card is provided to increase participant awareness of the risk of meningococcal infection and promote quick recognition and disclosure of any potential signs or symptoms of meningococcal infection experienced during the course of the study and to inform participants on what actions must be taken if they are experiencing signs or symptoms of infection.

The study staff will ensure that the participant/caregiver has the Participant Safety Card. The card will be reviewed at visits specified in the SoA, including the Hospital Discharge Visit if the anticipated hospital discharge is outside of a regularly scheduled visit (Section 1.3).

8.3.7. Vital Status

In the Primary Evaluation Period, vital status (survival yes/no) will be documented at Days 15, 30, 60 and 90 after CPB. For participants who withdraw consent for further participation in the study, all efforts will be made to collect data at withdrawal. In the Survival Follow-up Period, vital status will be documented at 365 days after CPB or ED, whichever comes first.

Vital status of participants may be obtained via telephone contact with the participant, participant's family, by contact with another healthcare provider, or local death registries.

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

All AEs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (Section 7).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.4.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs (serious and nonserious) will be collected from the signing of the ICF until end of the Primary Evaluation Period (Day 90, Visit 9).

All SAEs will be recorded and reported to Alexion or the designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.4. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE data after the Primary Evaluation Period (Day 90, Visit 9). However, if the Investigator learns of any SAE, including a death, at any time after a participant completes the Primary Evaluation Period, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion. The site can report this information on a paper Contingency Form for SAE Reporting via email or facsimile (see Section 10.3.4).

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs and Other Events

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and Investigators.
- Alexion is required to submit individual suspected unexpected serious adverse reaction (SUSAR) reports (defined in Section 10.3.2) in the format of MedWatch 3500 or CIOMS I Form to health authorities and Investigators as required. Forms submitted to Investigators will be blinded to treatment assignment. In limited

circumstances, the blind may be broken in the case of urgent safety issues that could compromise participant safety.

- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Under the European Union Clinical Trials Regulation (EU CTR) 2014/536, events other than SAEs (eg, unexpected events) that may impact the benefit-risk balance should be reported (Section 10.3.5).

8.4.5. Medication Error, Drug Abuse, and Drug Misuse

8.4.5.1. Timelines

If an event of medication error, drug abuse, or drug misuse occurs during the study, then the Investigator or other site personnel will report to Alexion or designee immediately but no later than 24 hours of when they become aware of it.

The full definitions and examples of medication error, drug abuse, and drug misuse can be found in Section 10.5.

8.4.5.2. Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

8.4.5.3. Drug Abuse

Drug abuse is the persistent or sporadic intentional, nontherapeutic excessive use of study intervention for a perceived reward or desired nontherapeutic effect.

8.4.5.4. Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of study intervention for medicinal purposes outside of the authorized product information, or for unauthorized study intervention, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

8.4.6. Adverse Events of Special Interest

Meningococcal infections will be considered to be adverse events of special interest (AESIs).

8.5. Treatment of Overdose

For this study, any dose of study intervention greater than that specified in the protocol will be considered an overdose. If dose cannot be established due to blinding, suspected overdose should be defined by volume administered.

Accidental overdose or suspected overdose without any association with laboratory abnormalities or clinical symptoms should not be considered as an AE. Overdose must be reported by the Investigator within 24 hours to Alexion regardless of its association with or without an AE.

Alexion does not recommend specific treatment for an overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

In the event of an overdose or suspected overdose, the Investigator should:

- Capture and forward the event, with or without associated AEs, to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Overdose Report Form within 24 hours of awareness.
- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE.
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
- For unblinded participants, document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics and Pharmacodynamics

- Blood samples for determination of serum ravulizumab concentrations and PD assessments (free C5) will be collected before and after administration of study intervention at the time points specified in the SoA (Section 1.3) according to applicable regulations.
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.
- Additional information on sample collection, including blood volume requirements, is provided in the Laboratory Manual.
- The Day 1 baseline PK and PD blood samples will be collected at predose, within 120 minutes, before administering study intervention at visits specified in the SoA (Section 1.3). The Day 1 predose blood sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose.
- On the day of surgery, samples will be collected prior to induction of anesthesia.
- Postdose PK and PD blood samples will be collected within 30 minutes after completing study intervention infusion. The postdose blood samples will be drawn from the participant's opposite, noninfused arm.

- Samples may be collected at any time on other study visits.

Study intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Please refer to the Laboratory Manual for details on sample collection, including blood volume requirements. Biomarker samples may be tested, and results analyzed after study completion for absolute values and change from baseline.

8.8.1. Blood Exploratory Biomarkers

Blood (serum and plasma) samples for exploratory assessments will be collected from all participants at the time points specified in the SoA (Section 1.3) according to applicable regulations.

Biomarkers to be measured may include, but are not limited to, assessments of the following:

- Complement pathway activation (eg, soluble C5b-9 [sC5b-9])
- Endothelial damage and/or activation (eg, 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])

8.8.2. Urine Exploratory Biomarkers

Urine samples for exploratory assessments will be collected from all participants at the time points specified in the SoA (Section 1.3).

Biomarkers to be measured may include, but are not limited to, assessments of the following:

- Complement pathway activation (eg, sC5b-9)
- Renal injury (eg, neutrophil gelatinase-associated lipocalin [NGAL])

8.8.3. Additional Biomarker Assessments

Residual blood and urine samples from exploratory biomarkers, PK, PD, and immunogenicity, will be stored for additional assessments (eg, related to the study intervention target, disease process, pathways associated with disease state, other complement-related diseases, and/or mechanism of action of ravulizumab). Samples will be retained for up to 25 years or in accordance with applicable regulations after termination of the study.

8.9. Participant-Reported Outcome Measures

Quality of life (QoL) scales will be completed by the participant prior to other study procedures at visits specified in the SoA (Section 1.3).

Participants in both cohorts will have the following validated QoL scales administered:

- Kidney Disease Quality of Life instrument – 36 items (KDQOL-36) (Section 10.8), a 36-item short form survey, is a widely used measure for patients on dialysis. Participants are asked to answer questions about their health, kidney disease, and effects of kidney disease on daily life.
- The European Quality of Life Group's 5-dimension 5-level (EQ-5D-5L) (Section 10.8) is a self-assessed, standardized instrument to measure health-related QoL and has been used in a wide range of health conditions. The EQ-5D-5L is a 5-scale participant-reported outcome tool measuring pain/discomfort, mobility, self-care, usual activities and anxiety/depression.
- The Functional Assessment of Chronic Illness Therapy (FACIT) -Fatigue scale (Section 10.8), version 4.0, is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days.

8.10. Healthcare Resource Utilization

Healthcare resource utilization associated with medical encounters will be collected in the CRF by the Investigator and study site personnel for all participants throughout the Primary Evaluation Period. Protocol-mandated procedures, tests, and encounters are excluded.

- Hospitalization from admission to discharge including admission date, discharge date as well as dates/time of ICU admission and discharge to another inpatient ward
- KRT: type/modality, frequency, start and stop dates, and reason for start/stop
- Duration of mechanical ventilation (dates and start/stop time)
- Discharge destination (eg, home, rehabilitation facility, hospice)
- Hospital readmission (emergency room or in-patient hospitalization; elective outpatient procedures that occur at a hospital are not considered readmission):
    - Primary reason will be assessed as either
        - Re-operation, which will always be 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 (for example, MI, stroke, heart failure, arrythmia)
        - AKI
        - Other reason
    - Hospitalization from readmission to discharge including date presenting to Emergency Room, inpatient admission date, discharge date and dates of ICU admission and discharge to another inpatient ward
    - Specific reason(s) for readmission will be reported as AE/SAE

Additional data collected (eg, concomitant medication as well as outpatient diagnostic and therapeutic procedures) may be used to conduct exploratory economic analyses.

8.11. Other Exploratory Assessments and Procedures

Exploratory assessment of biomarkers is presented in Section 8.8. Other exploratory endpoints include:

- AKI within Day 7 post CPB based on sCysC:
  - Highest AKI stage by KDIGO criteria
  - Occurrence of severe AKI (KDIGO Stage 2 or 3)

8.12. Post-treatment Follow-up Period

The minimum follow-up for safety will be 90 days from dosing of study intervention (Day 1, Visit 2). Participants in this study are expected to receive a single weight-based dose of study intervention and have cardiac surgery with CPB within 7 days of dosing (maximum interval between dosing and cardiac surgery with CPB is 15 days, should there be unexpected delay[s] to surgery) and will have all study visits and procedures as outlined in the SoA through the Day 90 Visit (Visit 9). The timing of post-operative (post CPB) visits on Days 3, 7, 15, 30, 60 and 90 will be based on the day of CPB, and with Day 1 post CPB being defined as the day after the participant comes off CPB. However, additional scenarios might arise during the conduct of the study:

a) If the participant is dosed study intervention and does not have cardiac surgery, or the surgery is delayed more than 15 days after dosing, the participant will have all subsequent study visits and procedures as outlined in SoA through the Day 90 Visit, with the timing of visits based on the day of dosing (Day 1, Visit 2);

b) If the participant is randomized but not dosed, the participant will have all study visits and procedures as outlined in the SoA through the Day 90 Visit, with timing of visits based on the day of randomization (which is Day 1, Visit 2);

c) If the participant withdraws consent or based on Investigator discretion, the decision for ED is made, Visit 9 will be immediately conducted.

8.13. Immunogenicity Assessments

Antidrug antibodies to ravulizumab (ie, ADA response) will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3) according to applicable regulations. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by Alexion or Alexion's designee.

Serum samples will be screened for antibodies binding to ravulizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of ravulizumab.

The detection and characterization of antibodies to ravulizumab will be performed using a validated assay method. Samples collected for detection of antibodies to ravulizumab will also be

evaluated for ravulizumab serum concentration to assess the impact of ADA on drug concentration profiles of ADA positive patients. ADA positive samples will be further characterized for antibody titer and presence of neutralizing antibodies.

8.13.1. ADA Variables

Immunogenicity variables include ADA status, response category, ADA or neutralizing antibody (NAb) incidence and titer over the duration of the study as follows. ADA status, response definitions and titer categories will be provided in the SAP.

ADA status categories

- ADA negative
- ADA positive

Participants who are ADA positive will be categorized as follows:

- Pre-existing immunoreactivity
- Treatment-emergent ADA responses
- Treatment-boosted ADA responses

ADA positive samples will be further characterized for neutralizing activity in the NAb assay. NAb status categories are as follows:

- NAb positive
- NAb negative

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

The primary hypothesis to be tested for this study is that ravulizumab will be superior to placebo in reducing the risk of MAKE event at 90 days following CPB (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.

9.1.2. 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.

9.2. Sample Size Determination

The sample size estimation was based on two-proportion difference using normal approximation method to compare the treatment difference in the proportion of participants experiencing MAKE events within 90 days post CPB between the ravulizumab and the placebo group.

The sample size estimation was conducted using PASS2022 under the following program:

- Proportions > 2 Independent Proportions > Test (Inequality) > Test for 2 Proportions

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 MAKE within 90 days post CPB 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 approximate 10% dropout rate. The assumption of 25% MAKE90 rate in placebo group was derived based on recent interventional and observational studies as described below.

Recent interventional studies aimed at reducing CSA-AKI reported in 9% to 10% of participants receiving placebo achieving MAKE endpoint at Day 30 (Jacob, 2015; Meersch, 2017; Venugopal, 2020) and 13% to 22% (Meersch, 2017; Thielmann, 2021) at Day 90. These studies included a variable proportion of participants with CKD (8% to 47%). A post-hoc analysis of the subgroup with CKD (pre-surgical eGFR < 60 mL/min/1.73m^2) from the Dexamethasone for Cardiac Surgery study reported that MAKE30 was 16.5% in the placebo group (Venugopal, 2020). Since these studies did not exclusively enroll CKD patients, a higher placebo rate will be expected for this study with enrollment of individuals at increased risk for AKI with pre-existing CKD and heightened predicted risk of renal failure using the STS risk calculator.

There is limited data from the other studies on the frequency of MAKE (or its individual component outcomes) for those with pre-existing CKD. Therefore, estimates of individual MAKE events were derived from observational studies along with this study data to inform the placebo rate assumption of 25% for the current study:

- **KRT 7% to 10%:** Interventional studies reported KRT in 6.5% to 7.5% of participants receiving placebo (Meersch, 2017; Thielmann, 2021). Observational studies from a variety of healthcare systems report post-operative KRT in 7% to 30% of patients with pre-existing CKD (Cho, 2021; Lau, 2021; Wu, 2011). By exclusively recruiting participants with CKD, at least 7% of participants requiring KRT is expected. Use of the STS renal failure risk calculation threshold for inclusion in the study is also expected to enrich for participants with highest risk of requiring KRT, especially amongst participants with pre-existing CKD Stage 3a.
- **Mortality 4% to 7%:** Interventional studies report mortality rates of 2% to 7% within 90 days following CPB (Dieleman, 2012; Meersch, 2017; Thielmann, 2021; Whitlock, 2015). In observational studies, AKI is independently associated with risk of mortality after CPB, with the highest risk in patients requiring acute KRT (Cho, 2021; Lau, 2021; Matsuura, 2020). Additionally, AKI superimposed on pre-existing CKD confers a higher risk of mortality following cardiac surgery (up to11%) (Cho, 2021). Therefore, by enrolling exclusively CKD patients, we expect overall mortality of approximately 5% to 6%.
- **SKD 17% to 25%:** Using changes in sCr or sCr-based eGFR, 19% to 22% of the CKD populations reported in observational studies have SKD by 3 months following CPB (Cho, 2021; Matsuura, 2020; Wu, 2011; Xu, 2019). AKI superimposed on CKD is the largest risk factor for SKD with 20% to 30% experiencing non-recovery back to baseline kidney function by 90 days (Cho, 2021; Matsuura, 2020; Wu, 2011). There are limited data from the interventional studies to directly inform the rate of SKD in

participants with pre-existing CKD. Recent studies have reported SKD rates of 7% to 12% in control/placebo groups without fully enriching for CKD (Meersch, 2017; Thielmann, 2021). The exclusive enrollment of participants with CKD is expected to increase the proportion of participants classified with SKD at 90 days compared to other CSA-AKI studies.

- **MAKE90 20% to 30%:** The frequency of individual events is not additive since an individual participant can often meet criteria for > 1 event within 90 days. Recent clinical studies (Meersch, 2017; Thielmann, 2021) reported approximately 30% of patients experienced more than 1 component of the MAKE (KRT, death, SKD). Assuming a similar pattern in the current study, the expected proportion of participants in the placebo group achieving the MAKE endpoint at 90 days is estimated to be 20% to 30% based on the integration of the various data sources summarized here; the assumed placebo rate is 25% for this study.

9.3. Populations for Analyses

The population sets used for analysis in this study are defined in Table 11.

Table 11: Analysis Populations

Population	Description
Intent-to-Treat Set (ITT)	All participants randomized to study intervention. Participants will be analyzed as randomized.
modified Intent-to-Treat Set (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. All cases of prospectively defined protocol deviations will be defined in the SAP prior to clinical database lock.
Post-operative Set (POS)	All participants in mITT and have stable pre-operative 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.
PK Analysis Set (PKAS)	All ravulizumab-treated patients with at least 1 post-baseline PK concentration available.
PD Analysis Set (PDAS)	All randomized participants who received study intervention and have at least 1 post dose PD measurement.
Immunogenicity Analysis Set (IAS)	All randomized participants who receive ravulizumab and have at least 1 reportable post- dose ADA result. Participants will be analyzed according to the study intervention they actually receive.

Note: Evaluable PK, PD, and ADA data are defined as non-missing results generated from samples that comply with sample integrity requirements during sample collection, storage, shipment, and bioanalysis.
Abbreviations: ADA = antidrug antibody; CPB = cardiopulmonary bypass; KRT = kidney replacement therapy; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAP = statistical analysis plan; sCr = serum creatinine

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate SAP. In general, descriptive statistics (n, mean, median, standard deviation, first and third quantiles, minimum, and maximum) will be provided by treatment group and visit for each quantitative variable, and frequencies and percentages will be provided by treatment group and visit for each qualitative variable. Graphical displays will be provided as appropriate. Baseline is defined as Day 1 randomization prior to administration of study intervention, except where otherwise noted below. The final analysis and study unblinding will occur once the last enrolled participant completes Day 90 Visit or early withdrawal.

Analyses will be performed using the SAS® software version 9.4 or higher.

9.4.1. Efficacy Analyses

9.4.1.1. Analyses of Primary Efficacy Endpoint(s)

The primary efficacy analysis will be based on the ITT Analysis Set. The primary endpoint is the MAKE90, defined as meeting at least 1 of the following criteria:

- Decrease from baseline in eGFR of ≥ 25% at Day 90 post CPB, or
- Initiation of KRT through Day 90 post CPB, or
- Death from any cause through Day 90 post CPB

As specified in the Section 3.1, the primary estimand is the population level treatment difference between ravulizumab and placebo in the proportion of participants experiencing MAKE at 90 days post CPB, which is 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 Cochran-Mantel Haenszel (CMH)-method adjusting for the 2 stratification variables.

Baseline and post-baseline 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.

For missing endpoint of MAKE90 due to partial or complete missing of individual components, missing of KRT initiation or death will be imputed as non-event, and missing eGFR values will be handled by multiple imputation in two 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. Rubin's rule will be used for combining results to yield multiple imputation point estimate and standard error.

The proportion of participants experiencing MAKE90 will be reported by treatment group. The p-value and 2-sided 95% confidence interval (CI) of the treatment difference in MAKE90 will be reported.

Multiple sensitivity analyses will be conducted based on the ITT Analysis Set to evaluate the robustness of results using different missing data imputation strategies from the primary analysis.

In one sensitivity analysis, the missing data of MAKE90 will be multiply imputed by treatment group based on logistic regression model. After imputation of missing data on MAKE90, the CMH method along with Rubin's rule will be applied in the same manner as main analysis.

A second sensitivity analysis will be conducted using control-based pattern imputation (Ratitch, 2011). For participants from the ravulizumab group, 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 based on a logistic regression model. In addition, tipping point analyses will be conducted based on the delta adjustment method to assess the sensitivity of the primary analysis results when the missing data mechanism for the eGFR deviates from the MAR assumption. Details of these sensitivity analyses will be documented in the SAP.

To assess the impact of the specified IEs on the study results, a supplementary hypothetical estimand on the primary endpoint will be defined in the SAP, which estimates the treatment effect in the hypothetical situation when no IE occurs. Details on how to analyze data collected post IEs will be detailed in the SAP. The estimator of this hypothetical estimand will also be the weighted average of treatment difference in the MAKE90 rate using CMH method adjusting for the 2 stratification variables.

In addition, the treatment policy estimand will be applied to other analysis populations (ie, mITT, Per Protocol Set [PPS] and Post-operative Set [POS]) to assess the robustness of the primary estimand effect in the ITT population. These estimands will be analyzed in the same manner as the primary treatment policy estimand with the exception that different analyses populations will be used.

9.4.1.2. Analyses of Key Secondary Efficacy Endpoints

The secondary efficacy analyses will be based on the ITT Analysis Set. A sequential testing procedure will be performed for the key secondary endpoints in the following order:

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

Definitions for the key secondary efficacy endpoints are provided in Table 4. As stated in Section 3.2, secondary estimands of the study are population level treatment differences in the proportions (for binary endpoints) or the median (for the length of post-operative ICU stay endpoint) between ravulizumab and placebo based on the treatment policy regardless of any IEs. For the length of post-operative ICU stay endpoint, the estimator will be the median treatment difference using the Hodges-Lehmann method; for other key secondary endpoints, the corresponding estimator will be the weighted average of treatment difference in the key secondary endpoint of interest using the CMH method adjusting for 2 stratification variables.

The highest observed sCr may be from central laboratory samples collected at specified study visits (Section 1.3) or from daily local laboratory sCr results at any time during the first 30 days (Section 10.2). Baseline sCr for defining AKI will be based on the average of the last sCr collected during Screening and on Day 1 prior to study intervention administration.

For the occurrence of severe AKI within 30 days post-surgery (defined in Table 4), participants must meet the criteria for KDIGO Stage 2 or 3 (defined in Table 5), with the highest observed sCR confirmed by at least 1 additional measurement obtained within ± 72 hours of the peak value.

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 multiple imputation method under the MAR assumption; 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; 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. To assess the robustness of results for these key secondary endpoints, sensitivity analyses will be conducted using imputation strategies different from the main analytic approach, including tipping point analyses. Details of these key secondary endpoints analyses will be documented in the SAP.

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 post-surgery and is alive at ICU discharge, where the post-operative ICU stay refers to the ICU admission transferred from initial hospitalization admission for surgery. A non-parametric analysis using stratified Wilcoxon method will be used for treatment comparison. The stratified Wilcoxon test will include 2 stratified variables in the randomization. The median, interquartile range, min and max 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.

The proportion of participants meeting each of other 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.

9.4.1.2.1. Association Between Key Secondary Endpoints and Clinical Outcomes

The association between the key secondary points of "occurrence of severe CSA-AKI (KDIGO Stage 2 or 3) 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

For the binary clinical outcomes of death, initiation of KRT and readmission to hospital, the 2 by 2 contingency table of clinical outcome and key secondary endpoint will be provided by treatment group and overall. Chi-square test will be performed for testing the correlation between two variables.

For the continuous clinical outcomes of duration of KRT and ventilation, the summary statistics will be provided by the key secondary endpoint category, by treatment group and overall. A linear regression or an analysis of variance (ANOVA) model will be fitted for the continuous clinical outcome with the key secondary endpoint as a covariate. The correlation coefficient will be estimated from the model to assess the correlation between the clinical outcome and the key secondary endpoint. If the key secondary endpoint meets the statistical significance under the sequential testing procedure, additional analyses may be considered to explore whether the treatment effect on the primary endpoint (MAKE90) is largely explained by the statistically significant key secondary endpoint.

The detailed procedure will be provided in the SAP.

9.4.1.3. Other Secondary Efficacy Analyses

9.4.1.3.1. MAKE30, MAKE60, MAKE90, and Individual Components

Similar to the primary endpoint MAKE90, which will be determined based on the CKD-EPI formula using sCysC, MAKE90 will also be determined based on the CKD-EPI formula using sCr. In addition, MAKE30 and MAKE60 endpoints will be determined similarly. The proportion of participants who experience MAKE at Days 30, 60, and 90 post CPB will be summarized by treatment group and visit. The point estimate and associated p-values and 2-sided 95% CIs for treatment difference will be presented using the CMH method, adjusted for stratification factors.

In addition, the individual MAKE component will be analyzed. The proportion of participants with decrease in eGFR $\geq$ 25% from baseline to Days 30, 60, and 90 post CPB, or with initiation of KRT through Days 30 and 60 post CPB or death from any cause through Days 30 and 60 post CPB will be summarized by treatment group and visit. The point estimate and associated 2-sided 95% CIs for treatment difference will be presented by visit using the CMH method, adjusting for stratification factors.

9.4.1.3.2. Occurrence of KRT or Death

The proportion of participants with KRT or death occurring through Day 30 and Day 60 post CPB will be summarized by treatment group. The point estimates and associated 2-sided 95% CI will be provided using the CMH method, adjusting for stratification factors.

9.4.1.3.3. Post-operative Acute Kidney Injury

The proportion of participants with CSA-AKI by highest stage observed within the first 3 and 7 days after CPB using modified KDIGO criteria (KDIGO, 2012; Khwaja, 2012) will be summarized by treatment group.

The proportion of participants with CSA-AKI and any AKI will be summarized at pre-specified visit by treatment group and visit. The point estimates and associated 2-sided 95% CIs will be estimated using the CMH method, adjusting for stratification factors.

9.4.1.3.4. Acute Kidney Injury Recovery, Improvement, Stabilization, or Progression

The proportion of participants with AKI recovery (complete or partial), improving AKI, stable AKI, or progressing AKI (Chawla, 2017) at Days 15, 30, 60, and 90 post CPB amongst participants who experience CSA-AKI within 7 days post CPB will be summarized by treatment group and visit. The point estimates and associated 2-sided 95% CIs will be estimated, using the CMH method adjusting for stratification factors (if appropriate).

9.4.1.4. Healthcare Resource Utilization

The length (days) of post-operative hospital stay will be calculated based on the date of hospital discharge or the date of post-operative death (whichever is earlier) minus the completion date of the surgery with CPB plus one, where the hospital stay refers to the hospital admission due to CPB operation. For participants on ventilators, the total duration (hours) on ventilator use will be calculated as the sum of the duration of each occurrence of mechanical ventilation. For patients on KRT, the duration (days) of KRT will be calculated based on the last date on KRT minus date of KRT initiation plus one.

The length of post-operative hospital and the durations on ventilator/KRT will be summarized for each treatment group using descriptive statistics. It will include the number of observations, mean, standard deviation, median, minimum, maximum, interquartile range (IQR), first quartile, and third quartile 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 Section 8.10) through Day 30 and Day 90 post CPB will be summarized by treatment group and visit. The point estimates and associated 2-sided 95% CIs will be estimated, using the CMH method adjusting for stratification factors (if appropriate).

9.4.1.5. Health-related QoL

The following QoL assessments will be summarized by treatment group at baseline and each post-baseline time point (SoA, Section 1.3) using descriptive statistics for the observed value as well as the change from baseline:

1. FACIT-Fatigue
2. EQ-5D-5L
3. KDQOL-36

The change from baseline will also be summarized for each treatment group from the mixed model repeated measures (MMRM) analysis; no formal treatment comparison will be made. The point estimate and two-sided 95% CI for the mean difference in these measurement scores will be presented.

9.4.1.6. Analyses of Exploratory Endpoints

Analyses of exploratory biomarkers data will be described in a separate analysis plan and may be summarized after study completion. Analyses of other exploratory endpoints will be detailed in the SAP.

9.4.1.7. Multiplicity Adjustment

A multiple testing procedure will include a test on the primary endpoint and then a pre-specified hierarchical test on the key secondary endpoints. The primary endpoint MAKE90 will be tested following the group sequential theory as detailed in the Section 9.5. If the primary endpoint is statistically significant, the key secondary endpoints will be tested in the fixed sequence as specified in Section 9.1.2 using the Pocock boundaries approximated by the Lan-DeMets alpha-spending function (Lan, 1983). The testing of key secondary endpoints will continue down the hierarchy only if the test for the preceding secondary endpoint is statistically significant.

If the study does not stop early for early futility or efficacy at the interim analyses, the Cui, Hung, & Wang (CHW) method (Cui, 1999) will be adopted in the final analysis of the primary and key secondary endpoints for the sample size re-estimation.

Under this pre-specified multiple testing procedure, the alpha-spending strategy following the group sequential theory for the primary endpoint and the Lan-DeMets Pocock boundaries for the key secondary endpoints, and CHW method for the final analysis, the overall type-I error will be controlled at a one-sided 0.025 level for multiplicity across primary and key secondary endpoints.

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

9.4.2. 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 Safety Set.

9.4.2.1. Adverse Events

The incidence of treatment-emergent adverse events (TEAEs), TEAEs leading to withdrawal from the study, and treatment-emergent serious adverse events (TESAEs) will be summarized by treatment group. 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. All 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 overall, by severity, and by relationship to study intervention. Detailed by-participant listings of TEAEs, TESAEs, related TEAEs, and TEAEs leading to withdrawal from the study will be provided. Participants having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity tables, a participant's most severe event within a category will be counted. AESIs (such as meningococcal infections) will be analyzed similarly.

9.4.2.2. Physical Examination and Vital Signs

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

Vital signs will be summarized descriptively by treatment group at baseline and post-baseline time points and for changes from baseline.

9.4.2.3. Clinical Laboratory Tests

Observed values and changes from baseline in clinical chemistry and hematology will be summarized descriptively by treatment group at baseline and at each post-baseline time point. For laboratory results that can be classified as normal, low, or high based on normal range values, shifts from baseline in classification will be summarized for all study visits.

9.4.3. Pharmacokinetic/Pharmacodynamic Analyses

The PK and PD analyses will include all data in the PK Analysis Set and PD Analysis Set, respectively.

Graphs of mean serum ravulizumab concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual participants may also be provided. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate.

The PD effects of ravulizumab will be evaluated by assessing the absolute values and changes and percentage changes from baseline in serum free C5 concentrations over time, as appropriate. Descriptive statistics will be calculated for the PD data at each sampling time, as appropriate.

9.4.4. Immunogenicity Analyses

All ADA analyses will be performed on the Immunogenicity Analysis Set (IAS) using the ADA variables included in Section 8.13.1.

The incidence of ADA response categories will be summarized as absolute occurrence (n) and percent of all participants (%) in the ravulizumab group at Day 90. Confirmed antibody positive samples will be further evaluated for antibody titer and the presence of neutralizing antibodies. Maximum ADA titer levels will be listed and summarized for ADA positive participants as absolute occurrence (n) and percent (%) of all participants.

Association of immunogenicity variable with impact on drug exposure, efficacy and safety may be explored. Additional details will be provided in the SAP.

9.4.5. Subgroup Analyses

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

- Participants with different CKD stage at baseline
- Participants with different surgical types during CPB
- Participants in age groups 18 to 60, 61 to 75, and > 75 years (Afilalo, 2016)
- Participants with body weight groups at baseline of ≥ 30 to ≤ 59 kg, ≥ 60 to ≤ 99 kg, ≥ 100 kg

- Participants with the following levels of albuminuria (measured as albumin to creatinine ratio [ACR]) at baseline (KDIGO, 2013)
  - < 30 mg albumin/g creatinine
  - ≥ 30 to < 300 mg albumin/g creatinine
  - ≥ 300 mg albumin/g creatinine
- Participants with and without diabetes mellitus
- Participants with and without post-baseline eGFR-modifying therapies

Additional subgroup analysis may be described in the SAP.

9.5. Interim Analyses

Two interim analyses are planned after approximately 30% (~220 participants) and 50% (~368 participants) of the randomized participants have completed the Primary Evaluation Period (ie, Day 90 post CPB Visit). An independent DMC will review unblinded study information provided by an independent DAC and make recommendations at the planned interim analyses (Section 9.6).

At the time of any interim analysis, if the prespecified futility criterion or early efficacy criterion is met, the DMC may recommend early stopping of the study. This will be a non-binding recommendation from the DMC to the Sponsor. Following this recommendation, additional analyses may be generated and reviewed by an unblinded team (independent of the study team).

The purpose of the first interim analysis is to assess early 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 the first interim analysis is less than 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 pre-specified futility criterion at the first interim analysis, the sponsor may continue the study without stopping the study for futility.

The second interim analysis will include futility, early efficacy, and sample size re-estimation assessments. For the futility and sample size re-estimation assessments, the conditional power for the primary endpoint analysis will be evaluated under the assumption of the observed effect size at the second interim analysis.

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

criterion is met. With the planned information fraction of 0.5 at the second interim analysis, it follows from the group sequential theory (Jennison, 1999) that the one-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 second interim analysis 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.

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 second interim analysis. Technical and analysis details for each planned interim analysis will be documented in an interim statistical analysis plan (iSAP) prior to the interim analysis.

9.6. Data Monitoring Committee

An independent 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 DAC during the conduct of the study for periodic safety review and two planned interim analyses. A DMC SAP will include details of the analysis plan for the periodic safety reviews. An iSAP will include technical and analysis details of the interim analyses. At each planned interim analysis, DMC will make formal recommendations based on the pre-specified criterion.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, per local regulations.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU CTR 536/2014, and all other applicable local regulations.
  - Promptly notifying Alexion of any (potential) serious breach of the protocol or regulations (including if a data breach compromises the integrity, confidentiality, or availability of the personal data of participants) so that legal and ethical obligations are met. A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- In certain regions/countries, Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - Alexion will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority (including data protection

authorities and, if applicable, affected participants in case of a personal data breach), IRB/IEC, and Investigators. Under EU CTR 536/2014, Alexion is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach, including personal data breaches.
  - A (potential) serious breach is promptly reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion.
  - The Sponsor and the site have taken all necessary steps to avoid personal data breaches and have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining, and keeping systems and IT [information technology] security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
  - Both the Sponsor and the site have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
  - In compliance with applicable laws, the data controller for the processing activity where the personal data breach occurred (the Sponsor or respectively the site) will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
  - If the personal data breach needs to be notified to participants, the notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the data controller and for data breaches occurred within the processing activities of the Sponsor as the data controller, the notification is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of the Sponsor, so that the Sponsor has no access to the identifying personal information of the participants. The site and/or Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
  - If a personal data breach occurs in a processor's systems, engaged by the Sponsor, the processor under contractual obligations with the Sponsor promptly and in due course after discovering the breach notifies the Sponsor and provides full cooperation with the investigation. In these cases, to the extent the Sponsor is the data controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is

performed by the site and/or Investigator, acting on behalf of the Sponsor, so that the Sponsor has no access to the identifying personal information of the participants.

- Where a personal data breach is suffered by the Study Monitor, the latter will provide the Sponsor with all of the information needed for notification of the breach, without disclosing data that allows the Sponsor directly or indirectly to identify the participants. The notification will be done by the Sponsor solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of reidentification of the participants. If the data breach must be notified to the data participants, the notification will be done directly by the Study Monitor in collaboration with the site and/or Investigator, acting on behalf of the Sponsor, so that the Sponsor has no access to the identifying personal information of the participants. The contract between the Sponsor and the Study Monitor shall expressly specify these conditions.
- The contract between the site and the Sponsor for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator or designee to obtain signed (written or electronic signature) informed consent from all study participants prior to performing any study-related procedures including screening assessments.
- The Investigator or designee will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or their legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include a statement that signed (written or electronic) informed consent was obtained before the participant was enrolled in the

study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).

- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or their legally authorized representative, as applicable. This document may require translation into the local language. Original signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened outside of the Screening window (Section 1.3) are required to sign a new ICF (Section 5.4).

10.1.4. Recruitment Strategy

Participants will be identified by qualified research staff. This may be done through a review of medical records, external referrals or using databases. Recruitment strategies may include study posters, referral letters, recruitment brochures, advertisements, social media posts, and websites, where permitted by local regulations. All recruitment materials will be submitted to local IRB/EC as required, for review and approval for use.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by a Trusted Third Party contracted by Alexion or by a Principal Investigator. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study- related and coded (pseudonymized) data will be used in accordance with applicable data protection law, and participants must also be informed of any individual rights they may have with regard to their personal data. Participants will be informed about how their personal study-related data will be disclosed and will be required to agree to the information contained in the informed consent and provide consent to the processing of their personal data, if required by applicable data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, and inspectors from regulatory authorities.
- Alexion as a data controller has implemented privacy and security controls designed to help protect participant personal data; including information security controls, firewalls, incident detection, and secure transfer measures.
- In the event of any accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data ("breach"), the controller has implemented

procedures and measures to promptly address and mitigate any risk to the data participant. In the event of a breach, the controller will notify the appropriate regulatory authorities and/or the data participant in accordance with applicable data protection law.

- The contract between Alexion and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- The GDPR (EU/2016/679) defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:
  - Access to the coded data will be limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
  - The coded data will be protected with security measures to avoid data alteration, loss, and unauthorized accesses and further de-identification techniques may be applied.
  - A data protection impact assessment (DPIA), where required, will apply to identify and mitigate privacy risks, if any, associated with each scientific research.
  - The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not considered scientific research according to the applicable data protection legislation. In particular, they will not be used to make decisions about future services available to the participant, such as insurance.
- In addition to having the participants' data and biosamples coded, the data are also protected by high-standard technical security means, such as strong access control and encryption.
- Participants are also protected legally by the following means if the level of disclosure of the coded data includes sharing of the latter with other third parties, as the participants will be explained in the ICF:
  - The participants' coded data are protected by contractual arrangements, Codes of Conduct, or certifications that set the rules for personal information protection to those available in European countries or other alternatives set forth in the law, as

well as any supplementary technical and organizational measures that may results out of conducted transfer impact assessments.

10.1.6. Committees Structure

An independent 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. 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 DAC during the conduct of the study and make formal recommendations on early stopping for futility or increasing sample size based on the pre-specified criterion.

10.1.7. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialregister.eu) as appropriate, and in accordance with national, regional, and local regulations. However, posting of study results per local regulations may be deferred to a later date for 1 of the following reasons:

- Study is still ongoing in other countries or regions
- Study is part of an ongoing review for approval by Health Authorities; study result data deferral request can be submitted

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on the CRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the Case Report Form Completion Guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.

- Alexion assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion. Clinical study documents and records required as part of the TMF are archived and stored by Alexion for at least 30 years.
- Quality tolerance limits (QTLs) will be predefined in the study specific risk register to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report (CSR).

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant. The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. CRFs must be completed by the Investigator or designee as indicated in the site delegation log. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available to Alexion, Alexion delegates, and health authorities, as requested. Source documents are filed at the investigational site.
- Alexion or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date of first site activation.

The first act of recruitment is the consenting of the first participant.

Study/Site Termination

Alexion or designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site Closure Visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or ICH GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

Alexion or health authority may terminate the study for reasonable cause. Conditions that may warrant termination of the study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk of the study intervention to participants enrolled or continuing in the study
- Alexion decision to suspend or discontinue testing, evaluation, or development of the study intervention

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, IRBs/IECs, regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication to peer-reviewed, indexed (eg, PubMed, Scopus, Embase) journals within 12 to 18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion Author Letter of Agreement prior to engaging in manuscript development.

- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- Primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Alexion will comply with the requirements for publication of study results as defined by the Pharmaceutical Research and Manufacturers of America and the International Committee of Medical Journal Editors recommendations and per the Alexion Publication Policy. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.
- Alexion will publish Plain Language Summaries and include participants and/or caregivers as reviewers for readability and understanding of lay person language.
- No compensation shall be provided to external Authors for authorship of publication, including drafting or revising a publication. Alexion may reimburse the presenting Author of an Alexion-supported publication for travel, lodging, and registration to present a poster or oral presentation at scientific meeting, consistent with the Alexion Global Procurement and Sourcing Procedure, the Alexion Antibribery Anticorruption Policy and the Alexion Global Travel and Expense Policy.
- Authors must disclose financial or personal affiliations that could be considered a conflict of interest in the publication.

10.1.12. Good Clinical Practice Compliance

Alexion and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 R2, EU CTR 536/2014, as well as all applicable national and local laws and regulations.

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

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

10.2. Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the study central laboratory unless otherwise noted. Please refer to the Laboratory Manual for specific testing schedules and details.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for eligibility, study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make an eligibility or a study intervention decision or response evaluation, the results must be available in the participant's source documents.
- Serum creatinine tests done locally as standard of care will be reported as follows:
  - All sCr tests done locally as standard of case will be recorded in the first 30 days post CPB and in the first 30 days following initiation or dose modification that occurs at any point post-baseline for select classes of eGFR-modifying drugs as listed below. The Investigator should regularly monitor patients with an elevated sCr > 1.5 × baseline per their local practice. Select classes of eGFR-modifying drugs include:

    ACE inhibitors

    Angiotensin receptor blockers

    SGLT-2 inhibitors

    Mineralocorticoid receptor antagonists

    Renin inhibitors (remikiren, aliskiren)
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional laboratory tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing (see Section 8.3.5).
- Investigators must document their review of each laboratory safety report.

Table 12: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Hemoglobin Hematocrit Platelet count RBC count RBC indices: 1. Mean corpuscular volume

Table 12: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
	2. Distribution width WBC count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical chemistry	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine (sCr) Cystatin C (sCysC) Glucose, nonfasting Potassium Sodium Total and direct bilirubin Total protein High-sensitivity cardiac Troponin T (hs-cTnT) Uric acid
Urine chemistry	Urinary albumin concentration Urinary protein concentration Urinary creatinine concentration Albumin/creatinine ratio (UACR) Protein/creatinine ratio (UPCR)
PK/PD	Serum PK Serum PD (free C5)
Immunogenicity	ADA and NAb
Exploratory Biomarkers (blood and urine)	Assessments may include, but are not limited to, biomarkers of complement activation (eg, soluble C5b-9), endothelial damage (eg, plasma TM), vascular inflammation (eg, TNF-RI), cell-cycle arrest (TIMP-2), and renal injury (eg, NGAL).

Table 12: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
Other tests	• Serum FSH and estradiol (required where postmenopausal status needs to be confirmed [see Section 10.6.1]) • Serum human chorionic gonadotropin pregnancy test (as needed for WOCBP)

Abbreviations: ADA = antidrug antibody; C5 = complement component 5; C5b-9 = terminal complement complex (membrane attack complex); NAb = neutralizing antibody; NGAL = neutrophil gelatinase-associated lipocalin; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RBC = red blood cell; TM = thrombomodulin; TIMP2 = tissue inhibitor of metalloproteinase 2; TNF-RI = tumor necrosis factor receptor 1; WBC = white blood cell; WOCBP = woman of childbearing potential

10.3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study intervention, whether or not considered related to the study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events Not Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE, while the procedure itself is recorded as concomitant procedure. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error.

Events Not Meeting the AE Definition
• Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

4. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A SUSAR is defined as:

An event that is serious, that has at least a reasonable possibility that it is related to the investigational medicinal product (IMP) as assessed by the Investigator and/or Alexion, and that is not listed in the appropriate Reference Safety Information (IB).

Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents.

SUSARs will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following regional, national, and local regulatory reporting requirements where applicable.

10.3.3. Recording and Follow-up of AE and/or SAE

Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the Alexion AE/SAE CRF page.

Recording of AE and/or SAE

- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities, including life-threatening or fatal)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.3.2. An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE above, not when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the electronic case report form (eCRF) and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study intervention.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.

Assessment of Causality

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection (EDC) Tool

- All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness.
- The primary mechanism for reporting an SAE to Alexion will be the EDC system.
- If the electronic system is unavailable or site staff is unable to process the SAE via the EDC system at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE Reporting via email or facsimile. Facsimile transmission or email may also be used in the event of electronic submission failure.
  - Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347
- The site will enter the SAE data into the EDC system as soon as it becomes available.

SAE Reporting to Alexion via an Electronic Data Collection (EDC) Tool
• When further information becomes available, the EDC should be updated immediately with the new information and an updated SAE report should be submitted to Alexion Global Patient Safety (GDS) within 24 hours of Investigator/site awareness. • After the participant has completed the Primary Evaluation Period no new data or changes to existing data are expected to be entered in the EDC system. • If a site receives a report of a new SAE from a study participant which the Investigator considers to be related to the study intervention, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via email or facsimile.

10.3.5. Unexpected Events

Apart from the reporting of SUSARs, there may be other events which are relevant in terms of benefit-risk balance, and which should be reported in a timely manner according to regional and national requirements (eg, EU CTR 2014/536 [48]). It is important for participant safety that, in addition to SAEs and reactions, all unexpected events that might materially influence the benefit-risk assessment of the IMP or that would lead to changes in the administration of an IMP or in overall conduct of a clinical study should be reported. Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as carcinogenicity).

Under the EU CTR 2014/536 (49), where unexpected events require an urgent modification of a clinical study, it should be possible for Alexion and the Investigator to take urgent safety measures without awaiting prior authorization. If such measures constitute a temporary halt of the clinical study, Alexion should apply for a substantial modification before restarting the clinical study.

10.4. Management of Potential Infusion-related Adverse Events During Ravulizumab Administration

Intravenous and infusion-related reactions are a potential risk with the use of monoclonal antibodies; these reactions can be nonimmune or immune mediated (eg, hypersensitivity reactions). Signs and symptoms may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing.

All administration, IV, and infusion-related reactions will be reported to the Investigator and qualified designee. The Investigator and qualified designee are responsible for detecting, documenting, and recording events that meet the definition of AE or SAE and remain responsible for following up events that are serious, considered related to the study intervention, or study procedures; or that caused the participant to discontinue ravulizumab (Section 7).

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

Participants who experience a reaction during the administration of ravulizumab should be treated according to institutional guidelines.

Participants who experience a severe reaction during administration of ravulizumab resulting in discontinuation of ravulizumab should undergo all scheduled safety, PK, and PD evaluations required by the protocol. Alexion must be notified within 24 hours of any infusion-related reaction requiring interruption or discontinuation of ravulizumab. All AEs that may indicate an infusion-related response will be graded according to the intensity categories listed in Section 10.3.3.

If anaphylaxis occurs according to the criteria listed in Table 13, then administration of subcutaneous epinephrine (1/1000, 0.3 mL to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Participants administered an antihistamine for the treatment or prevention of an infusion-related-reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

Table 13: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

• Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following:
  ○ Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  ○ Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

Table 13: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
• Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours): o Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula) o Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) o Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) o Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
• Reduced blood pressure after exposure to known allergen for that participant (minutes to several hours): o Systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that participant's baseline

Source: (Sampson, 2006)

10.5. Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

Any events of medication error, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Medication Error Report Form.

A medication error is not lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant

- Drug not administered as indicated, eg, wrong route, wrong device, or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be stored at room temperature
- Wrong participant received the medication (excluding IRT errors/ Randomization and Trial Supply Management errors)
- Wrong drug administered to participant (excluding IRT errors/ Randomization and Trial Supply Management errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this clinical study, drug abuse is defined as the persistent or sporadic intentional, nontherapeutic excessive use of study intervention for a perceived reward or desired nontherapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of study intervention for medicinal purposes outside of the authorized product information, or for unauthorized study intervention, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault on another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

10.6. Contraceptive Guidance and Collection of Pregnancy Information

10.6.1. Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the Following Categories Are Not Considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral tubal ligation or bilateral salpingectomy
    - Documented bilateral oophorectomy

- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
- **Note**: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause prior to the Day 1 Visit.
        – In the absence of 12 months of amenorrhea, a high FSH and estradiol levels in the postmenopausal range must be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
4. Permanent sterilization at least 6 weeks prior to the Day 1 Visit.

10.6.2. Contraception Guidance

Contraceptive use by male or female participants should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner of a male participant, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.6.3.1). In these cases, follow-up will be conducted on the

pregnant partner in the same manner as a female participant who becomes pregnant during the study.

10.6.2.1. Guidance for Female Participants

Female participants of childbearing potential, or where their menopausal status is in doubt, must have a negative pregnancy test (local urine or local or central serum) before the first dose of study intervention. Additional requirements for pregnancy testing during and after dosing with study intervention are indicated in the SoA (Section 1.3).

The Investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

The Investigator should evaluate the potential for contraceptive method in relationship to the first dose of study intervention.

Female participants must not donate ova from the Day 1 Visit at least until 8 months (generally 5.5 terminal half-lives) after their final dose of study intervention.

Female participants of childbearing potential must use a highly effective or acceptable method of contraception until at least 8 months after the final dose of study intervention.

Highly effective methods are:

1. Intrauterine device in place for at least 6 weeks prior to first dose of study intervention.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of study intervention.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of study intervention.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of study intervention.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study intervention.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of study intervention). Male partner is still required to use condom during heterosexual intercourse.
7. Sexual abstinence for female participants:
    a. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent female participants must refrain from heterosexual intercourse for at least 8 months after the final dose of study intervention.

Other methods of contraception that are not considered as highly effective for female participants, but are acceptable birth control methods that result in a failure rate of more than 1% per year include:

8. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
9. Male or female condom with or without spermicide
10. Cap, diaphragm, or sponge with spermicide
11. A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods)

The following methods of contraception are considered unacceptable in this study:

- Periodic abstinence (calendar, symptothermal or post ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Female condom and male condom should not be used together

10.6.2.2. Guidance for Male Participants

Contraception is the responsibility of the heterosexually active male participants in the study, regardless of his female partner's method of contraception.

Male participants who have had a vasectomy > 6 months prior to the first dose of study intervention must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to the first dose of study intervention and those who have not had a vasectomy must use a condom and spermicide (if locally available and consistent with local regulations) during heterosexual intercourse for at least 8 months after their final dose of study intervention.

Male participants must not donate sperm from the Day 1 Visit until 8 months (generally 5.5 terminal half-lives) after their final dose of study intervention.

10.6.2.2.1. Sexual Abstinence for Male Participants

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom and spermicide (if locally available and consistent with local regulations) during intercourse.

Periodic abstinence (eg, calendar, symptothermal, or post ovulation methods for a female partner) is not considered a highly effective method of contraception for male participants.

10.6.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants from dosing of study intervention until 8 months post dose.

Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study intervention via semen following paternal exposure.

If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion Global Patient Safety (GPS) via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GPS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to study intervention during breastfeeding must also be reported (via the "Pregnancy/Breastfeeding Reporting and Outcome Form") and any AEs experienced by the infant must be reported to Alexion GPS via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

10.6.3.1. Male Participants with Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate "Pregnancy/Breastfeeding Reporting and Outcome Form" and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.6.3.2. Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The information will be recorded on the "Pregnancy/Breastfeeding Reporting and Outcome Form" and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- For all Alexion products, both in development or postapproval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.7. Exploratory Biomarkers

Blood and urine samples will be collected for exploratory assessments related to ravulizumab or CSA-AKI and related diseases. These samples may also be used for further exploratory development of assays related to the mechanism of action of ravulizumab, disease process and/or pathways associated with CSA-AKI disease state.

- The results of biomarker analyses may be reported in the CSR or later in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a facility selected by Alexion that has adequate measures to protect confidentiality.
- The samples will be retained no longer than 25 years from the date Alexion approves the CSR or other period as per local requirements.

10.8. Participant-Reported Outcome Instruments

KDQOL-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

SAMPLE

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
2. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
3. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

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(SF-12v2® Health Survey Standard, United States (English))

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
4. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
6. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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(SF-12v2® Health Survey Standard, United States (English))

SAMPLE

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SAMPLE

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Your Kidney Disease

How true or false is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
13. My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SAMPLE

During the past 4 weeks, to what extent were you bothered by each of the following?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
17. Soreness in your muscles?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Chest pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Cramps?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Itchy skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Dry skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Shortness of breath?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
23. Faintness or dizziness?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Lack of appetite?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Washed out or drained?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Numbness in hands or feet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Nausea or upset stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[a]. (Hemodialysis patient only) Problems with your access site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[b]. (Peritoneal dialysis patient only) Problems with your catheter site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SAMPLE

Effects of Kidney Disease on Your Daily Life

Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease <u>bother</u> you in each of the following areas?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
29. Fluid restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Dietary restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Your ability to work around the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Your ability to travel?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Being dependent on doctors and other medical staff?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Stress or worries caused by kidney disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Your sex life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Your personal appearance?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

SAMPLE

EuroQol 5 Dimensions (EQ-5D-5L)



Header to be completed by Study Site	
Study Number: ALXN1210-ALS-308	Subject ID: _____
Date Completed: _____	Time Completed: _____
Completed by: ☐ Patient	

SAMPLE

Health Questionnaire

English version for the USA

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Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

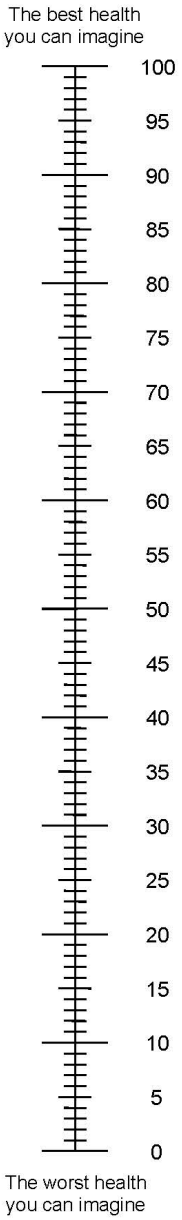
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

SAMPLE

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- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



SAMPLE

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FACIT-Fatigue Subscale version 4

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

SAMPLE - NOT FOR PATIENT USE

English (Universal)
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16 November 2007
Page 1 of 1

10.9. COVID-19 Risk Assessment

AKI can cause irreversible morbidity and even mortality, if untreated. As such, the benefit a participant may receive from treatment with ravulizumab is potentially significant.

Given that treatment for CKD may involve immunosuppression, there is theoretical concern that the risk for infection may be higher than in participants not receiving immunosuppressants. However, there is no specific data to further inform this risk. The site Investigator will therefore balance the risk/benefit considerations in the study participant taking these factors into account.

The potential operational risks identified, and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 14.

Table 14: Potential Operational Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform nonurgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new participants at sites unless the sites have the resourcing and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for IP and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the

Table 14: Potential Operational Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		reason the data is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; IP = investigational product

10.10. COVID-19 Vaccine Risk Assessment

There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ravulizumab. It is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished by ravulizumab administration, based on ravulizumab's mechanism of action. It is also unlikely that COVID-19 vaccination would impact ravulizumab's mechanism of action. Same precautions should be taken as described in Section 8.1.4 for vaccines.

Vaccination may further activate complement. As a result, participants with complement mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, participants should be closely monitored for disease symptoms after recommended vaccination.

Because vaccines may activate complement, if possible, consider vaccination when the underlying complement mediated disease is clinically controlled and when systemic C5 inhibitor concentration (and subsequent complement blockade) is relatively high, shortly after administration.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination.

The potential risks identified, and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 15.

Table 15: Potential Operational Risks and Mitigation Measures due to COVID-19 Vaccine

Risks Category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules and increase missed visits and/or participant study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures).	Capture specific information in the CRF that explains the reason for missing data (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine).

Abbreviations: COVID-19 = coronavirus disease 2019; CRF = case report form

10.11. Abbreviations

The following abbreviations and terms are used in this study protocol.

Table 16: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACE	angiotensin-converting enzyme
ACR	albumin to creatinine ratio
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
AKI	acute kidney injury
ANOVA	analysis of variance
AV	aortic valve
C5	complement component 5
C5b-9	terminal complement complex (membrane attack complex)
CABG	coronary artery bypass graft
CHW	Cui, Hung, & Wang
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CMH	Cochran-Mantel-Haenszel
CPB	cardiopulmonary bypass
CPR	cardiopulmonary resuscitation
CRF	case report form
CSA-AKI	cardiac surgery-associated acute kidney injury
CSR	clinical study report
CTIS	Clinical Trial Information System
DAC	Data Analysis Center
DGF	delayed graft function

Table 16: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
DMC	Data Monitoring Committee
DPIA	data protection impact assessment
EC	exclusion criterion
ECD	expanded criteria donor
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	early discontinuation
EDC	Electronic Data Collection
EMA	European Medicines Agency
eGFR	estimated glomerular filtration rate
EQ-5D-5L	European Quality of Life Group's 5-dimension 5-level (questionnaire)
eCRF	electronic case report form
ESKD	end-stage kidney disease
EU CTR	European Union Clinical Trials Regulation
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue (questionnaire)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IABP	intra-aortic balloon pump
IAS	Immunogenicity Analysis Set
IB	Investigator's Brochure
IC	inclusion criterion
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Table 16: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ICU	intensive care unit
IE	intercurrent event
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IP	investigational product
IQR	interquartile range
IRB	Institutional Review Board
IRI	ischemia/reperfusion injury
IRT	Interactive Response Technology
iSAP	interim statistical analysis plan
IT	information technology
ITT	Intent-to-Treat
IV	intravenous(ly)
KDIGO	Kidney Disease: Improving Global Outcomes (nonprofit foundation)
KDQOL-36	Kidney Disease Quality of Life instrument – 36 items (questionnaire)
KRT	kidney replacement therapy
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	myocardial infarction
mITT	modified Intent-to-Treat
MMRM	mixed model repeated measures
MV	mitral valve
NAb	neutralizing antibody
NGAL	neutrophil gelatinase-associated lipocalin
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
POS	Post-operative Set

Table 16: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
PPS	Per Protocol Set
PV	pulmonic valve
QoL	quality of life
QTL	quality tolerance limit
r	valve repair
R	valve replacement
RBC	red blood cell
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
RRR	relative risk reduction
SAE	serious adverse event
SAP	statistical analysis plan
sC5b-9	soluble C5b-9
sCr	serum creatinine
sCysC	serum Cystatin C
SGLT-2	sodium-glucose cotransporter-2
SKD	sustained kidney dysfunction
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
STS	Society of Thoracic Surgeons
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIMP-2	tissue inhibitor of metalloproteinase-2
TM	thrombomodulin
TNF-RI	tumor necrosis factor receptor I
TV	tricuspid valve
WBC	white blood cell
WOCBP	woman of childbearing potential

10.12. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 2	Global	28 Mar 2024	The primary reasons for the amendment were to modify the key secondary endpoints and the order of endpoints within the pre-specified fixed sequence testing procedure based on health authority feedback and to update the methodology for the sample size re-estimation for the final analysis. Additional updates included changes to the inclusion and exclusion criteria to clarify and simplify eligibility requirements.
Amendment 1	Global	12 Jun 2023	The primary reasons for the amendment were to address the requirements for conducting a clinical study under the EU CTR and clarify 2 inclusion criteria and 2 exclusion criteria.
Original protocol	Not applicable	30 Sep 2022	Not applicable

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