TITLE PAGE

Protocol Title: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants With Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)

Protocol Number: ALXN1210–NEPH–202

Amendment Number: 4.0

Compound: Ravulizumab (ALXN1210)

Study Phase: 2

Brief Title: Phase 2 Study of Ravulizumab in Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)

Sponsor Name: Alexion Pharmaceuticals, Inc.

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

Regulatory Agency Identifier Number(s)

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Sponsor Signatory:

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

[redacted] Date

[redacted]
Alexion Pharmaceuticals, Inc.

Medical Monitor 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 ICH E6 Guidelines 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

_____

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 4.0

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC and in the European Union Clinical Trials Regulation (EU CTR) 536/2014 Article 2, 2 (13) because it includes clarification of eligibility criteria and introduces the option to perform an interim analysis.

Overall Rationale for the Amendment:

The purpose of this amendment is to provide clarification for the exclusion criterion regarding history of hepatitis B and C. Consistent with the previous criteria, participants with active hepatitis B or C infection are excluded. Specified exclusion criteria has been implemented to align with ALXN1210-NEPH-202 local amendment 2.1 and other studies of ravulizumab. Potential inclusion of such participants does not have anticipated effects on efficacy or safety endpoints. Consistent with the IgAN cohort, the option to perform an early interim analysis for the LN cohort was added. This early interim analysis will not include hypothesis testing and will not impact the progression of the study.

Section # and Title	Description of Change	Brief Rationale
Section 2.3.1 Risk Assessment	Revised the text of immunogenicity	For clarification
Section 5.2.1 Common Exclusion Criteria	Revised the text of Exclusion Criterion #10	To clarify the target patient population to allow for expanded participant recruitment and to align with ALXN1210-NEPH-202 local amendment 2.1
Section 8.3.5.1 Virus Serology	Revised the description of HBV and HCV testing at Screening	To align with revision to Exclusion Criterion #10
Section 8.10 Immunogenicity Assessments	Revised the text of immunogenicity	For clarification
Section 9.5.2 Interim Analysis for Primary Endpoint	Revised the text for an early IA for either disease cohort	To allow the option to perform an early interim analysis in the LN cohort. The early interim analysis will not include hypothesis testing and will not impact the progression of the study.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants With Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)

Brief Title: Phase 2 Study of Ravulizumab in Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)

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Rationale:

Chronic kidney disease (CKD) has become a worldwide public health issue due to its high incidence, poor prognosis, and substantial economic burden. When not properly diagnosed and managed, CKD can lead to many adverse outcomes such as end-stage renal disease (ESRD). Despite advances in immunosuppressive treatments, certain types of glomerulonephritis such as lupus nephritis (LN) and immunoglobulin A nephropathy (IgAN) continue to respond poorly to treatment, resulting over time in CKD. There has been some progress in terms of approved treatments for patients with LN with recent approval of belimumab in multiple regions, including the US, EU, and Japan, and voclosporin in the US. At two years, belimumab showed a complete renal response (CRR) of 30.0% vs 20.0% compared to placebo (Furie, 2020). At one year, voclosporin showed a CRR of 40.8% vs 22.5% compared to placebo (Arriens, 2020). However, there remains a significant unmet need for interventions that would allow more novel, definitive, and tolerable treatments for patients with LN as well as for patients with IgAN, particularly in those who are at risk of progressive kidney disease.

The pathophysiology of glomerular diseases such as LN and IgAN involves a complex overlap of abnormal cellular immune response, loss of humoral immune tolerance, aberrant coagulation, and systemic inflammation. Complement dysregulation has emerged as an additional driving factor that interplays with these pathways in LN and IgAN. The narrow vessels and high perfusion in the kidney make this organ particularly susceptible to complement-mediated injury. Histologic evidence of complement deposition observed upon kidney biopsy of patients with either LN or IgAN suggests a pathological role. This theory is supported by the association of serum complement levels with disease activity and response to treatment, particularly in patients with LN.

The objectives of this study are to evaluate the safety and efficacy of ravulizumab (ULTOMIRIS®) administered by intravenous (IV) infusion compared to placebo and demonstrate proof-of-concept of the efficacy of terminal complement inhibition in participants with LN or IgAN.

Objectives and Endpoints

Objectives	Endpoints
Primary (Both Cohorts)	
To evaluate the efficacy of ravulizumab compared with placebo to reduce proteinuria in adult participants with LN or IgAN	Percentage change in proteinuria from baseline to Week 26 (based on 24-hr urine collection[s] at each time point)
Secondary (Both Cohorts)	
To evaluate the efficacy of ravulizumab compared with placebo to improve measures of kidney function in adult participants with LN or IgAN	Percentage change in proteinuria from baseline to Week 50 (based on 24-hr urine collection[s] at each time point)
	Percentage of participants with > 30% and > 50% reduction in proteinuria at Week 26 and Week 50 compared to baseline (based on 24-hr urine collection[s] at each time point)
	Change from baseline in eGFR at Week 26 and Week 50
	Absolute values and change from baseline in serum C3 and C4 concentrations at Week 26 and Week 50
Secondary (LN Cohort Only)	
To evaluate the efficacy of ravulizumab compared with placebo to improve measures of kidney function in adult participants with LN	Percentage of participants meeting the criteria for CRR at Week 26 and Week 50
	Percentage of participants meeting the criteria for PRR at Week 26 and Week 50
	Time to UPCR < 0.5 g/g as measured by spot urine sample
	Percentage of participants achieving corticosteroid taper to 7.5 mg/day at Weeks 14, 26, and 50
	Percentage of participants with Renal Flare through Week 50
	Percentage of participants with Extrarenal SLE Flare through Week 50
	Percentage of participants with Treatment Failure through Week 50
	Percentage of participants with Suboptimal Response through Week 50
	Absolute values and change from baseline in serum albumin at Week 26 and Week 50
Secondary (IgAN Cohort Only)	
To evaluate the efficacy of ravulizumab compared with placebo on measures of kidney function in adult participants with IgAN	Percentage of participants meeting the criteria for Partial Remission at Week 26 and Week 50

Objectives	Endpoints
PK/PD/Immunogenicity (Both Cohorts)	
To characterize the PK/PD of ravulizumab in adult participants with LN or IgAN	Absolute values and change from baseline in total C5 and free C5 concentrations over time
	Absolute values and change from baseline in ravulizumab concentrations over time
To characterize the potential for immunogenicity of ravulizumab in adult participants with LN or IgAN	Incidence of ADAs over time
Safety (Both Cohorts)	
To characterize the safety and tolerability of ravulizumab in adult participants with LN or IgAN	Incidence of AEs and SAEs over time

Abbreviations: ADA = antidrug antibody; AE = adverse event; C3, C4, and C5 = complement components 3,4, and 5; CRR = complete renal response; eGFR = estimated glomerular filtration rate; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis; PD = pharmacodynamics; PK = pharmacokinetics; PRR = partial renal response; SAE = serious adverse event; SLE = systemic lupus erythematosus; UPCR = urine protein to creatinine ratio

Overall Design

Study ALXN1210-NEPH-202 is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study of ravulizumab in addition to allowed concomitant therapy consistent with the standard of care in 120 adult participants (18 to 75 years of age) with either LN or IgAN. All participants must be naive to complement inhibitor treatment and have either a diagnosis of LN with an active flare or IgAN based on kidney biopsy, estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73m^2, and proteinuria [defined as urine protein to creatinine ratio (UPCR) ≥ 1 g/g from one 24-hr urine collection (LN cohort) or as mean protein ≥ 1 g/24-hr from 2 valid 24-hr collections (IgAN cohort)]. Participants in the IgAN cohort must have been treated with stable doses of the maximum tolerated renin-angiotensin system (RAS)-inhibiting medications and have controlled, stable blood pressure (< 140/90 mmHg) for ≥ 3 months prior to Screening.

Approximately 60 participants in each disease cohort will be randomly assigned in a 2:1 ratio to receive ravulizumab or placebo (40 ravulizumab, 20 placebo). Randomization will be stratified by whether corticosteroid induction treatment was initiated prior to Screening versus during the Screening Period for participants in the LN cohort and by mean proteinuria (1 to 2 g/day versus > 2 g/day) from 2 valid 24-hr urine collections during Screening Period for participants in the IgAN cohort.

The study consists of an up to 6-week Screening Period, a 26-week Initial Evaluation Period, a 24-week Extension Period, and a 36-week post-treatment Follow-up Period.

During the Initial Evaluation Period, all participants will receive a weight-based loading dose of ravulizumab or placebo on Day 1, followed by maintenance doses of ravulizumab or placebo on Day 15 and then once every 8 weeks (q8w) thereafter. Loading and maintenance doses will be determined based on body weight (see table below). All participants will receive allowed

concomitant therapy consistent with the standard of care for participants with LN and IgAN throughout the study.

During the 24-week Extension Period, participants in the LN cohort will continue to receive their randomized allocation of study drug (ravulizumab or placebo) q8w. Participants in the LN cohort will receive additional standard of care therapy in the event of a protocol-defined Renal Flare or Severe Extrarenal systemic lupus erythematosus (SLE) Flare. Approved novel treatment(s) for LN is allowed. Additional standard of care therapy for participants with Suboptimal Response is allowed at the clinical discretion of the Investigator in conversation with the Medical Monitor. For the IgAN cohort, participants in the placebo group will receive a blinded loading dose of ravulizumab at Week 26 and participants in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg at Week 26. Starting Week 28, all participants in the IgAN cohort will receive open-label weight-based doses of ravulizumab q8w until the end of the Extension Period.

During the 36-week Post-treatment Follow-up Period, all participants will continue to receive standard of care and will be monitored for safety, clinical events of interest, and kidney function. Participants who discontinue study drug early and agree to remain in the study should continue to attend their scheduled protocol visits until Week 50. During these visits, all assessments except for study drug administration should be performed according to the Schedule of Assessments. Participants who withdraw from the study will be followed for safety until 8 weeks after the last dose of study drug. The end of study is defined as the last participant's last visit in the Post-treatment Follow-up Period.

To ensure the adequacy of the dose regimen, an interim pharmacokinetics (PK)/ pharmacodynamics (PD) analysis for dose confirmation will be conducted by an independent clinical pharmacologist. The interim PK analysis will be conducted using masked PK/PD data from the first 10 participants treated with ravulizumab (a minimum of 3 participants in each disease-specific cohort). In the event of dose adjustments, the participants treated with the previous dose will switch over to the new dose and continue treatment on study but will be excluded from the primary efficacy analysis. Replacement participants may be enrolled to preserve study power.

Disclosure Statement: This is a parallel group treatment study with 2 disease cohorts of participants randomly assigned to 1 of 2 treatments that are participant, Investigator, and outcomes assessor blinded.

Number of Participants: Approximately 120 adult participants will be randomized. This will include approximately 60 participants in the LN cohort and approximately 60 participants in the IgAN cohort.

Intervention Groups and Duration:

Eligible participants will be enrolled into the study and will be randomized in a 2:1 ratio to receive either ravulizumab IV infusion or placebo IV infusion in combination with allowed concomitant therapy.

Ravulizumab will be supplied as a sterile, preservative-free 10 mg/mL solution in single-use vials, designed for administration via IV infusion by diluting into commercially available saline

(0.9% sodium chloride injection). Dosages will be based on the participant's body weight, as shown in the table below:

Body Weight Range (kg)[a]	Ravulizumab Loading Dose (mg)	Ravulizumab Maintenance Dose (mg)
≥ 40 to < 60	2400	3000
≥ 60 to < 100	2700	3900
≥ 100	3000	5400

a Dose regimen will be based on the last recorded study visit body weight. If the study drug is prepared the night before a visit, the weight from the most recent study visit should be used.

Placebo will have an identical appearance to that of ravulizumab.

For each participant, the total duration of study treatment (ravulizumab or placebo) will be up to 50 weeks and the total duration of study participation will be up to 86 weeks.

Data Monitoring Committee: No

Ethical Considerations and Benefit-Risk Assessment

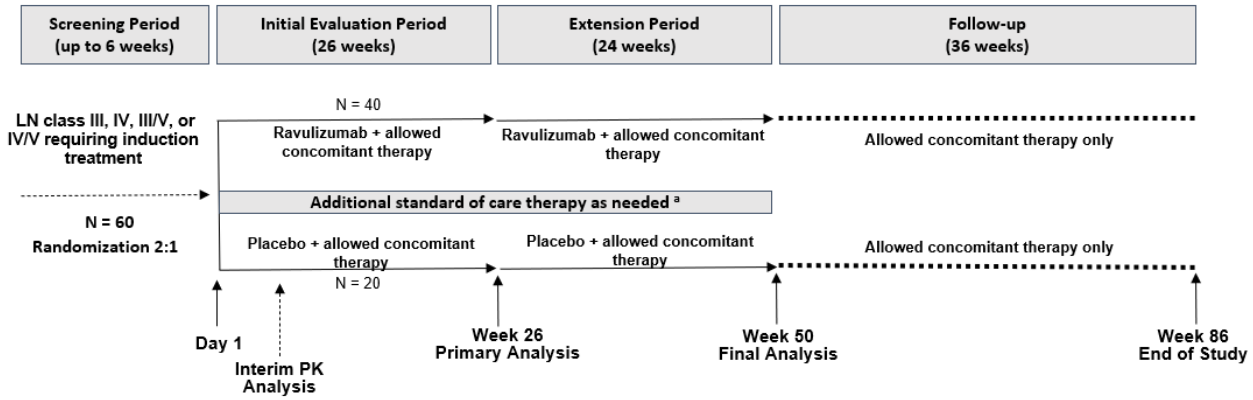
This study will be conducted as specified in this protocol and in accordance with the following:

- 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 ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

A thorough benefit-risk assessment has been performed for ravulizumab IV. Measures will be taken to minimize risk to study participants. The potential risks identified in association with ravulizumab IV are justified by the anticipated benefits that may be afforded to participants with LN or IgAN.

1.2. Study Design Schematics

Figure 1: Study Design Schematic – LN Cohort

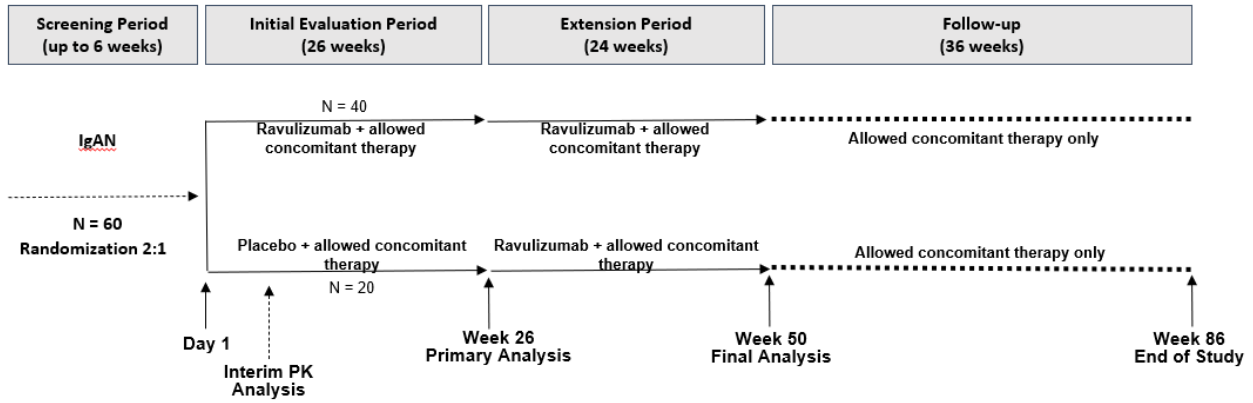


Note: Randomization will be stratified by whether corticosteroid induction treatment was initiated prior to Screening versus during the Screening Period. Allowed concomitant therapy consists of corticosteroids and mycophenolate mofetil. Weight-based dosing regimen (see table above) will be based on the last recorded study visit body weight.

[a] Participants will receive additional standard of care therapy in the event of a protocol-defined Renal Flare or Severe Extrarenal SLE Flare. Approved novel treatment(s) for LN is allowed. After Week 26, additional standard of care therapy for participants with Suboptimal Response is allowed at the clinical discretion of the Investigator in conversation with the Medical Monitor

Abbreviations: LN = lupus nephritis; PK = pharmacokinetics; SLE = systemic lupus erythematosus

Figure 2: Study Design Schematic – IgAN Cohort



Note: Randomization will be stratified by mean proteinuria (1 to 2 g/day versus > 2 g/day) based on 2 valid 24-hr urine collections during the Screening Period. Allowed concomitant therapy consisting of stable maximally tolerated dose of ACE inhibitors or ARBs. Weight-based dosing regimen (see table above) will be based on the last recorded study visit body weight.

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; IgAN = immunoglobulin A nephropathy; PK = pharmacokinetics

1.3. Schedule of Activities

Schedules of activities are provided as follows:

- Initial Evaluation Period: Screening to Week 26 (Day 183) Visit (LN cohort in Table 1 and IgAN cohort in Table 2)
- Extension Period (LN cohort in Table 3 and IgAN cohort in Table 4)
- Post-Treatment Follow-up (Both LN and IgAN cohorts in Table 5)

Table 1: Schedule of Activities During the Initial Evaluation Period: Screening to Week 26 Visit (LN Cohort)

Period	**Screen-ing**	**Initial Evaluation Period**										**Eval. for Renal Flare and Extrarenal SLE Flare**	**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		**Additional visits can be performed as needed. An ED Visit is required if participants discontinue early.**
Week	**Up to 6 W**		**W1** [a]	**W2**	**W4**	**W6** [b]	**W10**	**W14**	**W18**	**W22**	**W26/ ED**[c]		
Days and Window	**D -42 to -1**	**D1**	**D8 ± 2**	**D15 ± 3**	**D29 ± 3**	**D43 ± 5**	**D71 ± 5**	**D99 ± 5**	**D127 ± 5**	**D155 ± 5**	**D183 ± 5**		
General Assessments/Procedures													
Informed consent	X												
Inclusion/exclusion	X												Confirm eligibility prior to first dose of ravulizumab; participants may be rescreened once
Demographics	X												
Medical history	X												
LN history/diagnosis	X												LN guidelines in Section 10.9 and Section 10.10
Documentation of kidney biopsy	X												Biopsy obtained ≤ 6 months prior to Screening or during Screening. Send local pathology report and slides to Central Pathology Laboratory (Section 8.1.5.3)
Meningococcal, Hib and *S pneumoniae* vaccination	X				Completion of vaccination series according to national and local schedule guidelines								Section 8.1.6
Prior LN therapy	X												Record corticosteroid and MMF usage (Section 6.5.1)
Weight[d]	X	X	X	X	X	X	X	X	X	X	X		
Height	X												
Pregnancy test (WOCBP only)	X	X		X			X		X		X		Serum test required at Screening and ED; urine test all other visits
HIV, HCV, and HBV	X												

Table 1: Schedule of Activities During the Initial Evaluation Period: Screening to Week 26 Visit (LN Cohort)

Period	**Screen-ing**	**Initial Evaluation Period**										**Eval. for Renal Flare and Extrarenal SLE Flare**	**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		**Additional visits can be performed as needed. An ED Visit is required if participants discontinue early.**
Week	**Up to 6 W**		**W1** [a]	**W2**	**W4**	**W6** [b]	**W10**	**W14**	**W18**	**W22**	**W26/ ED**[c]		
Days and Window	**D -42 to -1**	**D1**	**D8 ± 2**	**D15 ± 3**	**D29 ± 3**	**D43 ± 5**	**D71 ± 5**	**D99 ± 5**	**D127 ± 5**	**D155 ± 5**	**D183 ± 5**		
Dispense participant safety card	X												Instruct participants to carry safety card at all times and bring it to scheduled visits
Efficacy Assessments													
24-hr urine collection[e]	X										X	X[f]	One collection is needed as soon as possible during Screening. Two collections must be obtained within 2 weeks prior to Week 26 (Section 8.2.1)
Morning spot urine sample[e]	X	X	X	X	X	X	X	X	X[g]	X	X	X	Obtain sample prior to dosing, vaccination, and biopsy
eGFR	X	X	X	X	X	X	X	X	X	X	X	X[f]	One additional blood draw for eGFR (serum creatinine) is required within 2 weeks prior to the Week 26 visit.
Monitor for Renal and Extrarenal SLE Flare [f]		Continuous monitoring										X	Refer to Section 3.2.1 and 3.2.2 for definitions. Document use of additional standard of care therapy and/or repeat biopsy[f], if applicable.
Blood sample for C3, C4, and CH50	X	X		X			X		X		X	X	
Safety Assessments													
Physical examination	X	X									X		
Abbreviated PE			X	X	X	X	X	X	X	X			
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X		

Table 1: Schedule of Activities During the Initial Evaluation Period: Screening to Week 26 Visit (LN Cohort)

Period	**Screen-ing**	**Initial Evaluation Period**										**Eval. for Renal Flare and Extrarenal SLE Flare**	**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		**Additional visits can be performed as needed. An ED Visit is required if participants discontinue early.**
Week	**Up to 6 W**		**W1** [a]	**W2**	**W4**	**W6** [b]	**W10**	**W14**	**W18**	**W22**	**W26/ ED**[c]		
Days and Window	**D -42 to -1**	**D1**	**D8 ± 2**	**D15 ± 3**	**D29 ± 3**	**D43 ± 5**	**D71 ± 5**	**D99 ± 5**	**D127 ± 5**	**D155 ± 5**	**D183 ± 5**		
ECG[i]	X										X		
Prior medications and procedures	X												
Concomitant medications, nonpharmacologic therapies, and procedures		Continuous monitoring										X	
Adverse events	Continuous monitoring											X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology and coagulation	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis and sediment	X	X	X	X	X	X	X	X	X	X	X	X	Obtain sample from a morning void prior to dosing
Participant safety card review		X	X	X	X	X	X	X	X	X	X	X	Confirm participants carry safety card at all times
Pharmacokinetic and Pharmacodynamic Assessments													
Blood samples for PK/PD[j]		B/P	X	T/P	X		T/P		T/P		T	X	Samples can be obtained anytime at ED Visit
Blood samples for ADA		B			X		T				T		Samples can be obtained anytime at ED Visit
Exploratory Assessments													
EQ-5D-5L		X					X				X		
SF-36		X					X				X		
FACIT-Fatigue		X									X		

Table 1: Schedule of Activities During the Initial Evaluation Period: Screening to Week 26 Visit (LN Cohort)

Period	**Screen-ing**	**Initial Evaluation Period**										**Eval. for Renal Flare and Extrarenal SLE Flare**	**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		**Additional visits can be performed as needed. An ED Visit is required if participants discontinue early.**
Week	**Up to 6 W**		**W1** [a]	**W2**	**W4**	**W6** [b]	**W10**	**W14**	**W18**	**W22**	**W26/ ED**[c]		
Days and Window	**D -42 to -1**	**D1**	**D8 ± 2**	**D15 ± 3**	**D29 ± 3**	**D43 ± 5**	**D71 ± 5**	**D99 ± 5**	**D127 ± 5**	**D155 ± 5**	**D183 ± 5**		
SLEDAI-2K		X									X	X	Perform as needed for evaluation of Extrarenal SLE Flare
Blood and urine samples for biomarkers	X	X		X			X		X		X	X	
Blood sample for anti-dsDNA and anti-C1q	X	B									X	X	
Blood and urine samples for RTCA	X	X		X			X		X		X		To be performed at selected sites only. See Section 8.9.3
Kidney biopsy[k]												X[k]	Send local pathology report and microscopy slides to the Central Pathology Laboratory (Section 8.1.5.3)
Administration of Study Intervention													
Randomization		X											
Allowed concomitant LN therapy	X	Continuous monitoring											Section 6.5.1
Ravulizumab or placebo		X		X			X		X		--[l]		Administer after all other required tests/procedures

Note: All assessments should be performed prior to administration of study drug on dosing days, unless otherwise specified.

[a] The Week 1 Visit is not required for participants enrolled after completion of the Dose Confirmation Analysis (Section 9.5.1).

[b] Visit can be conducted at the discretion of the Investigator.

[c] For participants who discontinue the study prior to the end of the Initial Evaluation Period, the ED Visit should be completed as soon as possible. In addition, a Follow-up Phone Call must be performed 8 weeks following the participant's last dose of study drug to collect information on concomitant medications, nonpharmacologic therapies and procedures, and AEs.

Table 1: Schedule of Activities During the Initial Evaluation Period: Screening to Week 26 Visit (LN Cohort)

[d] Weight should be obtained at every visit and measured predose on dosing visits. The dose regimen is based on the last recorded study visit body weight. If the study drug is prepared the night before a visit, the weight from the most recent study visit should be used.

[e] The 24-hr urine collection and spot urine samples must be obtained prior to or > 7 days after biopsy procedures.

[f] Renal Flare (as defined in Section 3.2.1) and/or Extrarenal SLE Flare (as defined in Section 3.2.2) may occur at any time through Week 50. Evaluation of Renal Flare requires a UPCR from a spot urine sample that is confirmed on a 24-hr urine collection as well as 2 serum creatinine samples obtained within a 2-week period. Evaluation of Renal and Extrarenal SLE Flare must be performed as soon as possible upon notification to the Investigator of symptom onset. If Renal Flare or Extrarenal SLE Flare occurs between scheduled visits, only the assessments for the Renal Flare/Extrarenal SLE Flare visit are needed. If Renal Flare or Extrarenal SLE Flare occur on a scheduled visit, all scheduled assessments should be performed for that visit as well as any additional assessments required for the evaluation of the flare.

[g] Two spot urine samples should be obtained the same morning at Week 18.

[h] Vital sign measurements include systolic and diastolic BP, pulse oximetry, heart rate, respiratory rate, and temperature. On dosing days, vital signs will be taken predose.

[i] Single 12-lead ECG will be collected at Screening and predose on Day 183 and any time on the ED Visit day. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[j] For indicated visits falling on dosing days, PK/PD samples will be collected predose (within 0.5 hours prior to the start of infusion) and at EOI (within 0.5 hours after the EOI from the participant's opposite, noninfused arm). 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 the dose. As noted, the postdose sample must be drawn from the opposite, noninfused arm. For indicated visits not falling on dosing days, samples may be collected at any time that visit day.

[k] Participants may receive a kidney biopsy for clinical reasons or for evaluation of a Renal Flare (as defined in Section 3.2.1) at the discretion of the Investigator. The local pathology report and microsection slides from kidney biopsies performed at other times during the study prior to Week 86 should also be sent to the Central Pathology Laboratory for review as soon as possible. Since examination of the biopsy pathology results may potentially unblind the study treatment (ravulizumab or placebo), Investigators and study site personnel should not examine the biopsy pathology results for immunohistochemistry of complement prior to Week 50.

[l] The primary efficacy endpoint assessment will be obtained prior to dosing on Day 183. Dosing on Day 183 is the start of the Extension Period. Please refer to additional Day 183 post-dose assessments in Table 3.

Abbreviations: ADA = antidrug antibody; AE = adverse event; B = baseline; BP = blood pressure; C3, C4, C1q = complement component 3, 4, and C1q; CH50 = 50% hemolytic complement activity; D = day; dsDNA = double-stranded DNA; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; EOI = end of infusion; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; Eval. = evaluation; FACIT = Functional Assessment of Chronic Illness Therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis; MMF = mycophenolate mofetil; P = postdose; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; RTCA = real time complement activity; SF-36 = Short Form (36) Health Survey; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) Modification; T = trough (predose); UPCR = urine protein to creatinine ratio; W = week; WOCBP = woman of childbearing potential

Table 2: Schedule of Activities During the Initial Evaluation Period: Screening to Week 26 Visit (IgAN Cohort)

Period	**Screen -ing**	**Initial Evaluation Period**									**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Additional visits can be performed as needed. An ED Visit is required if participants discontinue early.**
Week	**Up to 6 W**		**W1[a]**	**W2**	**W4**	**W10**	**W14**	**W18**	**W22**	**W26/ ED[b]**	
Days and Window	**D -42 to -1**	**D1**	**D8 ± 2**	**D15 ± 3**	**D29 ± 3**	**D71 ± 5**	**D99 ± 5**	**D127 ± 5**	**D155 ± 5**	**D183 ± 5**	
General Assessments/Procedures											
Informed consent	X										
Inclusion/exclusion	X										Confirm eligibility prior to first dose of ravulizumab; participants may be rescreened once
Demographics	X										
Medical history	X										
IgAN history/diagnosis	X										IgAN guidelines in Section 10.11
Documentation of kidney biopsy	X										Kidney biopsy performed during or prior to Screening (any time prior to Day 1). Send local pathology report and microscopy slides to Central Pathology Laboratory (Section 8.1.5.3)
Prior IgAN therapy	X										Record ACE/ARB usage (Section 6.5.2)
Meningococcal, Hib and *S pneumoniae* vaccination	X										Section 8.1.6
Weight[d]	X	X	X	X	X	X	X	X	X	X	
Height	X										
HIV, HCV, and HBV	X										
Pregnancy test (WOCBP only)	X	X		X		X		X		X	Serum test required at Screening and ED; urine test all other visits
Dispense participant safety card	X										Instruct participants to carry safety card at all times and bring it to scheduled visits
Efficacy Assessments											

Table 2: Schedule of Activities During the Initial Evaluation Period: Screening to Week 26 Visit (IgAN Cohort)

Period	**Screen -ing**	**Initial Evaluation Period**									**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Additional visits can be performed as needed. An ED Visit is required if participants discontinue early.**
Week	**Up to 6 W**		**W1[a]**	**W2**	**W4**	**W10**	**W14**	**W18**	**W22**	**W26/ ED[b]**	
Days and Window	**D -42 to -1**	**D1**	**D8 ± 2**	**D15 ± 3**	**D29 ± 3**	**D71 ± 5**	**D99 ± 5**	**D127 ± 5**	**D155 ± 5**	**D183 ± 5**	
24-hr urine collection[c]	X									X	2 valid 24-hour collections are required during Screening and within 2 weeks of the Week 26 Visit (Section 8.2.1)
Morning spot urine sample[c]	X	X	X	X	X	X	X	X[e]	X	X	Obtain sample prior to dosing
eGFR	X	X	X	X	X	X	X	X	X	X	
Blood sample for C3, C4, and CH50	X	X		X		X		X		X	
Safety Assessments											
Physical examination	X	X								X	
Abbreviated PE			X	X	X	X	X	X	X		
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	
ECG[g]	X									X	
Prior medications and procedures	X										
Concomitant medications, nonpharmacologic therapies, and procedures	Continuous monitoring										
Adverse events	Continuous monitoring										
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	
Hematology and coagulation	X	X	X	X	X	X	X	X	X	X	
Urinalysis and sediment	X[h]	X	X	X	X	X	X	X	X	X	Obtain sample from a morning void prior to dosing

Table 2: Schedule of Activities During the Initial Evaluation Period: Screening to Week 26 Visit (IgAN Cohort)

Period	**Screen -ing**	**Initial Evaluation Period**									**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Additional visits can be performed as needed. An ED Visit is required if participants discontinue early.**
Week	**Up to 6 W**		**W1[a]**	**W2**	**W4**	**W10**	**W14**	**W18**	**W22**	**W26/ ED[b]**	
Days and Window	**D -42 to -1**	**D1**	**D8 ± 2**	**D15 ± 3**	**D29 ± 3**	**D71 ± 5**	**D99 ± 5**	**D127 ± 5**	**D155 ± 5**	**D183 ± 5**	
Participant safety card review		X	X	X	X	X	X	X	X	X	Confirm participants carry safety card at all times
Pharmacokinetic and Pharmacodynamic Assessments											
Blood samples for PK/PD[i]		B/P	X	T/P	X	T/P		T/P		T	Samples can be obtained anytime at ED Visit
Blood samples for ADA		B			X	T				T	Samples can be obtained anytime at ED Visit
Exploratory Assessments											
EQ-5D-5L		X				X				X	
SF-36		X				X				X	
Blood and urine samples for biomarkers	X	X		X		X		X		X	
Blood and urine samples for RTCA	X	X		X		X		X		X	To be performed at selected sites only. See Section 8.9.3
Kidney biopsy (if indicated per Investigator)[j]		Continuous monitoring									Send the site pathology report and microscopy slides to the Central Pathology Laboratory (Section 8.1.5.3)
Administration of Study Intervention											
Randomization		X									
Allowed concomitant IgAN therapy	X	Continuous monitoring									Section 6.5.2
Ravulizumab or placebo		X		X		X		X		--[k]	Administer after all other required tests/procedures.

Table 2: Schedule of Activities During the Initial Evaluation Period: Screening to Week 26 Visit (IgAN Cohort)

[a] The Week 1 Visit is not required for participants enrolled after completion of the Dose Confirmation Analysis (Section 9.5.1).
[b] For participants who discontinue the study prior to the end of the Initial Evaluation Period, the ED Visit should be completed as soon as possible. In addition, a Follow-up Phone Call will be performed 8 weeks following the participant's last dose of study drug to collect information on concomitant medications, nonpharmacological therapies and procedures, and AEs.
[c] The 24-hr urine collection and spot urine samples must be obtained prior to or > 7 days after biopsy procedures.
[d] Weight should be obtained at every visit and measured predose on dosing visits. The dose regimen is based on the last recorded study visit body weight. If the study drug is prepared the night before a visit, the weight from the most recent study visit should be used.
[e] Two spot urine samples should be obtained the same morning at Week 18.
[f] Vital sign measurements include systolic and diastolic BP, pulse oximetry, heart rate, respiratory rate, and temperature. On dosing days, vital signs will be taken predose.
[g] Single 12-lead ECG will be collected at Screening and predose on Day 183 and any time on the ED Visit day. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
[h] For participants in the IgAN cohort, eligibility for hematuria can be determined via the local laboratory.
[i] The PK/PD samples will be collected predose (within 0.5 hours prior to the start of infusion) and at EOI (within 0.5 hours after the EOI from the participant's opposite, noninfused arm). 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 the dose. As noted, the postdose sample must be drawn from the opposite, noninfused arm. For indicated visits not falling on dosing days, samples may be collected at any time that visit day.
[j] In the event that a participant has a kidney biopsy (performed at the discretion of the Investigator for clinical reasons as part of standard of care), the local pathology report and microscopy slides should be sent to the Central Pathology Laboratory as soon as possible. Because examination of the kidney biopsy pathology may potentially unblind the study treatment (ravulizumab or placebo), Investigators and study site personnel should not examine the biopsy pathology for immunohistochemistry of complement prior to Week 50.
[k] The primary efficacy endpoint assessment will be obtained prior to dosing on Day 183. Dosing on Day 183 is the start of the Extension Period. Please refer to additional Day 183 post-dose assessments in Table 4.

Abbreviations: ADA = antidrug antibody; ACE = angiotensin-converting enzyme; AE = adverse event; ARB = angiotensin II receptor blocker; B = baseline; BP = blood pressure; C3, C4 = complement component 3 and 4; CH50 = 50% hemolytic complement activity; D = day; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; EOI = end of infusion; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; HBV = hepatitis B virus; HCV = hepatitis C virus; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; IgAN = immunoglobulin A nephropathy; P = postdose; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; RTCA = real time complement activity; SF-36 = Short Form (36) Health Survey; T = trough (predose); W = week; WOCBP = woman of childbearing potential

Table 3: Schedule of Activities During the Extension Period: Week 26 Dose Administration, Week 34 to Week 50 Visits (LN Cohort)

Period	Extension Period				Eval. for Renal Flare and Extrarenal SLE Flare and Suboptimal Response	Notes
Visit	11	12	13	14		Additional visits can be performed as needed. An ED Visit should be performed if participants discontinue early.
Week	W26	W34	W42	W50/ED[a]		
Days and Window	D183	D239 ± 7	D295 ± 7	D351 ± 7		
General Assessments/Procedures						
Weight[b]		X	X	X		
Pregnancy test (WOCBP only)		X	X	X		Serum pregnancy test required at ED; urine pregnancy test all other visits.
Efficacy Assessments						
24-hr urine collection				X	X[c]	Two 24-h urine collections required within 2 weeks prior to the Week 50 Visit (Section 8.2.1). Renal Flare and Suboptimal Response require a 24-hr urine for confirmation
Morning spot urine sample		X	X	X	X	Obtain sample prior to dosing
eGFR		X	X	X	X[c]	One additional blood draw for eGFR (serum creatinine) is required within 2 weeks prior to the Week 50 Visit.
Monitor for Renal Flare and/or Extrarenal SLE Flare and/or Suboptimal Response[c]	Continuous monitoring				X	Refer to Section 3.2.1, Section 3.2.2, and Section 3.2.3 for definitions. Document use of additional standard of care therapy and/or repeat biopsy[f] if applicable
Blood sample for C3, C4, and CH50		X	X	X	X	
Safety Assessments						
Physical examination				X		
Abbreviated physical examination		X	X			
Vital signs[d]		X	X	X		
ECG[e]				X		
Concomitant medications, nonpharmacologic therapies, and procedures	Continuous monitoring				X	

Table 3: Schedule of Activities During the Extension Period: Week 26 Dose Administration, Week 34 to Week 50 Visits (LN Cohort)

Period	**Extension Period**				**Eval. for Renal Flare and Extrarenal SLE Flare and Suboptimal Response**	**Notes**
Visit	**11**	**12**	**13**	**14**		**Additional visits can be performed as needed. An ED Visit should be performed if participants discontinue early.**
Week	**W26**	**W34**	**W42**	**W50/ED[a]**		
Days and Window	**D183**	**D239 ± 7**	**D295 ± 7**	**D351 ± 7**		
Adverse events	Continuous monitoring				X	
Clinical chemistry		X	X	X	X	
Hematology and coagulation		X	X	X		
Urinalysis and sediment		X	X	X		Obtain sample from a morning void prior to dosing
Participant safety card review		X	X	X	X	Confirm participants carry safety card at all times
Pharmacokinetic and Pharmacodynamic Assessments						
Blood samples for PK/PD		T/P	T/P	X		Collect samples at any time during the Week 50/ED Visit
Blood samples for ADA		T	T	X		Collect samples at any time during the Week 50/ED Visit
Exploratory Assessments						
SF-36				X		
EQ-5D-5L				X		
FACIT-Fatigue				X		
SLEDAI-2K				X	X	Perform as needed for evaluation of Extrarenal SLE Flare
Blood samples for anti-dsDNA and anti-C1q				X	X	
Blood and urine samples for biomarkers		X	X	X	X	
Optional kidney biopsy[f]				X[g]	X[f]	Send the local pathology report and microscopy slides to the Central Pathology Laboratory (Section 8.1.5.3)
Administration of Study Intervention						
Allowed concomitant LN therapy	Continuous monitoring				X	Section 6.5.1
Ravulizumab or placebo	X	X	X			Administer after all other required tests/procedures

Table 3: Schedule of Activities During the Extension Period: Week 26 Dose Administration, Week 34 to Week 50 Visits (LN Cohort)

Note: During the Extension Period, participants in the LN cohort will continue to receive their randomized allocation of study drug (ravulizumab or placebo).

[a] For participants who discontinue the study prior to the end of the Extension Period, the ED Visit should be completed as soon as possible. In addition, a Follow-up Phone Call will be performed 8 weeks following the participant's last dose of study drug to collect concomitant medications, nonpharmacological therapies and procedures, and AEs.

[b] Weight should be obtained at every visit and measured predose on dosing visits. The dose regimen is based on the last recorded study visit body weight. If the study drug is prepared the night before a visit, the weight from the most recent study visit should be used.

[c] Renal Flare (as defined in Section 3.2.1) and/or Extrarenal SLE Flare (as defined in Section 3.2.2) and/or Suboptimal Response (as defined in Section 3.2.3) may occur at any time through Week 50. Evaluation of Renal Flare requires a UPCR from a spot urine sample that is confirmed on a 24-hr urine collection as well as 2 serum creatinine samples obtained with a 2-week period. Evaluation of Renal and Extrarenal SLE Flare and Suboptimal Response must be performed as soon as possible upon notification to the Investigator of symptom onset or lack of response. If Renal Flare or Extrarenal SLE Flare or Suboptimal Response occurs between scheduled visits, only the assessments for the Renal Flare/Extrarenal SLE Flare/Suboptimal Response visit are needed. If Renal Flare or Extrarenal SLE Flare or Suboptimal Response occur on a scheduled visit, all scheduled assessments should be performed for that visit as well as any additional assessments required for the evaluation of the flare or lack of response.

[d] Vital sign measurements include systolic and diastolic BP, pulse oximetry, heart rate, respiratory rate, and temperature. On dosing days, vital signs will be taken predose.

[e] Single 12-lead ECG will be collected at any time on Day 351 and the ED Visit. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[f] Participants may have a kidney biopsy for clinical reasons or for evaluation of a Renal Flare (as defined in Section 3.2.1) at the discretion of the Investigator. The local pathology report and microscopy slides from kidney biopsies performed at other times during the study prior to Week 86 should be sent to the Central Pathology Laboratory as soon as possible. Because examination of the kidney biopsy pathology may potentially unblind the study treatment (ravulizumab or placebo), Investigators and study site personnel should not examine the biopsy pathology for immunohistochemistry of complement prior to Week 50.

[g] Participants will be asked to undergo an optional repeat kidney biopsy after completion of the Extension Period. If a participant agrees to a repeat renal biopsy, it should be performed at the Week 50 Visit or within 4 weeks (by Week 54).

Abbreviations: ADA = antidrug antibody; AE = adverse event; BP = blood pressure; C3, C4, C1q = complement components 3, 4, and C1q; CH50 = 50% hemolytic complement activity; D = day; dsDNA = double-stranded DNA; ECG = electrocardiogram; ED = early discontinuation; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; eGFR = estimated glomerular filtration rate; Eval. = evaluation; FACIT = Functional Assessment of Chronic Illness Therapy; LN = lupus nephritis; P = postdose; PD = pharmacodynamics; PK = pharmacokinetics; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) Modification; SF-36 = Short Form (36) Health Survey; T = trough (predose); UPCR = urine protein to creatinine ratio; W = week; WOCBP = woman of childbearing potential

Table 4: Schedule of Activities During the Extension Period: Week 26 Dose Administration, Week 28 to Week 50 Visits (IgAN Cohort)

Period	**Extension Period**					**Notes**
Visit	**10**	**11**	**12**	**13**	**14**	**Additional visits can be performed as needed. An ED Visit should be performed if participants discontinue early.**
Week	**W26**	**W28**	**W36**	**W44**	**W50/ED[a]**	
Days and Window	**D183**	**D197 ± 7**	**D253 ± 7**	**D309 ± 7**	**D351 ± 7**	
General Assessments/Procedures						
Weight[b]		X	X	X	X	
Pregnancy test (WOCBP only)		X	X	X	X	Serum pregnancy test required at ED; urine pregnancy test all other visits
Efficacy Assessments						
24-hr urine collection					X	Obtain 2 valid 24-hr urine collections within 2 weeks of the Week 50 Visit (Section 8.2.1).
Morning spot urine sample		X	X	X	X	Obtain sample prior to dosing
eGFR		X	X	X	X	
Blood sample for C3, C4, and CH50		X	X	X	X	
Safety Assessments						
Physical examination					X	
Abbreviated physical examination		X	X	X		
Vital signs[c]		X	X	X	X	
ECG[d]					X	
Concomitant medications, nonpharmacologic therapies, and procedures	Continuous monitoring					
Adverse events	Continuous monitoring					
Clinical chemistry		X	X	X	X	
Hematology and coagulation		X	X	X	X	
Urinalysis and sediment		X	X	X	X	Obtain sample from a morning void prior to dosing

Table 4: Schedule of Activities During the Extension Period: Week 26 Dose Administration, Week 28 to Week 50 Visits (IgAN Cohort)

Period	Extension Period					Notes
Visit	**10**	**11**	**12**	**13**	**14**	**Additional visits can be performed as needed. An ED Visit should be performed if participants discontinue early.**
Week	**W26**	**W28**	**W36**	**W44**	**W50/ED[a]**	
Days and Window	**D183**	**D197 ± 7**	**D253 ± 7**	**D309 ± 7**	**D351 ± 7**	
Participant safety card review		X	X	X	X	Confirm participants carry safety card at all times
Pharmacokinetic and Pharmacodynamic Assessments						
Blood samples for PK/PD		T/P	T/P	T/P	X	Collect samples at any time during the Week 50/ED Visit
Blood samples for ADA		T	T	T	X	Collect samples at any time during the Week 50/ED Visit
Exploratory Assessments						
SF-36					X	
EQ-5D-5L					X	
Blood and urine samples for biomarkers		X	X	X	X	
Kidney biopsy (if indicated per Investigator)[e]	Continuous monitoring					Send the site pathology report and microscopy slides to the Central Pathology Laboratory (Section 8.1.5.3)
Administration of Study Intervention						
Allowed concomitant IgAN therapy	Continuous monitoring					Section 6.5.2
Ravulizumab[f]	X	X	X	X		Administer after all other required tests/procedures

Note: During the Extension Period, the IgAN placebo group will switch to ravulizumab such that all IgAN participants will be treated with ravulizumab when the study becomes open label for the IgAN group. Participants in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg at Week 26 and continue to receive the weight-based dosing thereafter.

[a] For participants who discontinue the study prior to the end of the Extension Period, the ED Visit should be completed as soon as possible. In addition, a Follow-up Phone Call will be performed 8 weeks following the participant's last dose of study drug to collect concomitant medications, nonpharmacological therapies and procedures, and AEs.

[b] Weight should be obtained at every visit and measured predose on dosing visits. The dose regimen is based on the last recorded study visit body weight. If the study drug is prepared the night before a visit, the weight from the most recent study visit should be used.

[c] Vital sign measurements include systolic and diastolic BP, pulse oximetry, heart rate, respiratory rate, and temperature. On dosing days, vital signs will be taken predose.

[d] Single 12-lead ECG will be collected at any time on Day 351 and the ED Visit. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Table 4: Schedule of Activities During the Extension Period: Week 26 Dose Administration, Week 28 to Week 50 Visits (IgAN Cohort)

[e] Participants may receive kidney biopsy (performed at the discretion of the Investigator for clinical reasons as part of standard of care). The local pathology report and microscopy slides from kidney biopsies performed at other times during the study prior to Week 86 should be sent to the Central Pathology Laboratory as soon as possible. Since examination of the biopsy pathology results may potentially unblind the study treatment (ravulizumab or placebo), Investigators and study site personnel should not examine the biopsy pathology results for immunohistochemistry of complement prior to Week 50.

[f] Participants in the IgAN cohort will receive weight-based doses of ravulizumab (Table 9) q8w until the end of the Extension Period.

Abbreviations: ADA = antidrug antibody; AE = adverse event; BP = blood pressure; C3, C4, = complement components 3, 4; CH50 = 50% hemolytic complement activity; D = day; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; IgAN = immunoglobulin A nephropathy; P = postdose; PD = pharmacodynamics; PK = pharmacokinetics; q8w = once every 8 weeks; SF-36 = Short Form (36) Health Survey; T = trough (predose); W = week; WOCBP = woman of childbearing potential

Table 5: Schedule of Activities During Post-Treatment Follow-up Period (Both LN and IgAN Cohorts)

Period	Post-Treatment Follow-up Period				Notes
Visit	**15**	**16**	**17**	**18**	
Week	**W52[a] (IgAN only)**	**W62**	**W74**	**W86/EoS**	
Days and Window	**D365 ± 7**	**D435**	**D519**	**D603**	
Efficacy Assessments					
Record UPCR results (local laboratory)		X	X	X	Record local laboratory values from the participant's most recent testing prior to or on the study visit. Spot urine samples are sufficient; morning voids are preferred.
Record serum creatinine results (local laboratory)		X	X	X	Record local laboratory values from the participant's most recent testing prior to or on the study visit
Monitor for renal flare and extrarenal SLE flare (LN cohort)		X	X	X	Document in the participant's CRF for the 12-week period since the previous study visit.
Monitor for renal disease progression (IgAN cohort)		X	X	X	
Allowed concomitant therapy for LN or IgAN	Continuous monitoring				
Safety Assessments					
Concomitant medications, nonpharmacologic therapies, and procedures	X			X	Phone visit
Adverse events	X			X	Phone visit

[a] For participants in the IgAN cohort, a Follow-up Phone Call will be performed 8 weeks following the participant's last dose of study drug to collect information on concomitant medications, nonpharmacological therapies, and procedures, and AEs.

Abbreviations: AE = adverse event; CRF = case report form; D = day; EoS = End of Study; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis; SLE = systemic lupus erythematosus; UPCR = urine protein to creatinine ratio; W = week

2. INTRODUCTION

2.1. Study Rationale

CKD has become a worldwide public health issue due to its high incidence, poor prognosis, and substantial economic burden (Lv, 2019). When not properly diagnosed and managed, CKD can lead to many adverse outcomes such as ESRD. Despite advances in immunosuppressive treatments, certain types of glomerulonephritis such as LN and IgAN continue to respond poorly to treatment, resulting over time in CKD. There has been some progress in terms of approved treatments for patients with LN with recent approval of belimumab in multiple regions, including the US, EU, and Japan, and voclosporin in the US. At two years, belimumab showed a CRR of 30.0% vs 20.0% compared to placebo (Furie, 2020). At one year, voclosporin showed a CRR of 40.8% vs 22.5% compared to placebo (Arriens, 2020). However, there remains a significant unmet need for interventions that would allow more novel, definitive, and tolerable treatments for patients with LN as well as for patients with IgAN, particularly in those who are at risk of progressive kidney disease.

The pathophysiology of glomerular diseases such as LN and IgAN involves a complex overlap of abnormal cellular immune response, loss of humoral immune tolerance, aberrant coagulation, and systemic inflammation. Complement dysregulation has emerged as an additional driving factor that interplays with these pathways in LN and IgAN. The narrow vessels and high perfusion in the kidney make this organ particularly susceptible to complement-mediated injury. Histologic evidence of complement deposition observed upon kidney biopsy of patients with either LN or IgAN suggests a pathological role. This theory is supported by the association of serum complement levels with disease activity and response to treatment, in particular in patients with LN (Thurman, 2015).

Ravulizumab (ULTOMIRIS®) is a humanized monoclonal antibody that, like eculizumab (SOLIRIS®), binds to complement component 5 (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 was designed through minimal targeted engineering to substitute 4 amino acids in the eculizumab heavy chain (Sheridan, 2018). These changes extend the half-life of ravulizumab relative to eculizumab, while preserving the high degree of specificity and selectivity of eculizumab for binding to C5 (Sahelijo, 2015). Both ravulizumab and eculizumab bind to the same site on C5. Ravulizumab is administered by IV infusion q8w in adults. The weight-based dosing regimen of ravulizumab, is approved in multiple global regions for treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) and adult and pediatric patients with atypical hemolytic uremic syndrome (aHUS). A detailed description of the chemistry, pharmacology, efficacy, and safety of ravulizumab is provided in the Investigator's Brochure (IB).

The objectives of this study are to evaluate the efficacy and safety of ravulizumab administered by IV infusion compared to placebo and demonstrate proof-of-concept of the efficacy of terminal complement inhibition in patients with LN or IgAN.

2.2. Background

2.2.1. Lupus Nephritis

Lupus nephritis occurs in approximately 50% of patients with SLE, an autoimmune disorder caused by loss of tolerance to self-antigens, the production of autoantibodies, and deposition of complement-fixing immune complexes (ICs) in injured tissues (Bao, 2015). The diagnosis of LN is determined by kidney biopsy according to the 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) nomenclature and classification revised from the 2003 report (Bajema, 2018; Markowitz, 2007). In total, there are 6 classes of LN: Classes I to VI (Markowitz, 2007). The subset of patients with SLE that develop LN have the worst prognosis (Hoover, 2016). Lupus nephritis leading to CKD is an independent major risk factor for overall mortality and morbidity attributed to cardiovascular disease and septic shock. With current induction and maintenance therapies, the 5-year mortality is approximately 20% and the risk of developing ESRD at 5, 10, and 15 years is 11%, 17%, and 22%, respectively (Mageau, 2019). Recurrence of LN after treatment (renal flare) occurs within 1 year in up to 25% of patients and is associated with an increased risk of CKD progression (Almaani, 2017).

The pathophysiology of LN involves multiple overlapping pathways where complement serves as a mediator of an abnormal immune response (Bao, 2015; Pickering, 2000; Schur, 1988). The terminal complement components (C5a and terminal complement complex [C5b-9]) trigger acute cellular inflammatory responses through activation of interleukin and cytokine signaling. Complement also serves to fix immunoglobulins and ICs in the kidney. In fact, complement and complement split products are a prominent histologic finding in kidney biopsies of patients with LN (Biesecker, 1981; Wilson, 2019). Serum levels of these autoimmune and complement biomarkers are linked with disease activity (Birmingham, 2015; Dall'Era, 2011). Decreases in complement components 3, 4, and 1q (C3, C4, and C1q) are associated with de novo LN and LN flares. Likewise, levels of complement biomarkers correlate with disease activity in SLE (Kim, 2019). Restoring complement regulation may improve renal responses through acute anti-inflammatory effects and lasting effects on IC deposition in the kidney. Thus, anti-C5 therapy is promising for both induction treatment of active proliferative LN and maintenance treatment of chronic LN.

The American College of Rheumatology (ACR), and joint recommendations from the European League Against Rheumatism (EULAR) and European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), recommend immunosuppression treatment for Class III, IV, III/V, and IV/V LN also called "proliferative" LN (Bertsias, 2012). The guidelines agree on induction treatment with glucocorticoids plus mycophenolate mofetil (MMF) or cyclophosphamide. For maintenance therapy, the guidelines agree on MMF or azathioprine, with or without low dose glucocorticoids. In patients with LN, the main goal of therapy is prevention of CKD progression, ESRD, and death. Lack of achievement of remission, in particular complete remission, is one of the major risk factors for progression of renal disease. Hence, short-term complete and partial renal remissions are used to assess the efficacy of standard of care and novel therapies. However, after 6 to 12 months of treatment, only 10% to 40% of patients achieve a CRR with standard of care (Parikh, 2016).

2.2.2. IgA Nephropathy

IgAN, also known as Berger's disease, is the most common global primary glomerulonephropathy that can progress to renal failure (Lai, 2016). Immunoglobulin A (IgA) nephropathy is a lifelong disease leading to CKD and progresses to ESRD in 30% to 40% of patients over the course of 20 to 30 years (Lai, 2016). Patients initially present with hematuria and hypertension, and proteinuria develops as the disease progresses. Diagnosis of IgAN is made by renal biopsy demonstrating IgA immunofluorescence in the glomeruli usually co-dominant with C3 according to the Oxford Classification nomenclature (KDIGO, 2021; Rizk, 2019; Trimarchi, 2017).

The pathophysiology of IgAN is related to the overproduction of under-glycosylated immunoglobulin A1 (IgA1) which accumulates in the kidney glomeruli. However, aberrant galactosylation alone is insufficient to induce renal injury; glycan-specific IgA and immunoglobulin G (IgG) autoantibodies that recognize the under-galactosylated IgA1 molecule likely also contribute. This process leads to the local inflammation and complement activation in the kidney (Oortwijn, 2008). Both the alternative and lectin complement pathways may be activated, leading to generation of anaphylatoxins, and the membrane attack C5b-9, with subsequent promotion of inflammatory mediators (Maillard, 2015). C4 and C3 complexes and activated C3 products are elevated in up to 30% of patients with IgAN. Activated C3 products are associated with elevated levels of proteinuria and hematuria compared to patients with IgAN who have normal levels, and correlate with deterioration of renal function (Zwirner, 1997). Complement activity on kidney biopsy and circulating complement proteins are associated with disease activity and progression of CKD. Together, these findings suggest a role of complement in the pathophysiology and the prognostic value of complement biomarkers in IgAN (Rizk, 2019).

C5 inhibition is a potential target for treatment of patients with IgAN at high risk of progression to kidney disease (ie, significant proteinuria despite optimal RAS blockade) (Reich, 2007). Blocking the C5b-9 membrane attachment complex, and thereby preventing the downstream molecular and cellular consequences, has potential for therapeutic efficacy in patients with IgAN.

Treatments for IgAN include RAS-blocking agents, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). These therapies are aimed at controlling blood pressure, preserving kidney function through decreasing intraglomerular pressure which in turn reduces proteinuria, and suppressing the immune response. These treatments are insufficient in preserving renal function as the proportions of patients who progress to CKD and ESRD are high. Patients with baseline hypertension and proteinuria > 1 g/day are at increased risk for progression (Reich, 2007).

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks of ravulizumab is provided in the IB.

2.3.1. Risk Assessment

Based on cumulative safety data from clinical studies of ravulizumab in patients with PNH and aHUS, and post-marketing experience, ravulizumab is well tolerated up to 5400 mg, and exposure to ravulizumab has not raised unexpected safety concerns.

Ravulizumab functions by blocking terminal complement; therefore, participants have increased susceptibility to serious infections, in particular *Neisseria meningitidis* (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 6.

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 8.10. IV administration of any investigational product may result in infusion-related reactions. Management of potential infusion-related reactions is described in Section 10.4.

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this protocol amendment. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.1.11.

Table 6: Potential Risks and Mitigation Strategies

Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
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 B) per the inclusion criteria and Schedule of Assessments. Prophylactic antibiotics will be required for participants (if initiated on C5 inhibition less than 2 weeks after start of vaccination series). 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 (Schedule of Assessments, Section 1.3).

Table 6: Potential Risks and Mitigation Strategies

Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential Risks		
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 participants treated with ravulizumab remains unclear. Since the relevance of serious infection with ravulizumab therapy has not been confirmed in clinical studies, this remains a potential risk. In this study, because participants with LN will be immunosuppressed due to concomitant steroid and MMF use, they will be at increased risk of serious infections due to the immunosuppressant use.	All participants will be required to be vaccinated for Hib and *S pneumonia,* according to current national/local guidelines, in addition to *N meningitidis*. Healthcare professionals and participants should have increased awareness 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.
Immunogenicity	Treatment with any therapeutic protein has the potential to induce an immune response. Potential clinical consequences may include hypersensitivity, anaphylaxis or related type of reactions or loss of efficacy. Fewer than 1% of participants in the ravulizumab Phase 2 and 3 studies had positive ADA samples.	Monitoring for hypersensitivity and serious infusion-related reactions will be conducted as part of safety assessments for this study (Section 10.4). Infusion should be stopped in the event of any intervention-related severe adverse events like systemic hypersensitivity or anaphylaxis. In case of suspected SAEs of hypersensitivity or anaphylaxis, additional ADA samples may be collected during or in proximity of the event.
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. Women and men enrolled in the study, and their spouses/partners, must use a highly effective or acceptable method of contraception for a period of 8 months following the final dose of study intervention. Breastfeeding should be discontinued during treatment and up to 8 months after treatment with ravulizumab (Section 10.6).

Abbreviations: ADA = antidrug antibodies; C5 = complement component 5; Hib = *Haemophilus influenzae* type b; LN = lupus nephritis; MMF = mycophenolate mofetil; SAE = serious adverse event

2.3.2. Benefit Assessment

LN and IgAN are life-long diseases that lead to progressive loss of kidney function. As kidney function declines, patients may suffer the morbidity and mortality associated with advanced CKD, dialysis, and kidney transplant. While there has been some progress in terms of approved treatments for patients with LN with recent approval of belimumab in multiple regions and voclosporin in the US, there remains a large unmet need for novel interventions, particularly in patients who are at risk of progressive kidney disease. For patients with LN, current off-label immunosuppressive or cytotoxic therapies as well as recently approved drugs still provide inadequate clinical response (low rates of CRR and high risks of relapse) and are associated with significant side effects limiting their tolerability and long-term use. These side effects can lead to chronic diseases such as hypertension, osteoporosis, diabetes, obesity, and infertility. For patients with IgAN, patients with persistent proteinuria despite treatment with ACE inhibitors and ARBs are particularly at risk of progression of kidney disease. Available data from IgA studies on the role of immunosuppressive therapy are not conclusive as most are relatively small and have limited follow-up (Lai, 2016). Development of new therapies targeting the underlying pathologic processes is critical to improving the care of patients with LN or IgAN.

Multiple sources of evidence suggest aberrant complement is a key mediator in the pathophysiology of LN and IgAN (Section 2.2). Participants in the study may benefit from clinical improvement and decreased risk of kidney disease progression. Additionally, though ravulizumab is being tested as add-on treatment to allowed concomitant therapy consistent with the standard of care, in patients with LN there is potential for a less intensive course of background immunosuppression and improved safety profile.

2.3.3. Overall Benefit: Risk Conclusion

There is a high unmet need for effective therapies for patients with LN or IgAN because clinical outcomes are poor with the currently available standard of care. Given the cumulative data on the role of complement in LN and IgAN disease progression, the potential risks of ravulizumab are justified by the anticipated clinical benefits.

3. OBJECTIVES AND ENDPOINTS

3.1. Overview of Objectives and Endpoints

Objectives	Endpoints
Primary (Both Cohorts)	
To evaluate the efficacy of ravulizumab compared with placebo to reduce proteinuria in adult participants with LN or IgAN	Percentage change in proteinuria from baseline to Week 26 (based on 24-hr urine collection[s] at each time point)
Secondary (Both Cohorts)	
To evaluate the efficacy of ravulizumab compared with placebo to improve measures of kidney function in adult participants with LN or IgAN	Percentage change in proteinuria from baseline to Week 50 (based on 24-hr urine collection[s] at each time point)
	Percentage of participants with > 30% and > 50% reduction in proteinuria at Week 26 and Week 50 compared to baseline (based on 24-hr urine collection[s] at each time point)
	Change from baseline in eGFR at Week 26 and Week 50
	Absolute values and change from baseline in serum C3 and C4 concentrations at Week 26 and Week 50
Secondary (LN Cohort Only)	
To evaluate the efficacy of ravulizumab compared with placebo to improve measures of kidney function in adult participants with LN	Percentage of participants meeting the criteria for CRR at Week 26 and Week 50 (as defined in Section 3.2.5)
	Percentage of participants meeting the criteria for PRR at Week 26 and Week 50 (as defined in Section 3.2.5)
	Time to UPCR < 0.5 g/g as measured by spot urine sample
	Percentage of participants achieving corticosteroid taper to 7.5 mg/day at Weeks 14, 26, and 50
	Percentage of participants with Renal Flare (as defined in Section 3.2.1) through Week 50
	Percentage of participants with Extrarenal SLE Flare (as defined in Section 3.2.2) through Week 50
	Percentage of participants with Treatment Failure (as defined in Section 3.2.4) through Week 50
	Percentage of participants with Suboptimal Response (as defined in Section 3.2.3) through Week 50
	Absolute values and change from baseline in serum albumin at Week 26 and Week 50

Objectives	Endpoints
Secondary (IgAN Cohort Only)	
To evaluate the efficacy of ravulizumab compared with placebo on measures of kidney function in adult participants with IgAN	Percentage of participants meeting the criteria for Partial Remission at Week 26 and Week 50 (as defined in Section 3.2.6)
PK/PD/Immunogenicity (Both Cohorts)	
To characterize the PK/PD of ravulizumab in adult participants with LN or IgAN	Absolute values and change from baseline in total C5 and free C5 concentrations over time
	Absolute values and change from baseline in ravulizumab concentrations over time
To characterize the potential for immunogenicity of ravulizumab in adult participants with LN or IgAN	Incidence of ADAs over time
Safety (Both Cohorts)	
To characterize the safety and tolerability of ravulizumab in adult participants with LN or IgAN	Incidence of AEs and SAEs over time
Exploratory (Both Cohorts)	
To evaluate the efficacy of ravulizumab compared with placebo on hematuria in adult participants with LN or IgAN	Effect on hematuria as measured by - Absolute value and change from baseline in RBC in urine from baseline to Week 26 and Week 50 - Percentage of participants with < 10 RBC/hpf
To assess quality of life based on participant-reported outcomes in adult participants with LN or IgAN based on treatment with ravulizumab compared with placebo	Change from baseline in SF-36 at Week 26 and Week 50
	Change from baseline in EQ-5D-5L at Week 26 and Week 50
To evaluate complement and autoimmune biomarkers in adult participants with LN or IgAN	Absolute values and change from baseline in levels of biomarkers in blood, urine, and kidney tissue at Week 26 and Week 50
Exploratory (LN Cohort Only)	
To assess the efficacy of ravulizumab in exploratory efficacy endpoints	Time to CRR and PRR (using spot UPCR)
	Percentage of participants with Overall Renal Response at Week 26 and Week 50 (CRR and PRR)
	Time to UPCR > 50% decrease from baseline (using spot UPCR)
To assess quality of life based on participant -reported outcomes	Change from baseline in FACIT-Fatigue score at Week 26 and Week 50

Objectives	Endpoints
To assess the efficacy of ravulizumab in other exploratory endpoints	Absolute values and change from baseline in anti-dsDNA and anti-C1q antibodies at Week 26 and Week 50
	Histology changes from baseline to Week 50
Exploratory (IgAN Cohort Only)	
To assess the efficacy of ravulizumab in exploratory efficacy endpoints	Slope of eGFR computed from baseline to Week 26 and Week 50

Abbreviations: ADA = antidrug antibody; AE = adverse event; C3, C4, C5, and C1q = complement components 3, 4, 5, and C1q; CRR = complete renal response; dsDNA = double-stranded DNA; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQoL 5-Dimensions 5-Level; FACIT = Functional Assessment of Chronic Illness Therapy; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis; PD = pharmacodynamics; PK = pharmacokinetics; PRR = partial renal response; RBC = red blood cell; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; SLE = systemic lupus erythematosus; UPCR = urine protein to creatinine ratio

3.2. Definitions for Endpoints

3.2.1. Renal Flare (LN Cohort Only)

Renal Flare is determined in the opinion of the Investigator in addition to the criteria outlined below:

- For participants who achieve CRR (Section 3.2.5), a Renal Flare is the reproducible recurrence of proteinuria ≥ 1 g/g
- For all other participants, a Renal Flare is either of the following:
  - Reproducible increase of serum creatinine > 25% higher than baseline or above the upper limit of normal, plus any one of the following:
    - Reproducible proteinuria ≥ 75% higher than baseline
    - Worsening active urinary sediment compared to baseline as defined by an increase of ≥ 5 red blood cells (RBCs)/ high power field (hpf) or new RBC casts (based on local laboratory results from at least 2 samples)
    - Kidney biopsy newly conducted since the biopsy used for eligibility demonstrating LN Class III or IV activity
  - Reproducible doubling of the UPCR from a 24-hour urine collection compared with the lowest previous value obtained after the first dose of study drug.
- **Reproducibility of proteinuria** requires that the proteinuria based on a UPCR from a morning spot urine collection is confirmed by UPCR calculated on a 24-hour urine collection obtained within a 2-week period.
- **Reproducibility of serum creatinine** requires 2 blood tests within a 2-week period.

Participants who meet criteria for the protocol-defined Renal Flare will receive additional standard of care therapy (as defined in Section 6.6). The Medical Monitor should be notified of the Renal Flare by the Investigator or Sub-investigator.

Any renal flare that does not meet the protocol-defined Renal Flare criteria may be treated with a limited duration of increased oral corticosteroids (< 14 days) after discussion with the Medical Monitor. Such treatment will not be considered additional standard of care therapy and will not be considered Treatment Failure.

Renal Flare criteria will be recorded on the Renal Flare case report form (CRF).

3.2.2. Extrarenal Systemic Lupus Erythematosus Flare (LN Cohort Only)

Extrarenal SLE Flare is defined as an increase in Systemic Lupus Erythematosus Disease Activity Index Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) Modification (SLEDAI–2K) ≥ 4 points (see Section 8.9.2 and Section 10.12) that is not accounted for by proteinuria, hematuria, urinary cellular casts, hypocomplementemia, or an increase in anti-double-stranded DNA (anti-dsDNA) antibody level.

Participants in the LN cohort who meet the criteria for Extrarenal SLE Flare may receive additional standard of care therapy, if considered clinically appropriate by the Investigator (as defined in Section 6.6). If additional standard of care therapy is administered, the event is considered a Severe Extrarenal SLE Flare.

Participants will be allowed to receive a limited number of corticosteroid treatments for non-severe extrarenal SLE flare, if clinically warranted as outlined below. Such treatment will not be considered additional standard of care therapy and will not be considered Treatment Failure.

- Up to 2 corticosteroid treatments will be allowed for a non-severe extrarenal SLE flare.
  - One corticosteroid treatment will be allowed between Week 12 (end of steroid taper) and Week 22 (4 weeks prior to Week 26 primary endpoint).
  - One corticosteroid treatment will be allowed between Week 26 and Week 46 (4 weeks prior to final analysis).
- Each treatment course should be no longer than 14 days in duration with the steroid dose returning to 7.5 mg/day by Day 14.
- Up to a total of 20 mg/day (prednisone or prednisone equivalent) is permitted.
- There can be no concurrent worsening of renal disease (as defined by the criteria for a Renal Flare).

3.2.3. Suboptimal Response (LN Cohort Only)

A Suboptimal Response is determined in the opinion of the Investigator in addition to the following criteria after the Week 26 Visit:

- Reproducible proteinuria ≤ 25% decreased compared to baseline based on UPCR on a 24-hour urine collection performed by the central laboratory

Reproducibility of proteinuria requires that the proteinuria based on a UPCR from a spot urine collection is confirmed by a central laboratory UPCR calculated on a 24-hour urine collection obtained within a 2-week period.

Participants with Suboptimal Response must be discussed with the Investigator and Medical Monitor. Participants with Suboptimal Response will stay in the study and continue to receive study drug. Intensification of current standard of care or introduction of new immunosuppressive therapies are allowed per the clinical discretion of the Investigator in conversation with the Medical Monitor and will be considered additional standard of care therapy.

Participants with Suboptimal Response will be included as Treatment Failure.

3.2.4. Treatment Failure (LN Cohort Only)

Treatment Failure is defined as the occurrence of any of the following events:

- Receipt of additional standard of care therapy (as defined in Section 6.6) at any time up to Week 50 for protocol-defined Renal Flare, Severe Extrarenal SLE Flare, or Suboptimal Response

Increase in corticosteroids for extrarenal SLE flare not meeting the protocol definition of Severe Extrarenal SLE Flare, renal flare not meeting protocol definition for Renal Flare, lack of response not meeting the protocol definition for Suboptimal Response, other medical conditions or surgery limited to ≤ 14 days duration are **not** included in Treatment Failure.

Participants who meet the criteria for Treatment Failure may continue to receive the study medication and stay in the study.

3.2.5. Complete and Partial Renal Response (LN Cohort Only)

CRR and partial renal response (PRR) will be assessed at Week 26 and Week 50.

To achieve CRR (Rovin, 2019), participants in the LN cohort must meet all 3 of the following criteria:

- A decrease in mean UPCR to ≤ 0.5 g/g based on two 24-hr urine collections obtained within 2 weeks prior to the study visit (Week 26 or Week 50)
- eGFR > 60 mL/min/1.73 m^2 or no eGFR reduction ≥ 20% from the baseline value based on the mean of 2 values. The first eGFR value must be obtained within 2 weeks prior to the study visit (Week 26 or Week 50) and the second eGFR value will be obtained on the study visit (Week 26 or Week 50).
- No Treatment Failure (as defined in Section 3.2.4)

To achieve PRR (Rovin, 2019), participants in the LN cohort must meet all 3 of the following criteria:

- A decrease in UPCR > 50% compared to the baseline value based on the mean of two 24-hr urine collections obtained within 2 weeks prior to the study visit (Week 26 or Week 50)
- eGFR > 60 mL/min/1.73 m^2 or no eGFR reduction ≥ 20% from the baseline value based on the mean of 2 values. The first eGFR value must be obtained within 2 weeks

prior to the study visit (Week 26 or Week 50) and the second eGFR value will be obtained on the study visit (Week 26 or Week 50)

- No Treatment Failure (as defined in Section 3.2.4)

3.2.6. Partial Remission (IgAN Cohort Only)

Partial Remission will be defined as mean proteinuria < 1 g/24-hrs based on 2 valid 24-hr urine collections obtained within 2 weeks prior to the study visit (Week 26 or Week 50).

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study of ravulizumab in addition to allowed concomitant therapy consistent with the standard of care in adult participants (18 to 75 years of age) with either LN or IgAN. All participants must be naive to complement inhibitor treatment and have either a diagnosis of LN with an active flare or IgAN based on kidney biopsy, eGFR ≥ 30 mL/min/1.73 m^2, and proteinuria [defined as UPCR ≥ 1 g/g from one 24-hr urine collection (LN cohort) or as mean protein ≥ 1 g/24-hr from 2 valid 24-hr collections (IgAN cohort)]. Participants in the IgAN cohort must have been treated with stable doses of the maximum tolerated RAS-inhibiting medications and have controlled, stable blood pressure (< 140/90 mmHg) for ≥ 3 months prior to Screening.

The study consists of an up to 6-week Screening Period, a 26-week Initial Evaluation Period, a 24-week Extension Period, and a 36-week post-treatment Follow-up Period. Thus, the total treatment duration is 50 weeks and the total study duration is up to 86 weeks.

Participants will be screened for eligibility for up to 6 weeks during the Screening Period. Approximately 120 adult participants with either LN or IgAN will be enrolled into the study. For each disease cohort, 60 participants will be randomly assigned in a 2:1 ratio to receive ravulizumab or placebo (40 ravulizumab, 20 placebo). Randomization will be stratified by whether corticosteroid induction treatment was initiated prior to Screening versus during the Screening Period for participants in the LN cohort and by mean proteinuria (1 to 2 g/day versus > 2 g/day) from 2 valid 24-hr urine collections during the Screening Period for participants in the IgAN cohort.

For participants in the LN cohort, all screening laboratory assessments should be performed as soon as possible after signing of the informed consent form (ICF). All participants in the LN cohort should be randomized as soon as possible once eligibility is confirmed.

All participants are required to have meningococcal vaccination; however, for participants in the IgAN cohort, every effort should be made to start the meningococcal vaccination series at least 14 days prior to randomization in order to avoid antibiotic prophylaxis and minimize the potential triggering of innate immunity with possible effects on proteinuria and hematuria.

During the Initial Evaluation Period, all participants will receive a weight-based loading dose of ravulizumab or placebo on Day 1, followed by weight-based maintenance doses of ravulizumab or placebo on Day 15 and then q8w thereafter (Table 8). All participants will receive allowed concomitant therapy consistent with the standard of care for participants with LN and IgAN throughout the study as defined in Section 6.5.

During the 24-week Extension Period, participants will continue to receive study drug (ravulizumab or placebo):

- Participants in the LN cohort will continue to receive their randomized allocation of study drug (ravulizumab or placebo) q8w until the end of the Extension Period. Participants will receive additional standard of care therapy in the event of a protocol-defined Renal Flare or Severe Extrarenal SLE Flare. Additional standard of care

therapy for participants with Suboptimal Response is allowed at the clinical discretion of the Investigator in conversation with the Medical Monitor.

- Participants in the IgAN cohort randomized to the placebo group will switch to receive a blinded loading dose of ravulizumab at Week 26 and then open-label weight-based dosing of ravulizumab q8w until the end of the Extension Period.
- Participants in the IgAN cohort randomized to the ravulizumab group will receive a blinded dose of 900 mg ravulizumab at Week 26 and then open-label weight-based dosing of ravulizumab q8w until the end of the Extension Period.

During the 36-week Post-treatment Follow-up Period, participants will continue to receive standard of care, at the discretion of the Investigator, and will be monitored for safety, clinical events of interest, and kidney function.

Participants who discontinue study drug early and agree to remain in the study should continue to attend their scheduled protocol visits until Week 50. During these visits, all assessments except for study drug administration should be performed according to the Schedule of Assessments.

Participants who withdraw from the study will be followed for safety until 8 weeks after the last dose of study drug.

The end of study is defined as the last participant's last visit in the Post-treatment Follow-up Period.

To ensure the adequacy of the dose regimen, an interim PK/PD analysis for dose confirmation will be conducted by an independent clinical pharmacologist (Section 9.5.1). The interim PK analysis will be conducted using masked PK/PD data from the first 10 participants treated with ravulizumab (a minimum of 3 participants in each disease-specific cohort). In the event of dose adjustments, the participants treated with the previous dose will switch over to the new dose and continue treatment on study but will be excluded from the primary efficacy analysis. Replacement participants may be enrolled to preserve study power.

4.2. Scientific Rationale for Study Design

A randomized, double-blind, placebo-controlled study design is selected to provide the most robust evidence of the efficacy of ravulizumab on clinical response, disease progression, and safety. Randomization minimizes the effects of baseline differences and confounding factors on the study endpoints. The use of a placebo comparator allows for the analysis of the true treatment effect of ravulizumab by minimizing the risk of selection bias. An unequal randomization scheme was chosen to decrease the number of participants receiving placebo. A single randomization stratum was selected for each cohort to ensure equal distribution of baseline characteristics that may impact the endpoints. The 50-week treatment duration provides adequate time to assess the safety and efficacy endpoints to demonstrate proof of concept for both cohorts in a Phase 2 study.

The standard of care allowed concomitant therapies employed in this protocol are consistent with recent clinical studies in patients with LN (Rovin, 2019) and IgAN (Rauen, 2015).

4.2.1. Rationale for Primary Endpoint

The primary endpoint for the study is percent change from baseline to Week 26 in 24-hr proteinuria.

Change in proteinuria is considered a valid surrogate endpoint for kidney survival in glomerular diseases. Change in proteinuria is also an acceptable endpoint for clinical studies as concluded during a scientific workshop facilitated by the National Kidney Foundation in collaboration with FDA and EMA in 2018 (Coresh, 2019). A decline in proteinuria in response to treatment is a strong predictor of kidney survival (Hebert, 2001; Wilmer, 2003) and a > 20% relative treatment effect over standard of care in change in proteinuria is considered clinically relevant (Holtkamp, 2020; Levey, 2020). Changes in proteinuria become evident before traditional markers of kidney survival (eg, ESRD, dialysis, or transplant); thus, it is especially useful to detect signs of efficacy for a proof-of-concept study. Accordingly, the effect of ravulizumab on the percentage reduction of proteinuria at Week 26 compared to baseline was selected as the primary endpoint for this study. It is expected that 26 weeks of treatment with ravulizumab will provide participants who respond to complement inhibition sufficient time to achieve reduction of proteinuria.

The gold standard for measuring proteinuria is a complete 24-hr urine collection.

Proteinuria is further justified in this Phase 2 study because of the role of active inflammation in both diseases leading to proteinuria as a clinical manifestation of active inflammation in the kidney. Ravulizumab has potent and rapid onset of anti-inflammatory effects that may be demonstrated through changes in proteinuria. Proteinuria may also result from irreversible scarring of renal tissue. Therefore, the presence of potentially reversible and active inflammatory kidney disease is ensured by requiring hematuria in participants with IgAN, and active class III or IV LN on kidney biopsy in participants with LN. Additionally, relatively preserved renal function with eGFR > 30 mL/min/1.73 m^2 is required for both disease cohorts.

4.2.2. Rationale for Key Secondary Endpoints

Change in eGFR is a key secondary endpoint for both disease cohorts since it is considered a suitable surrogate marker for renal survival in clinical studies of glomerular diseases (Coresh, 2019).

A key secondary endpoint for the LN cohort is CRR which predicts a beneficial prognosis and is often used in Phase 3 studies (KDIGO, 2021; Korbet, 2000; Pakchotanon, 2018; Chen, 2008). Some participants may not experience all components of CRR. Thus, additional secondary endpoints including the proportion of participants that achieve the individual components of CRR and PRR (Section 3.2.5) will be analyzed. Similarly, achievement of the CRR components may occur at different time points after study drug initiation. Thus, the time to achieve each CRR, PRR, the individual components, and UPCR < 0.5 g/g in participants will be evaluated to better characterize the potential benefit of ravulizumab treatment. Other secondary endpoints for the LN cohort aimed to provide additional characterization of ravulizumab treatment effect are described in Section 9.4.1.2.

A key secondary endpoint for the IgAN cohort is the percentage of participants with Partial Remission as defined by mean proteinuria < 1 g/day on 2 valid 24-hr urine collections. Achievement of < 1 g/day proteinuria improves prognosis and is associated with kidney survival

through reduced risk of CKD progression to dialysis or transplant (Reich, 2007). Furthermore, proteinuria is an important risk factor in validated prediction tools used to stratify patients into risk categories and guide patient management (Barbour, 2019).

4.3. Justification for Dose

The ravulizumab dose regimen for the proposed study is based on the established PK-PD relationships that demonstrate the direct link between drug concentration and complement inhibition. Clinical studies of ravulizumab in PNH and aHUS have demonstrated the importance of maintaining concentration at the end of the dosage interval (C_{trough}) above the established free C5-based PK threshold, and this target of complete terminal complement inhibition is expected to be necessary to achieve optimal efficacy in IgAN and LN. The proposed dosing regimen was identified using a modeling and simulation (M&S) framework previously used to support the approval of the PNH and aHUS indications for ULTOMIRIS (US Prescribing Information [USPI]).

The proposed dosing regimen is modified from the approved dosing regimen in PNH and aHUS indications to account for the influence of the potential intrinsic factors, such as high levels of proteinuria and complement activation in renal pathology, on antibody PK. This is supported by the PK results from eculizumab clinical trials in idiopathic membranous glomerulopathy (IMG) patients with high proteinuria and rheumatoid arthritis (RA) patients with minimal proteinuria, confirming that patients with IMG had significantly lower drug levels at trough compared to RA patients at the same dosing regimen of 8 mg/kg eculizumab every 2 weeks (trough mean levels of approximately 18.5 µg/mL in participants with IMG versus 30 to 32 µg/mL in participants with RA) (Study C99-001 in RA and Study C99-004 in IMG). This observed impact of proteinuria on antibody PK is also in agreement with a clinical study of rituximab in membranous nephropathy with high proteinuria confirming that patients with membranous nephropathy exhibited a shorter half-life, decreased exposures, and increased antibody clearance compared to the reference patient populations (Fogueri, 2019). In a study of adalimumab in focal segmental glomerulosclerosis (FSGS) patients with proteinuria, a linear relationship was seen between increasing proteinuria and the increase in antibody clearance (Roberts, 2013). In light of this evidence demonstrating a relationship between proteinuria and antibody clearance, the results from M&S analysis show that the expected increase in ravulizumab clearance, based on mean proteinuria levels of approximately 3 to 4 g/day at baseline for participants in the study, may result in inadequate levels of C5 suppression in patients with ≥ 60 kg body weight using the labeled dosing regimen for PNH/aHUS. Therefore, an optimal dosing regimen should be identified to maintain immediate (after the loading dose), complete and sustained (throughout the entire active treatment course) terminal complement inhibition in all participants for the proposed study.

The proposed dosing regimen presented in Table 8 was derived based on the established exposure-response relationships of ravulizumab Phase 3 studies, assuming an expected 30% higher clearance based on mean proteinuria levels of approximately 3 to 4 g/day at baseline for participants in the study. The PK simulations using the established population PK model of ravulizumab were conducted to identify maintenance doses to be the optimal population dose providing the majority of participants (defined as 97.5th percentile) with necessary PK coverage (ravulizumab trough concentrations > target threshold of 175 µg/mL) to achieve complete and

sustained terminal complement suppression, a level shown to be optimal for efficacy in PNH and aHUS Phase 3 studies. The impact of weight on exposure, namely higher exposures in lighter participants as compared to heavier participants, suggested the need for weight-based dosing, consistent with the labeled dosing regimen of ravulizumab for PNH/aHUS.

As shown in Table 8, the loading regimen in this study for all 3 body weight categories is the same as the labeled regimen for aHUS/PNH. Further, the q8w maintenance regimen for 40 to < 60 kg participants is the same as the current labeled dose. Maintenance doses for participants in the 60 to < 100 kg and ≥ 100 kg body weight ranges are higher by 18% and 50%, respectively, than the currently labeled dosing regimen for PNH/aHUS. However, the exposures are predicted to be similar to those observed in Phase 3 studies due to the expected higher clearance. Ravulizumab IV has been tested at doses up to 5400 mg in Study ALXN1210-PNH-201 without demonstrating adverse findings, consistent with a large safety margin. In all cases, the predicted maximum (peak) serum concentration observed after study drug administration (C_{max}) is estimated to be well below the highest observed C_{max} for an individual patient in previous trials (ie, approximately 2680 µg/mL), even assuming no change in ravulizumab clearance due to proteinuria.

Adequacy of the proposed dose regimen will be confirmed for adult participants with LN and IgAN through initial masked analysis of PK/PD data by an independent clinical pharmacologist in an initial cohort of participants with an option for dose adjustment for the subsequent participants (Section 9.5.1).

4.4. Remote Visit Options in Times of Emergency

To ensure participant safety and treatment continuity in times of emergency (eg, COVID-19 pandemic), the following will apply where participants are not able to reach the study sites, and until participants are able to resume study visits at the site.

Participants may have an opportunity to receive ravulizumab administration remotely at a medical facility that is located near the participant's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities.

Remote visit options may be at the Investigator's discretion and oversight, in accordance with the local regulations, and conducted by a qualified medical professional. Remote visit options may include visits conducted at the participant's home (excluding visits that require ravulizumab administration), an alternative qualified healthcare facility or virtually through phone or video conference. All assessments for the study visit day should be conducted according to the Schedule of Assessments (Section 1.3). Information about adverse events (AEs), concomitant medications, allowed concomitant therapies, and disease-related signs or symptomatology must be sent to the Investigator's site for evaluation on the day of the remote visit. In case of any signs or symptoms indicating a serious adverse event (SAE) or Renal Flare, the participant will need to be evaluated at the study site.

4.5. End of Study Definition

A participant is considered to have completed the study if they have completed all periods of the study including the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study globally (Week 86, End of Study [EoS] Visit) (Section 1.3).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

To be eligible to participate in the study, participants in both cohorts must meet all of the below criteria.

5.1.1. Common Inclusion Criteria for Both Cohorts

Age

1. Participant must be ≥ 18 and ≤ 75 years of age at the time of signing the informed consent.

Weight

2. Body weight ≥ 40 kg at Screening

Sex

3. Male or female

   Female participants of childbearing potential, male participants, and male participants with female partners of childbearing potential must follow protocol specified contraception guidance as described in Section 10.6

Informed Consent

4. Capable of giving informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

Vaccinations and Antibiotics

5. To reduce the risk of meningococcal infection (*N meningitidis*), all participants must be vaccinated against meningococcal infection from serogroups A, C, W, Y, and B within 3 years prior to, or at the time of, randomization according to national/local guidelines. Participants who do not meet this requirement will be vaccinated against meningococcal infection prior to randomization according to national/local guidelines and will receive prophylactic antibiotics for at least 2 weeks after meningococcal vaccination if randomization occurs < 2 weeks after initial vaccination.
6. All participants must also receive vaccinations for *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* prior to randomization, unless previously vaccinated, according to current national/local vaccination guidelines.

Disease Characteristics

7. Local pathology report from the biopsy used for diagnosis must be available (Section 8.1.5)

Prior/Concomitant Therapy

8. Participants on sodium-glucose cotransporter-2 (SGLT-2) inhibitors (eg, empagliflozin) must be on a stable dose for ≥ 3 months with no planned change in dose during the study

5.1.2. Inclusion Criteria Specific for LN Cohort

Disease Characteristics

9. Clinical diagnosis of SLE by 2019 ACR and EULAR criteria as outlined in Section 10.9
10. Diagnosis of 2018 Revised ISN/RPS classification (Section 10.10) (active focal or diffuse proliferative LN Class III or IV confirmed by biopsy obtained ≤ 6 months prior to Screening or during Screening Period. Participants may co-exhibit Class V disease. Participants with de novo or relapsing disease may be eligible.
11. Clinically active LN at Screening requiring/receiving immunosuppression induction treatment in the opinion of the Investigator
12. Proteinuria with UPCR ≥ 1 g/g based on one 24-hour urine collection during the Screening Period (Section 8.2.1)

5.1.3. Inclusion Criteria Specific for IgAN Cohort

Disease Characteristics

13. Established diagnosis of primary IgAN based on kidney biopsy obtained any time prior to or during the Screening Period
14. Mean proteinuria ≥ 1 g/day on 2 complete and valid 24-hour urine collections during the Screening Period (Section 8.2.1)
15. For participants with a kidney biopsy used for eligibility > 1 year prior to Screening:
    - Presence of hematuria as defined by a positive result on urine dipstick for blood or ≥ 10 RBC/hpf microscopy on urine sediment as documented by the local laboratory. Presence of hematuria documented by the central laboratory may also be acceptable.
16. Compliance with stable and optimal dose of RAS inhibitor treatment including maximum allowed or tolerated ACE inhibitor and/or angiotensin receptor blocker dose for ≥ 3 months prior to Screening with no expected change in dose during the study (participants with established intolerance to RAS inhibitors may be included).
17. Controlled and stable blood pressure over the past 3 months < 140/90 mmHg

5.2. Exclusion Criteria

5.2.1. Common Exclusion Criteria for Both Cohorts

Participants from both cohorts are excluded from the study if any of the below criteria apply.

Medical Conditions

1. Estimated GFR < 30 mL/min/1.73 m^2 during Screening calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

2. For patients with eGFR < 45 mL/min/1.73 m^2 at Screening, presence of any of the following in glomeruli on most recent kidney biopsy prior or during the Screening Period:
   a. ≥ 50% interstitial fibrosis and tubular atrophy
   b. ≥ 50% glomerular sclerosis
   c. ≥ 50% active crescent formation
3. Concomitant significant renal disease other than LN or IgAN on the most recent biopsy prior to or during the Screening Period
4. History of kidney transplant or planned kidney transplant during the Treatment Period
5. History of other solid organ (heart, lung, small bowel, pancreas, or liver) or bone marrow transplant; or planned transplant during the Treatment Period
6. Splenectomy or functional asplenia
7. Institutionalization by administrative or court order or known medical or psychological condition(s) 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
8. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of the Screening Period
9. History of malignancy within 5 years of Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence
10. Evidence of active hepatitis B infection (positive hepatitis surface antigen [HBsAg] or positive core antibody (anti-HBc) with negative surface antibody [anti-HBs]) or active hepatitis C viral infection (HCV antibody positive, except for patients with documented successful treatment and documented sustained virologic response [SVR]) at Screening
11. Known history of human immunodeficiency virus (HIV) infection as documented by HIV-1/HIV-2 testing or positive HIV-1/HIV-2 antibody titer at Screening
12. Bone marrow insufficiency with absolute neutrophil count < 1.3 x 10^3/μL; thrombocytopenia (platelet count < 50,000/mm^3)
13. Active systemic bacterial, viral, or fungal infection within 14 days prior to randomization
14. History of *N meningitidis* infection
15. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins or inability to take or tolerate the standard of care allowed concomitant therapies (Section 6.5), with the exception of RAS inhibitors for the IgAN cohort (IC 16).

Prior/Concomitant Therapy

16. Received biologic, including but not limited to belimumab or rituximab, ≤ 6 months prior to Screening
17. Previously received a complement inhibitor (eg, eculizumab) at any time

Prior/Concurrent Clinical Study Experience

18. Participation in another investigational drug or investigational device study within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater

Other Exclusions

19. Pregnant, breastfeeding, or intending to conceive during the course of the study

5.2.2. Exclusion Criteria Specific for LN Cohort

20. Participants who have initiated any of the following treatments for the current active LN flare:
    a. Cyclophosphamide ≤ 6 months prior to Screening
    b. Calcineurin inhibitors ≤ 3 months prior to Screening
    c. A cumulative dose of IV methylprednisolone > 3 g
    d. Mycophenolate mofetil > 2 g/day (or equivalent) for ≥ 4 consecutive weeks prior to Screening
    e. Oral corticosteroids ≥ 0.5 mg/kg/day for ≥ 4 consecutive weeks prior to Screening
21. Uncontrolled hypertension (systolic blood pressure > 160 or diastolic blood pressure > 110 mmHg) on 2 or more measurements during the Screening Period
22. Clinically active SLE-related cerebritis, seizures, pericarditis, stroke, or stroke syndrome requiring treatment

5.2.3. Exclusion Criteria Specific for IgAN Cohort

23. Diagnosis of rapid progressive glomerulonephritis as measured by eGFR loss ≥ 30% over a period of 3 months prior to or during the Screening Period
24. Secondary etiologies of IgAN (eg, SLE, cirrhosis, celiac disease)
25. Clinically active Henoch-Schonlein purpura (IgA vasculitis) requiring treatment
26. Prednisone or prednisone equivalent > 20 mg/day for > 14 consecutive days or any other systemic immunosuppression for the treatment of IgAN ≤ 6 months prior to Screening
27. Blood pressure of ≥ 140/90 mmHg during the Screening Period confirmed on 2 measures > 30 minutes apart
28. Body mass index ≥ 38 kg/m^2

5.3. Lifestyle Considerations

There is no lifestyle restriction 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 treated with ravulizumab or are not randomized to either treatment group. 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 AEs, including any SAEs and any AEs related to 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 up to a maximum of 1 time based on discussion and agreement between the Investigator and the Medical Monitor. If a potential participant is rescreened outside the 6-week Screening Period, then all Screening assessments and procedures must be repeated.

6. STUDY INTERVENTION

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

For this study, the study intervention will include the administration of study drug (ravulizumab or placebo) in addition to allowed concomitant therapy consistent with the standard of care.

6.1. Study Intervention(s) Administered

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, clear, colorless solution with the same buffer components, but without active ingredient. Additional details are presented in Table 7.

Table 7: Study Intervention(s) Administered

Study Drug 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
IMP or NIMP/AxMP	IMP	IMP
Use	Experimental	Placebo comparator

Abbreviations: AxMP = auxiliary medicinal product; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product

The dosing regimen (Table 8) consists of a loading dose followed by maintenance dosing administered q8w. The maintenance dosing will be initiated 2 weeks after the loading dose administration.

Weight-based dosing will be based on the participant's body weight recorded at the day of the infusion visit. If the weight at the day of the infusion cannot be obtained, the weight recorded during the most recent prior study visit may be used.

Table 8: Weight-based Doses of Ravulizumab

Body Weight Range (kg)[a]	Loading Dose (mg)	Maintenance Dose (mg)
≥ 40 to < 60	2400	3000
≥ 60 to < 100	2700	3900
≥ 100	3000	5400

a Dose regimen will be based on the last recorded study visit body weight. If the study drug is prepared the night before a visit, the weight from the most recent study visit should be used.

At the scheduled dosing visits (Section 1.3), study drug should be administered after all other tests and procedures have been completed, excluding the postdose sample collections (PK/PD/biomarkers).

During the Initial Evaluation Period (Day 1 through Week 26), participants in each cohort will be randomized 2:1 to receive blinded doses of ravulizumab or placebo.

- Ravulizumab group: participants will receive a blinded loading dose of ravulizumab via IV infusion on Day 1, followed by a blinded maintenance dose at Week 2 then q8w thereafter through the end of the Initial Evaluation Period
- Participants in the placebo group will receive a blinded matching placebo dose via IV infusion on Day 1, followed by a blinded matching placebo dose at Week 2, then q8w thereafter through the end of the Initial Evaluation Period.

During the Extension Period (Week 26 through Week 50), participants in the LN cohort will continue on the same maintenance regimen. In the IgAN cohort, participants in the placebo group will switch to receive a blinded loading dose of ravulizumab at Week 26 and participants in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg at Week 26. Starting at Week 28, all participants in the IgAN cohort will receive open-label weight-based doses of ravulizumab (Table 9) q8w until the end of the Extension Period.

Table 9: Reference Chart for Weight-Based Dosing in IgAN Cohort

Study Period	Ravulizumab or Placebo Dosing	Body Weight (kg)[a]	Ravulizumab Dose (mg)	Ravulizumab Volume (mL)	Placebo Volume (mL)	Diluent (0.9% Sodium Chloride) Volume (mL)	Total Volume (mL)
Ravulizumab Group							
Initial Evaluation Period	Loading dose (Day 1)	≥ 40 to < 60	2400	240	0	240	480
		≥ 60 to < 100	2700	270	0	270	540
		≥ 100	3000	300	0	300	600
	Maintenance dose (Days 15, 71, 127)	≥ 40 to < 60	3000	300	0	300	600
		≥ 60 to < 100	3900	390	0	390	780
		≥ 100	5400	540	0	540	1080
Extension Period	Blinded dose[b] (Day 183)	≥ 40 to < 60	900	90	150	240	480
		≥ 60 to < 100	900	90	180	270	540
		≥ 100	900	90	210	300	600
	Maintenance dose (Days 197 to 351 q8w)	≥ 40 to < 60	3000	300	0	300	600
		≥ 60 to < 100	3900	390	0	390	780
		≥ 100	5400	540	0	540	1080
Placebo Group							
		≥ 40 to < 60	0	0	240	240	480

Table 9: Reference Chart for Weight-Based Dosing in IgAN Cohort

Study Period	Ravulizumab or Placebo Dosing	Body Weight (kg)[a]	Ravulizumab Dose (mg)	Ravulizumab Volume (mL)	Placebo Volume (mL)	Diluent (0.9% Sodium Chloride) Volume (mL)	Total Volume (mL)
Ravulizumab Group							
Initial Evaluation Period	Loading dose (Day 1)	≥ 60 to < 100	0	0	270	270	540
		≥ 100	0	0	300	300	600
	Maintenance dose (Days 15, 71, 127)	≥ 40 to < 60	0	0	300	300	600
		≥ 60 to < 100	0	0	390	390	780
		≥ 100	0	0	540	540	1080
Extension Period	Blinded loading dose[c] (Day 183)	≥ 40 to < 60	2400	240	0	240	480
		≥ 60 to < 100	2700	270	0	270	540
		≥ 100	3000	300	0	300	600
	Maintenance dose (Days 197 to 351, q8w)	≥ 40 to < 60	3000	300	0	300	600
		≥ 60 to < 100	3900	390	0	390	780
		≥ 100	5400	540	0	540	1080

[a] Dose regimen will be based on the participant's most recently recorded body weight. Contact the Alexion Medical Monitor if a participant's weight drops below 40 kg during the study treatment period (Initial Evaluation Period or the Extension Period).
[b] Blinded dose on Day 183 (Week 26) for participants who were randomized to the ravulizumab group and are entering into the Extension Period.
[c] Blinded loading dose on Day 183 (Week 26) for participants who were randomized to the placebo group and are entering into the Extension Period.

6.2. Preparation/Handling/Storage/Accountability

Upon arrival of the study drug at the study site, the study drug kits should be removed from the shipping container and stored in their original cartons under refrigerated conditions at 2°C to 8°C (35°F to 46°F) and protected from light. Study drugs should not be frozen.

Study drugs must be stored in a secure, limited-access storage area with temperature monitored daily.

Infusions of study drug should be prepared using aseptic technique. Ravulizumab and placebo need to be further diluted in a 1:1 ratio with 0.9% sodium chloride. Ravulizumab and placebo will be filtered with a 0.2 micron filter during infusion.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Only participants enrolled in the study may receive the study drug and only authorized site staff may supply or administer the study drug. All study drug 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 drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
  - This responsibility includes the reporting of any product complaints to productcomplaints@alexion.com within 1 business day. 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 participant, 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.
  - The Investigator 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. Investigational product will not be returned to the Sponsor or disposed of until accountability has been fully monitored.
- Further guidance regarding preparation, handling, storage, accountability and final disposition of unused study drug is provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Participants will be randomized on Day 1 after the Investigator has verified that they are eligible. All eligible participants will be randomly assigned to ravulizumab or placebo in a 2:1 ratio using Interactive Response Technology (IRT).

To balance the effects of potential confounding factors between the ravulizumab and placebo arms, randomization will be stratified by whether corticosteroid induction treatment was initiated prior to Screening versus during the Screening Period for participants in the LN cohort and by mean proteinuria (1 to 2 g/day versus > 2 g/day) from 2 valid 24-hour urine collections during the Screening Period for participants in the IgAN cohort.

6.3.2. Blinding

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 assignments during the Initial Evaluation Period. The blinding will be maintained by using identical study drug 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.

The primary endpoint evaluation will occur for each disease-specific cohort after all participants in the disease-specific cohort complete the Week 26 Visit or withdrawn from the study prior to Week 26. Alexion will be unblinded at this time to conduct the primary analysis.

After completion of the Initial Evaluation Period, participants in the LN cohort will continue receiving their randomized study drug and both the participants and the investigative site personnel will remain blinded for the remaining 24-week Extension Period. For the IgAN cohort, participants in the placebo group will switch to receive a blinded loading dose of ravulizumab after completion of the protocol-required assessments at the Week 26 Visit and participants in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg at Week 26. The 900 mg dose at Week 26 was chosen to ensure maintenance of complete C5 inhibition until the next scheduled maintenance dose. Following completion of the Week 26 Visit, participants in the IgAN cohort will receive open-label ravulizumab treatment during the 24-week Extension Period.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator will be able to unblind the patient's treatment allocation directly using the IRT. If a patient's intervention assignment is unblinded, the Sponsor 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, as applicable.

When an AE is unexpected or related and serious, the blind will be broken for that specific participant only. The blind will be maintained for 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, 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), and/or Institutional Review Boards (IRBs).

Any participant who is unblinded during the Initial Evaluation Period will be withdrawn from the study.

Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

6.4. Study Drug Compliance

During this study, participants in both cohorts will receive all study drug infusions under the supervision of the Investigator, or designee.

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

The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

6.5. Allowed Concomitant Therapy

Information regarding prior use of disease-specific treatment, including immunosuppression induction treatment for participants in the LN cohort, and ACE inhibitors and/or ARBs for participants in the IgAN cohort, will be documented in CRF.

All information regarding allowed concomitant treatment during the study will be documented in CRF.

6.5.1. Allowed Concomitant Therapy for LN Cohort

During the course of the study, participants in the LN cohort will receive allowed concomitant therapy consistent with the standard of care for induction and maintenance treatment of LN.

- For participants who have not started corticosteroid induction treatment prior to Screening:
  - Participants will receive a cumulative dose of 1 gram of methylprednisolone IV administered in 1 or multiple divided doses or oral equivalent during the Screening Period (prior to Day 1).
  - During the Screening Period and no later than Day 2, all participants will receive oral corticosteroids with prednisone or prednisone equivalent with starting doses as outlined in Table 10. The starting minimum and maximum dose allowed are 30 mg/day and 60 mg/day, respectively. A corticosteroid taper will commence on Week 2 (Day 14). From Week 12 to Week 26, the target dose is 7.5mg/day. Following Week 26, participants may remain on 7.5 mg/day or continue to taper at the clinical discretion of the Investigator until Week 46. From Week 46 to Week 50, the dose of corticosteroids must not be changed.
  - During the Screening Period and no later than Day 1, participants will receive a cumulative dose of 1 to 1.5 g/day of MMF any time after completion of the IV

methylprednisolone during the Screening Period and no later than Day 1. The dose can be administered in multiple divided doses. Participants will continue to receive 1 to 1.5 g/day for 1 week.

  - After receiving 1 to 1.5 g/day for 1 week, the dose will be increased per the discretion of the Investigator to a cumulative dose of 2 to 3 g/day of MMF no later than by Week 4 (Day 28). The dose can be administered in multiple divided doses. Participants will continue to receive 2 to 3 g/day of MMF until Week 50 after which it may be decreased or discontinued based on the Investigators' judgment and the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines (KDIGO, 2021).

- For participants who have initiated corticosteroid induction treatment prior to Screening and do not meet Exclusion Criterion 20 (Section 5.2.2):
  - If the participant already received methylprednisolone IV ≥ 1 g or equivalent and is receiving MMF ≥ 2 g/day prior to Screening, then methylprednisolone IV will not be given. The participant may continue the current MMF dose during Screening and during the treatment period the dose of MMF should be adjusted to achieve 2 to 3 g/day no later than Day 28 (4 Weeks). MMF will be continued at 2 to 3 g/day until Week 50, after which it may be decreased or discontinued based on the Investigator's judgment and the KDIGO clinical practice guidelines (KDIGO, 2021).
  - If the participant already received methylprednisolone IV ≥ 1 g or equivalent and is receiving MMF < 2 g/day prior to Screening, then methylprednisolone IV will not be given and the MMF dose will be increased during the Screening Period (no later than Day 1) to a cumulative dose of 1 to 1.5 g/day. Participants will continue to receive 1 to 1.5 g/day for 1 week after which the MMF dose will be increased per the discretion of the Investigator to 2 to 3 g/day to be achieved no later than Week 4 (Day 28). These doses can be administered in multiple divided doses. Participants will continue to receive 2 to 3 g/day until Week 50, after which it may be decreased or discontinued based on the Investigator's judgment and the KDIGO clinical practice guidelines (KDIGO, 2021).
  - If a participant is already receiving prednisone or prednisone equivalent, the dose will be continued until Day 2 at which time prednisone or prednisone equivalent should be administered (the minimum and maximum dose allowed are 30 mg/day and 60 mg/day, respectively) as outlined in Table 10. The prednisone dose will be tapered starting on Week 2 (Day 14) according to the schedule. From Week 12 to Week 26, the target dose is 7.5 mg/day. Following Week 26, participants may remain on 7.5 mg/day or continue to taper at the clinical discretion of the Investigator until Week 46. From Week 46 to Week 50, the dose of corticosteroids must not be changed.

Table 10: Corticosteroid Taper for Participants With Lupus Nephritis

	Prednisone or Equivalent Dose (mg/day) According to Baseline Body Weight			
Study week	**40 to 60 kg**	**61 to 80 kg**	**81 to 100 kg**	**> 101 kg**
Screening to Week 2[a]	30	40	50	60
2	25	35	40	50
4	25	30	30	40
6	20	25	20	30
8	15	20	15	20
10	10	15	10	10
12[b]	7.5	7.5	7.5	7.5

[a] The minimum and maximum starting doses of prednisone are 30 mg and 60 mg, respectively.
[b] From Week 12 to Week 26, the target dose is 7.5 mg/day. Following Week 26, participants may remain on 7.5 mg/day or continue to taper at the clinical discretion of the Investigator until Week 46. From Week 46 to Week 50, the dose of corticosteroids must not be changed.

Other considerations regarding MMF dosing:

- An equivalent dose of enteric-coated mycophenolic acid sodium (MPS) may be used instead of MMF (ie, 360 mg dose MPS is equivalent to a 500 mg dose of MMF)
- Investigators may adjust the dosage of MMF due to tolerance or AEs. After the symptoms resolve, the Investigator should attempt to increase MMF (or equivalent) to the goal level. If symptoms return, then the participant should be continued on the highest tolerable dose.
- Any changes to the dose of MMF and the justification will to be documented in the CRF.

Other considerations regarding the corticosteroid taper:

- All participants will have a scheduled corticosteroid taper starting on Day 14. Participants will reduce their prednisone dose according to their baseline body weight over 10 weeks until the dose is 7.5 mg/day by Week 12 (Table 10). From Week 12 to Week 26, the target dose is 7.5 mg/day. Following Week 26, participants may remain on 7.5 mg/day or continue to taper at the clinical discretion of the Investigator until Week 46. From Week 46 to Week 50, the dose of corticosteroids must not be changed.
- Deviations from the scheduled corticosteroid taper for any reason other than Renal Flare or Extrarenal SLE Flare will confound interpretation, so every attempt should be made to adhere to the tapering schedule.
- If disease is too clinically active in the opinion of the Investigator to begin the corticosteroid taper after Week 2, then the participant may continue to receive his or her initial corticosteroid dose for up to an additional 28 days. Similarly, participants who have started the taper and whose disease is too clinically active to continue

tapering, may remain at the same taper dose achieved for up to an additional 28 days. Failure to achieve the corticosteroid taper by Week 12 will not be considered as Treatment Failure and will be captured as a secondary endpoint.

- However, the prednisone dose may NOT be increased beyond the taper dose achieved unless participant meets the protocol-defined criteria for Renal Flare (Section 3.2.1) and/or Severe Extrarenal SLE Flare (Section 3.2.2) in which case these participants will receive additional standard of care therapy and will be included as Treatment Failures.

6.5.2. Allowed Concomitant Therapy for IgAN Cohort

The allowed concomitant therapies for participants in the IgAN cohort will be consistent with standard of care and include the maximally tolerated dose of RAS-blocking agents, such as ACE inhibitors or ARBs.

The allowed concomitant treatment should be held stable throughout the Treatment Period of the study.

6.6. Additional Standard of Care Therapy for LN Cohort

Participants in the LN cohort will receive additional standard of care therapy in the event of a protocol-defined Renal Flare (Section 3.2) or Severe Extrarenal SLE Flare (Section 3.2.2). Additional standard of care therapy is defined as intensification of current standard of care or introduction of new immunosuppressive therapies. After Week 26, additional standard of care therapy for participants with Suboptimal Response (Section 3.2.3) is allowed at the clinical discretion of the Investigator in conversation with the Medical Monitor.

The specific choice of additional standard of care therapy(ies) is generally at the discretion of the Investigator and may include approved medications for LN (eg, voclosporin, belimumab).

The following guidelines for corticosteroid dosing for protocol-defined Renal Flare and Severe Extrarenal SLE Flares should be considered to maintain treatment consistency:

- Participants with protocol-defined Renal Flare may be treated with prednisone up to 0.5 mg/kg/day (not to exceed 60 mg/day) for up to 2 weeks. Prednisone will then be tapered weekly to 10 mg/day within 6 weeks after the initial prednisone increase. Prednisone may further be tapered to ≤ 7.5 mg/day at the discretion of the Investigator.
- Participants with Severe Extrarenal SLE flare may be treated with prednisone up to 1 mg/kg/day (not to exceed 60 mg/day) for up to 2 weeks. Prednisone will then be tapered every 2 weeks to achieve 7.5 mg/day within 12 weeks after the initial corticosteroid increase.
- Intravenous corticosteroids in equivalent doses may be allowed if gastrointestinal involvement temporality precludes oral corticosteroid use.

Prednisone ≥ 10 mg for ≤ 14 days will not be considered additional standard of care therapy in the following instances:

- Renal flares not meeting the protocol defined criteria for Renal Flare (see Section 3.2.1)
- Mild and non-severe Extrarenal SLE flares (see Section 3.2.2)
- Other medical conditions or surgery

The use of additional standard of care therapy should be discussed directly between the Investigator and Medical Monitor.

Additional standard of care therapy will be documented in the participant's CRF according to the CRF completion guidelines with the indication entered as "Renal Flare", "Severe Extrarenal SLE Flare", or "Suboptimal Response."

6.7. Concomitant Therapy

6.7.1. Allowed Medications and Therapies

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 6.7.2, may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the CRF (Section 8.5.2).

If adequate blood pressure control is not achieved during the study, participants may receive additional antihypertensive agents, but not agents that affect proteinuria during the study. It is recommended that nonsteroidal anti-inflammatory drugs (NSAIDs) not be initiated during the study due to the possibility of adverse effects on renal function. They may be used, however, if necessary for the control of symptoms.

For participants in the LN cohort:

- Pneumocystis pneumonia prophylaxis is allowed at the discretion of the Investigator.
- Treatment with antimalarial agents such as hydroxychloroquine are strongly recommended unless contraindicated.
- Measures to prevent and treat osteoporosis are strongly encouraged during the study; these measures may include any, or all, of the following: calcium carbonate or citrate, Vitamin D, and bisphosphonates.
- Immunosuppressive drugs for additional standard of care therapy are allowed.

6.7.2. Disallowed Medications and Therapy

Participants in both cohorts are prohibited from receiving any of the following medications and therapies during the entire duration of study participation:

- Experimental interventions or therapies
- Eculizumab

- New use or modification of the dose of SGLT-2 inhibitors and direct renin antagonists
- New use or modification of the dose of RAS inhibitor treatment

In the event that a participant receives a prohibited medication and/or therapy, the participant should discontinue study drug (Section 7.1) with the exception of SGLT-2 inhibitors and direct renin antagonists (SGLT-2 inhibitors and direct renin antagonists are prohibited but may not require discontinuation of study drug based on the discussion and approval of the Investigator and Medical Monitor).

Participants in the IgAN cohort are also prohibited from receiving any of the following medications and therapies during the entire duration of study participation:

- Hydroxychloroquine
- Immunosuppressive agents (eg, MMF)
- Systemic corticosteroids for > 14 consecutive days (short-term steroid course for ≤ 14 days for medical conditions not related to IgAN or surgery are permitted)

6.8. Dose Modification

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

The adequacy of the dosing regimen will be confirmed through interim analysis of PK/PD data as described in Section 9.5.1. If the initial dosing regimen does not result in the anticipated PK/PD data, the dosing regimen may be modified for subsequent participants according to PK/PD data.

6.9. Intervention After the End of the Study

After a participant completes the Treatment Period (ie, end of Extension Period) or withdraws from the study, study drug will not be administered.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

A participant has the right to discontinue study drug at any time.

Participants must permanently discontinue the study drug for any of the following reasons:

- Serious hypersensitivity reaction
- Severe uncontrolled infection
- Serious infusion reaction (such as bronchospasm with wheezing or requiring ventilator support or symptomatic hypotension, refer to Section 10.4) or serum sickness-like reactions manifesting 1 to 14 days after drug administration
- Use of disallowed medication as defined in Section 6.7.2
- Pregnancy or planned pregnancy
- Participant is unblinded during the Initial Evaluation Period

In addition, the study drug may be permanently discontinued for any of the following reasons:

- Adverse event that would, in the opinion of the Investigator, make continued participation in the study an unacceptable risk
- Deviation(s) from the protocol
- Significant non-compliance
- Alexion or the Investigator deems it is necessary for the participant
- Study termination

The reason for discontinuation of study drug will be recorded in the source documents and CRF.

If the study drug is definitively discontinued, every effort should be made to have the participant continue the study visits as per the SoA through Week 50/EoS. If a participant discontinues study drug due to an AE, including SAEs, the event should be followed as described in Section 10.3.3.

Participants who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgment, as applicable.

If the participant does not agree to continue with the study visits, the following activities should be completed:

- Early Discontinuation Visit should be performed as outlined in the SoA (Section 1.3).
- A Follow-up Phone Call will be performed 8 weeks following the participant's last dose of study drug to collect information on concomitant medications, nonpharmacological therapies and procedures, and AEs.

7.2. Participant 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 withdrawal 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.
- At the time of study withdrawal, an Early Discontinuation (ED) Visit should be conducted, whenever possible, per the Schedule of Assessments (Section 1.3). A Safety Follow-up Phone Visit should be conducted at least 8 weeks after the final dose of study drug to collect information on any AEs and concomitant medications.
- The participant will be permanently discontinued from the study drug at the time of study withdrawal.
- 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, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the source records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be 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 and reschedule the missed visit as soon as possible and 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.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Procedures for study termination and closure of specific sites are provided in Section 10.1.9.

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.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- 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 or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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.

8.1.3. Demographics

Demographic parameters, including age, sex, race, and ethnicity will be documented in the CRF.

8.1.4. Medical History

The participant's relevant medical history, including prior and concomitant conditions/disorders, treatment history, disease status (naïve vs relapse) if available (LN cohort only), and family history of relevant diseases will be evaluated at Screening by the Investigator and documented in the source documents and CRF. Any changes to medical history occurring during the Screening Period and prior to first dose of study drug on Day 1 will be documented prior to study drug administration.

8.1.5. Kidney Biopsy

8.1.5.1. Screening Kidney Biopsy

The diagnosis of LN and IgAN is based on a kidney biopsy obtained prior to or during the Screening Period. Eligibility will be determined using the local pathology report according to standardized globally recognized guidelines, as follows:

- For participants in the LN cohort, kidney biopsies must have been obtained ≤ 6 months prior to Screening or during the Screening Period; eligibility will be based on the ISN/RPS classification guidelines (Section 10.10).
- For participants in the IgAN cohort, kidney biopsies may have been obtained any time prior to Day 1 (Section 10.11; Haas, 1997; Trimarchi, 2017).

The local pathology report must be entered in the CRF during Screening according to the CRF completion guidelines. In particular, the degree of IgG, IgA, immunoglobulin M (IgM), C3, and C1q (both cohorts); the activity score/class (LN cohort only); and the mesangial and endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy, and the presence of crescents (MEST-C) score (IgAN cohort only), will be obtained from the local pathology reports, if available, and documented in the CRF.

8.1.5.2. Kidney Biopsy During Study

Kidney biopsies may be performed any time during the study at the discretion of the Investigator for renal flare or other indications.

For participants in the LN cohort, a repeat biopsy at the end of the Extension Period (Week 50) will be optional and may be performed up to Week 54.

8.1.5.3. Central Pathology Laboratory

A Central Pathology Laboratory will be used to confirm the diagnosis on the kidney biopsy used for eligibility to minimize interpersonal variation in histological scoring. The Central Pathology Laboratory will be blinded to treatment allocation.

The Central Pathology Laboratory will review:

- All kidney biopsies used for eligibility for participants in the LN cohort
- Kidney biopsies performed within 1 year of Screening or during Screening for participants in the IgAN cohort
- All kidney biopsies performed during the study any time prior to ED or completion of the Extension Period (Week 50)

The following should be sent to the Central Pathology Laboratory as soon as feasible according to the instructions in the Central Pathology Laboratory Manual.

- Copy of the local pathology report
- All light microscopy slides (Hematoxylin and eosin stain [H/E], Periodic acid–Schiff, Jones & Trichrome stains)

- If available, unstained microscopy slides of the kidney biopsy should also be sent to the Central Pathology Laboratory for exploratory analyses of biomarkers (Section 8.8.3). The site should send all available unstained slides, up to a maximum of 8 slides.

Every effort should be made to obtain the microscopy slides from the site pathology laboratory and ship them to the Central Pathology Laboratory. Upon confirmation with the Central Pathology Laboratory, the original biopsy slides from each participant will be returned to the study site as soon as possible. Unstained slides used for exploratory biomarker analyses will not be returned. If the shipment of microscopy slides to the Central Pathology Laboratory is prohibited due to local regulations, a slide scanner may be used to send digital images of the slides electronically, according to the instructions in the Central Pathology Laboratory Manual.

8.1.6. 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 within 3 years prior to or at the time of the first infusion of study drug. Participants who have not been vaccinated prior to starting study drug for any reason, should receive appropriate prophylactic antibiotics prior to and for at least 2 weeks after vaccination. Vaccines against serotypes A, C, Y, W135, and B where available, are recommended in preventing the commonly pathogenic meningococcal serotypes. Participants must receive the complete primary vaccination series and be revaccinated if indicated according to current national vaccination guidelines. Vaccination may not be sufficient to prevent meningococcal infection.

Participants should be administered prophylactic antibiotics for meningococcal infection until at least 2 weeks after vaccination if randomization occurs < 2 weeks after initial vaccination. Consideration should be given per official guidance and local practice on the appropriate use of prophylactic antibacterial agents. 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 8.3.1). 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.

Meningococcal serogroups ACWY and B (where available) vaccinations are required during Screening for participants who do not meet criteria for previous vaccination. The vaccination series will be completed during the study according to national and local vaccination schedule guidelines.

In participants with IgAN, every effort should be made to start the meningococcal vaccination series at least 14 days prior to randomization.

All participants must also be vaccinated against *Hib* and *S pneumoniae* prior to randomization, unless previously vaccinated, according to current national/local vaccination guidelines.

Vaccination status and administration of any vaccines, including those for *N meningitidis, Hib,* and *S pneumoniae* will be recorded on the CRF.

8.2. Efficacy Assessments

8.2.1. 24-hour Urine Collection

For the determination of proteinuria, 24-hour urine collection will be obtained during Screening, Week 26, and Week 50, and will be analyzed by a central laboratory. In addition to protein, albumin, sodium, and creatinine will also be quantified in each of the 24-hour urine collections. Both UPCR as well as albumin to creatinine ratios (UACRs) will also be calculated in an aliquot of the 24-hour urine collection.

Rigorous exercise and significant change in diet (in particular, salt intake) should be avoided within 48 hours before collection of 24-hour urine samples, whenever possible.

The collection should be obtained prior to or > 7 days after biopsy procedures and prior to administration of ravulizumab or placebo on dosing days.

The 24-hour urine collections could occur at the participant's home by a mobile nurse if agreed upon with the Investigator and the participant, according to local regulations. The collection will be recorded in the CRF according to the CRF completion guidelines.

LN Cohort

For participants in the LN cohort, proteinuria will be measured by UPCR. A single 24-hour urine collection will be obtained at Screening to assess eligibility. Two separate 24-hour urine collections will be obtained within 2 weeks prior to the Week 26 Visit (to assess the primary endpoint) and Week 50 Visit (to assess a secondary endpoint).

Confirmation of a protocol-defined Renal Flare or Suboptimal Response requires a single 24-hour urine collection within 2 weeks of the spot urine sample (Section 3.2.1 and Section 3.2.3).

IgAN Cohort

Participants in the IgAN cohort will be required to provide 2 separate complete and valid 24-hour urine collections during the Screening Period (to assess eligibility), at Week 26 (to assess the primary endpoint), and at Week 50 (to assess a secondary endpoint). The 2 valid 24-hour urine collections should be obtained within 2 weeks before the Week 26 and Week 50 Visits.

Completeness of the 24-hour urine collection will be estimated from rate of creatinine excretion. Normal values of creatinine excretion vary with age and body weight. Hence, a 24-hour urine collection is considered valid if all the following criteria are met, otherwise the urine collection is required to be repeated:

- The collection is between 22 to 26 hours in duration (ie, time from the initial discarded void to the last void/attempt to void).
- No voids are missed between the start and end time of the collection as indicated by the participant's urine collection diary.

- The 24-hour creatinine content is within 30% of expected range as estimated by the following formula: [(140-age) × weight]/5000, where weight is in kilograms. This result is multiplied by 0.85 in women (Ix, 2011).
- The maximum variation in total 24-hour urine creatinine between the 2 urine collections must be ≤ 30%.

Urine collections that deviate from the above criteria will be reviewed by the Medical Monitoring team and may be considered acceptable if determined to be not clinically significant.

If any of the collections do not meet the validity criteria outlined above, **the collection must be repeated as soon as possible** within the time frames outlined in the SoA (Section 1.3) in order to ensure that 2 valid collections are obtained for each of the study time points.

8.2.2. Spot Urine Sample

Urinary protein, albumin, and creatinine levels from morning spot urine sample prior to dosing will also be measured during Screening and during the study per the SoA (Section 1.3) to assess the effect of ravulizumab on UPCR and UACR.

Two consecutive spot urine samples will be obtained for participants in both disease cohorts at the Week 18 Visit.

The spot urine sample should be obtained prior to or > 7 days after biopsy procedures and prior to administration of ravulizumab or placebo on dosing days.

Spot urine samples conducted as routine standard of care will be used for UPCR during the Post-treatment Follow-up Period per the SoA (Section 1.3). The UPCR results will be recorded in the participant's CRF.

8.2.3. Estimated Glomerular Filtration Rate

Changes in renal function will be monitored using measurements of eGFR (mL/min/1.73m^2) and creatinine clearance on a 24-hour urine collection as outlined in the SoA (Section 1.3). The eGFR calculation will be based on the CKD-EPI formula for all participants using serum creatinine collected prior to study drug administration, if applicable.

For the determination of CRR and PRR at Week 26 and Week 50, 2 serum creatinine samples will be obtained within 2 weeks prior to each of these study visits. The blood sample collection could occur at the participant's home if agreed upon with the Investigator and the participant. The collection will be recorded in the CRF according to the CRF completion guidelines.

The change from baseline in eGFR will be measured throughout the course of the study. In addition, the slope of eGFR will be computed through Week 26 and Week 50 for participants in the IgAN cohort.

8.2.4. Hematuria

For participants in both disease cohorts, hematuria from spot urine samples will be evaluated to assess the effect of ravulizumab on disease course. The degree of hematuria will be assessed by examination of the spun urine sediment by microscopy (RBC/hpf).

Single void collections for random spot urine sample for hematuria evaluation should be collected. If the Investigator determines that the hematuria is transient due to menses in women or exercise, the sample may need to be repeated.

Random spot urine samples for hematuria measurement will be collected throughout the study as outlined in the SoA (Section 1.3) and will be analyzed by a central laboratory. On dosing days, samples should be collected prior to study drug administration, if applicable.

The local hematuria evaluation by microscopy or urinary dipstick will be utilized to determine eligibility for the study at Screening for participants with IgAN.

8.3. Safety Assessments

8.3.1. Participant Safety Card

Before the first dose of the study drug, 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 drug. 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.

At each visit throughout the study, the study staff will ensure that the participant has the Participant Safety Card.

8.3.2. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, musculoskeletal, and neurological state (with emphasis on presence/degree of edema).
- An abbreviated physical examination will include, at a minimum, a body-system relevant examination based upon Investigator judgment and participant symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Additional physical examinations can be performed as medically indicated during the study at the Investigator's discretion.
- Height and weight will also be measured and recorded.

8.3.3. Vital Signs and Pulse Oximetry

- Temperature (°C or °F), heart rate, respiratory rate, systolic and diastolic blood pressure (mmHg), and pulse oximetry will be assessed.
- Blood pressure and pulse measurements will be assessed with the participant in a seated position using a completely automated device. 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 at study drug dosing visits.

8.3.4. Electrocardiograms

- Single 12-lead electrocardiogram (ECGs) will be conducted locally to obtain heart rate, PR, QRS, interval between the start of the Q wave and the end of the T wave in an ECG (QT), and corrected QT interval (QTc) intervals (QT interval will be corrected for heart rate using Fridericia's formula [QTcF].)
- Single 12-lead ECG will be performed at Screening, at the end of the Initial Evaluation Period (prior to dosing on Day 183), and at the end of the Extension Period (Day 351). For participants that discontinue study drug, an ECG should be performed at the ED Visit.
- Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- The Investigator or Sub-investigator will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results.

8.3.5. Clinical Safety Laboratory Assessments

- 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).
- The Investigator must review the 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 laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study drug 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 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, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3.5.1. Virus Serology

Testing for HIV-1 and HIV-2 is required for all participants prior to enrollment. Participants who are HIV antibody positive will not be enrolled.

Similarly, participants who are positive at the Screening Visit for HBsAg, anti-HBc with negative anti-HBs, or HCV antibody positive (except for participants with documented successful treatment and documented sustained viral response) will not be enrolled.

8.3.6. Pregnancy

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

A negative pregnancy test is required for WOCBPs before study drug administration.

- Any female participant who becomes pregnant while participating in the study will be discontinued from the study drug.
- 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 discontinues the study drug or 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 drug 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.

8.4. 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 drug or study procedures, or that caused the participant to discontinue the study drug (see Section 7).

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

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 Week 86 or, if the participant discontinues study drug early, 8 weeks (56 days) after last dose of study drug is administered.

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. 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 conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify Alexion.

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

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards 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 and forwarded to Investigators as necessary. Consistent with Alexion policy and procedures for blinded clinical studies, these reports 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 EU CTR 536/2014, events other than SAEs (eg, unexpected events) that may impact the benefit-risk balance should be reported. See definitions in Section 10.3.5.

8.4.5. Medication Error, Drug Abuse, and Drug Misuse

Medication error, drug abuse, and drug misuse will be collected from signing of the applicable version of the ICF through the last scheduled procedure shown in the SoA (Section 1.3).

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, non-therapeutic excessive use of study intervention for a perceived reward or desired non-therapeutic effect.

8.4.5.4. Drug Misuse

Drug misuse is the intentional and inappropriate use 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.

8.4.6. Adverse Events of Special Interest

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

8.5. Review of Prior and Concomitant Medications and Procedures

8.5.1. Prior Medications and Procedures

Prior medications and/or vaccines (including vitamins, herbal preparations, and those discussed in the exclusion criteria [Section 5.2]) and procedures (any therapeutic drug, such as surgery/biopsy or physical therapy) that the participant takes or undergoes within 30 days before the start of Screening or during the Screening Period before the first dose of study drug, as well

as any meningococcal vaccine administered within the last 3 years, will be recorded in the participant's CRF.

For participants in the IgAN cohort:

- ACE inhibitors and ARBs during 3 months prior to the first dose
- Blood pressure medications received during the 3 months prior to the first dose

Information regarding the prior use of disease-specific treatment will be recorded for both cohorts, including immunosuppression induction treatment for participants in the LN cohort.

8.5.2. Concomitant Medications and Procedures

Concomitant medications (including any medication, vitamin, herbal preparation or supplement) and procedures (defined in Section 6.7) are those received on or after the first study drug date (Day 1), including those started before Day 1 and continued after Day 1. At each study visit, participants should be questioned about any new medication or nondrug therapies or changes to concomitant medications and nondrug therapies since the last visit. Concomitant medications and nondrug therapies should be recorded in the source documents and the participant's CRF including:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Any concomitant medication 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 6.7.2, may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full, in the participant's source documents and CRF.

Information regarding the use of disease-specific treatment received during the course of the study will be recorded in the source documents and the participant's CRF, including:

- For participants in the LN Cohort:
  - Additional standard of care therapy (Section 6.6) for protocol-defined Renal Flare, Severe Extrarenal SLE Flare, or Suboptimal Response
  - Treatment(s) for non-severe extrarenal SLE flare or other renal flare not defined in protocol

Vaccination and antibiotics administered for prophylaxis of meningococcal infection (if applicable) will also be recorded.

The Medical Monitor should be contacted if there are any questions regarding concomitant medications or procedures.

Allowed concomitant therapy and corticosteroid tapering for participants with LN is discussed in Section 6.5.1 and allowed concomitant therapy for participants with IgAN is discuss in Section 6.5.2.

8.6. Treatment of Overdose

For this study, any dose of ravulizumab greater than that specified in the protocol will be considered an overdose. If dose cannot be established during the Initial Evaluation Period 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.
- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Obtain a plasma sample for PK analysis from the date of the last dose of study intervention 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.

8.7. Pharmacokinetics and Pharmacodynamics

- Blood samples for determination of serum drug concentrations and PD assessments (free and total C5) will be collected before and after administration of study drug at the time points specified in the SoA (Section 1.3).
- 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 90 minutes before administering study drug at visits specified in the SoA (Section 1.3). The predose blood sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose.
- For all subsequent visits falling on dosing days, samples will be collected predose (within 0.5 hours prior to the start of infusion). 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 the dose.
- Postdose PK and PD blood samples will be collected within 0.5 hours after completing study drug infusion. The postdose blood samples will be drawn from the participant's opposite, noninfused arm.
- For indicated visits not falling on dosing days, samples may be collected at any time that visit day.
- In the event of an unscheduled visit, PK and PD blood sample will be collected as soon as possible.
- Ravulizumab PK in urine may be conducted as an exploratory analysis based on findings from impact of proteinuria on serum PK.

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.

8.8. Biomarkers

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

8.8.1. Blood Exploratory Biomarkers

Blood (whole blood, serum & plasma) samples for biomarker research 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 dysregulation (eg, soluble C5b-9 [sC5b-9] etc)

8.8.2. Urine Exploratory Biomarkers

Urine samples for biomarker research 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 dysregulation (sC5b-9 etc)
- Renal injury biomarkers (eg, neutrophil gelatinase-associated lipocalin [N-GAL], etc)
- Creatinine

8.8.3. Kidney Biopsy Tissue Exploratory Biomarkers

Kidney tissue biopsies will be stained for the presence of biomarkers which provide clinical evidence of the disease pathophysiology and response to treatment (eg, C5b-9, etc).

For participants in the LN cohort who undergo repeated kidney biopsy(s) during the study, the LN classification will be assessed.

8.8.4. Additional Biomarker Research

Residual blood, urine, and biopsy samples from exploratory biomarkers, PK, PD, and immunogenicity, as well as residual samples from 24-hour urine collections will be stored for additional method developments of assays (eg, prognostics and/or companion diagnostics related to the study drug target, disease process, pathways associated with disease state, other complement-related diseases, and/or mechanism of action of ravulizumab).

Samples will be retained to enable further analysis on ravulizumab continues but no longer than 5 years after termination of the study or other period as per local requirements.

8.9. Other Exploratory Assessments

8.9.1. Autoantibodies (LN Cohort Only)

Blood samples will be collected for anti-dsDNA and anti-C1q) autoantibodies during Screening and according to the SoA (Section 1.3) through the end of the Extension Period (Day 351).

8.9.2. SLEDAI–2K (LN Cohort Only)

The SLEDAI–2K tool (Section 10.12) assesses disease activity across 24 disease descriptors. The total score ranges from 0 to 105, with higher scores representing more significant degrees of disease activity.

The 18 disease descriptors of the SLEDAI–2K assessment will be used for the determination of Extrarenal SLE Flare (Section 3.2.2). Extrarenal SLE Flare is defined as an increase in SLEDAI-2K $\geq$ 4 points that is not accounted for by the disease descriptors of proteinuria, hematuria, urinary casts, hypocomplementemia, pyuria, or an increase in anti-dsDNA antibody level. Each disease descriptor is evaluated if present at the time of the visit or within the preceding 30 days.

8.9.3. Real Time Complement Activity

Blood and urine samples will be collected (at selected study sites only) for exploratory Real Time Complement Activity (RTCA) during Screening and according to the SoA (Section 1.3) through the end of the Initial Evaluation Period (Day 183). The RTCA analysis will be performed at clinical sites using freshly collected whole blood dipotassium ethylenediaminetetraacetic acid (K2EDTA) and urine samples. Blood and urine samples for RTCA will be collected prior to administration of study drug on dosing days, if applicable. The results will be de-identified using the participant study identification number and all site personnel will be blinded from the RTCA results.

8.9.4. Participant-Reported Outcome Measures

Quality of life scales will be administered by the Investigator or a qualified site staff prior to other study procedures at visits specified in the SoA (Section 1.3).

Participants in both cohorts will have the following validated quality of life scales administered:

- The Short Form (36) (SF-36v2) Health Survey (Section 10.13) will be used to assess the participant's quality of life. In the SF-36v2 Questionnaire, participants will be instructed to rate their health and capacity to perform activities of daily living in 8 domains including physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health during the last 4 weeks. Raw domain scores will be determined and transformed to a 0 to 100 scale as described in the SF-36v2 manual. Domains get scored from 0 to 100 with lower scores indicating increased disability.
- The EuroQoL 5-Dimensions 5-Level (EQ-5D-5L) (Section 10.14) is a self-assessed, standardized instrument to measure health-related quality of life 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.

Participants in the LN cohort will also have the following validated quality of life scales administered:

- The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (Section 10.15), 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. Immunogenicity Assessments

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

ADA positive samples will be further characterized for antibody titer and presence of neutralizing antibodies. Additional analyses may be performed on collected ADA samples for further analysis or characterization.

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

8.11. Genetics

Genetics data are not collected in this study. There are no prespecified genetic analyses in this study.

8.12. Medical Resource Utilization

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.13. Post-treatment Follow-up Period

During the 36-week Post-treatment Follow-up Period, participants will continue to receive standard of care and will be monitored for clinical events of interest and kidney function.

All participants will be followed for safety until 8 weeks after the participant's last dose of study drug to collect information on concomitant medications, nonpharmacological therapies and procedures, and AEs. The final safety evaluation for participants in the LN will occur at the Week 50 Visit and participants in the IgAN cohort will have a Follow-up Phone Call performed at Week 52.

Participants are not required to come into the clinic for the Post-treatment Follow-up Period visits. At each Post-treatment Follow-up Visit through Week 86, the information described below will be documented in the participant's CRF for the 12-week period since the previous study visit.

For participants in both cohorts, the following laboratory results will be documented:

- Record the UPCR results from the participant's most recent standard of care testing conducted by local laboratory. Spot urine studies may be used; a morning void is preferred.
- Record serum creatinine results from the participant's most recent standard of care testing conducted by local laboratory.

For participants in the LN cohort, information will include, but is not limited to:

- In the Investigator's opinion, did the patient experience a renal flare or extrarenal flare
- Documentation of any changes in immunosuppression therapy (intensified, new agent, or change in dose)
- Progression of kidney disease including dialysis and kidney transplant

For participants in the IgAN cohort, information will include, but is not limited to:

- Progression of kidney disease including dialysis and kidney transplant
- Documentation of any changes in immunosuppressive therapy (new agent or change in dose)
- Documentation of any changes in alternative therapy (new agent or change in dose)

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

The primary hypothesis for this study is that ravulizumab is superior to placebo in decreasing proteinuria. Hypothesis testing will be one-sided and performed at the 0.05 level of significance.

9.2. Sample Size Determination

This study plans to enroll 60 participants in both the IgAN and LN cohorts in a 2:1 ratio to ravulizumab and placebo, for a total of 120 participants.

In March 2018, a National Kidney Foundation (NKF)-sponsored workshop on surrogate endpoints for clinical studies in early stages of CKD proposed that a 20% to 30% reduction in the geometric mean of proteinuria was likely to be necessary to ensure a significant treatment effect on the clinical outcome (Levey, 2020; Holtkamp, 2020).

Individual patient data from relevant studies in IgAN was previously used to estimate variability and expected changes in proteinuria for patients treated with placebo in addition to allowed concomitant standard of care treatment (Fellstrom, 2017). Based on this data, the geometric mean ratio (GMR) of 26-week to baseline proteinuria values is assumed to be 0.85 (ie, a 15% reduction in proteinuria) for the placebo group. In order to target at least a 30% relative treatment effect, the GMR is assumed to be 0.55 (ie, a 45% reduction in proteinuria) for the ravulizumab group.

Expected changes in proteinuria and associated variability were not available on the log-scale for patients with LN; however, 2 studies of patients with LN who were treated with MMF showed mean proteinuria values of approximately 4.0 g/day at baseline and approximately 2.0 g/day at Week 24 (Appel, 2009; Ginzler, 2005). The GMR of 26-week to baseline proteinuria values is assumed to be 0.60 (ie, a 40% reduction in proteinuria) for the placebo group. In order to target at least a 30% relative treatment effect, the GMR is assumed to be 0.40 (ie, a 60% reduction in proteinuria) for the ravulizumab group.

Sample size calculations are based on a one-sided two-sample t-test of log-transformed proteinuria values. The log change from baseline in proteinuria is calculated as log(0.85) and log(0.55) for the placebo and ravulizumab treatment groups, respectively, for the IgAN cohort, and as log(0.60) and log(0.40) for the placebo and ravulizumab treatment groups, respectively, for the LN cohort. A common standard deviation (SD) of log change is assumed to be 0.60 (Fellstrom, 2017). Under these assumptions and an anticipated 10% drop out rate, a sample size of 60 participants (40 participants randomized to ravulizumab, 20 participants randomized to placebo) will provide approximately 80% power to detect a treatment difference with a one-sided significance level of 0.05 in each cohort.

9.3. Populations for Analyses

The following populations are defined for this study:

Population	Description
Randomized Set	All randomized participants. Participants will be analyzed as randomized for reporting disposition, demographics, and baseline characteristics.
Full Analysis Set (FAS)	All randomized participants who receive at least 1 dose of study drug. Participants will be analyzed as randomized for reporting efficacy data.
Modified Full Analysis Set (mFAS)	The mFAS is a subset of the FAS, excluding participants who were impacted by COVID-19.
Safety Set	All participants who receive at least 1 dose of study drug. Participants will be analyzed according to the study drug they actually received for reporting exposure and safety data.
Per Protocol Set	All randomized participants who receive at least 1 dose of study drug and without important protocol deviations.
Pharmacokinetic (PK) Analysis Set	All participants who receive at least 1 dose of study drug and who have evaluable PK data.
Pharmacodynamic (PD) Analysis Set	All participants who receive at least 1 dose of study drug and who have evaluable PD data.

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetics

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP). All efficacy and safety analyses will be summarized separately for the Initial Evaluation Period, Extension Period, and Post-treatment Follow-up Period. Limited data will be collected during the Post-treatment Follow-up Period and will be summarized descriptively as applicable.

Summary statistics will be computed and displayed by treatment group and by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of participants, mean, SD, minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate.

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

The analyses for participants in the LN cohort and participants with IgAN cohort will be conducted and reported separately. Participants in each disease-specific cohort will be analyzed as randomized, regardless of actual treatment received.

9.4.1. Efficacy Analyses

9.4.1.1. Analyses of Primary Efficacy Endpoint

The primary analysis of the primary efficacy endpoint will be based on the Full Analysis Set (FAS).

For the LN cohort, proteinuria will be measured by UPCR in g/g derived from a single 24-hour urine collection at Screening and the mean of 2 separate 24-hour urine collections at Week 26.

For the IgAN cohort, proteinuria will be measured by absolute protein in g/day derived from the mean of 2 valid 24-hour urine collections.

To reduce skewness, the natural logarithm will be used to transform proteinuria values before analysis. An analysis of covariance (ANCOVA) will be used for the primary efficacy endpoint to compare reductions in proteinuria between the ravulizumab and placebo treatment groups. The ANCOVA model will include change from baseline in log-transformed proteinuria as the response variable and will adjust for baseline log proteinuria and the randomization stratification factor. The treatment effect will be evaluated using the least squares mean difference between treatment groups. The point estimate and two-sided 90% confidence interval (CI) for the mean difference of log-transformed proteinuria will be back-transformed (via exponentiation) to obtain the GMR and corresponding two-sided 90% CI. The values will then be expressed as percentage change in adjusted geometric mean of proteinuria at Week 26 relative to baseline.

For the LN cohort, data collected on or after receipt of additional standard of care therapy will be imputed using the proteinuria value from the 24-hour urine collection performed at the time of Renal Flare for the primary efficacy analysis. Additional sensitivity analyses will be performed to assess the impact of the missing data and assumptions.

For the IgAN cohort, participants initially randomized to the placebo group will receive ravulizumab in the Extension Period. Therefore, analysis of the secondary endpoints during the Extension Period will be summarized separately for each treatment group and baseline for the placebo group will be re-defined as the last measurement taken before the first dose of ravulizumab during the Extension Period (ie, the Week 26 measurement).

The primary efficacy endpoint analysis will also be performed on the Per Protocol Set.

Full details of these analyses will be provided in the SAP.

9.4.1.2. Analyses of Secondary Efficacy Endpoints

The secondary efficacy analyses will be descriptive in nature and will be based on the FAS.

9.4.1.2.1. Secondary Efficacy Analyses for Both LN Cohort and IgAN Cohort

- The percentage change from baseline in proteinuria at Week 50 will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include change from baseline in log-transformed proteinuria as the response variable and fixed, categorical effects of treatment group, randomization stratification factor, visit, and treatment group by visit interaction as well as a fixed, continuous effect of baseline log proteinuria as a covariate. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each participant. If this analysis fails to converge, a first-order autoregressive covariance matrix will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.
- For the IgAN cohort, participants initially randomized to the placebo treatment group will switch to receive ravulizumab at Week 26. Therefore, the percentage change

from baseline in proteinuria at Week 50 will be summarized descriptively for each treatment group from the MMRM analysis and no formal treatment comparison will be made. For the LN cohort, the treatment effect will be evaluated using a contrast for treatment group-by-visit term at Week 50. The point estimate and two-sided 90% CI for the mean difference of log-transformed proteinuria will be back-transformed (via exponentiation) to obtain the GMR and corresponding two-sided 90% CI. The values will then be expressed as percentage change in adjusted geometric mean of proteinuria at Week 50 relative to baseline.

- The percentage of participants with > 30% and > 50% reduction in proteinuria at Week 26 and Week 50 will be summarized by treatment group by calculating the point estimate and two-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method.
- The following endpoints will be summarized at baseline and each postbaseline time point by treatment group using descriptive statistics for the observed value as well as the change from baseline:
  - eGFR
  - Serum C3 and C4 concentrations

9.4.1.2.2. Secondary Efficacy Analyses for LN Cohort Only

The following secondary endpoints will be summarized by treatment group by calculating the point estimate and two-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method:

- Percentage of participants meeting the criteria for CRR as well as individual components of CRR (defined in Section 3.2.5) at Week 26 and Week 50
- Percentage of participants meeting the criteria for PRR (defined in Section 3.2.5) at Week 26 and Week 50
- Percentage of participants with achieving corticosteroid taper (defined in Section 6.5.1) at Week 14, Week 26, and Week 50
- Percentage of participants with protocol-defined Renal Flare (defined in Section 3.2.1) through Week 50
- Percentage of participants with protocol-defined Severe Extrarenal SLE Flare (defined in Section 3.2.2) through Week 50
- Percentage of participants with Treatment Failure (defined in Section 3.2.4) through Week 50
- Percentage of participants with Suboptimal Response (defined in Section 3.2.3) through Week 50

Time to UPCR ≤ 0.5 g/g will be summarized based on spot urine samples. A Kaplan-Meier cumulative distribution curve will be generated for treatment group, and a log-rank test comparing the curves will be performed. The corresponding summary table will present by treatment group the cumulative distribution function (CDF) estimate, the number of participants

at risk, the number of participants responding, and the number of participants censored at each postbaseline time point. The table will also present the first quartile, median, and third quartile, along with two-sided 95% CI, of time to UPCR ≤ 0.5 g/g.

Serum albumin will be summarized at baseline and each postbaseline time point by treatment group using descriptive statistics for the observed value as well as the change from baseline.

9.4.1.2.3. Secondary Efficacy Analyses for IgAN Cohort Only

The percentage of participants meeting the criteria for Partial Remission (defined in Section 3.2.6) at Week 26 and Week 50 will be summarized by treatment group by calculating the point estimate and two-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method.

9.4.1.3. Multiplicity Adjustment

The secondary efficacy analyses will be descriptive in nature and no adjustment for multiplicity will be performed.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Set and will be based on the actual treatment received.

9.4.2.1. Adverse Events

The following definitions will be used for AEs:

- Treatment-emergent adverse event (TEAE): Any AE that starts during or after the first dose of study drug. Adverse events that start 56 days or later after the last dose of study drug will not be considered as treatment emergent.
- Treatment-emergent SAE (TESAE): A TEAE that is serious

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study drug discontinuation, drug-related TEAEs, and TESAEs will be summarized by treatment group for each disease cohort separately. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or higher and will be summarized by System Organ Class (SOC) and Preferred Term overall, by severity, and by relationship to study drug.

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

9.4.2.2. Physical Examination and Vital Signs

Adverse changes from baseline in physical examination findings will be classified as AEs and analyzed accordingly.

Vital signs will be summarized descriptively by treatment group at baseline and postbaseline time points and for changes from baseline separately for each disease cohort.

9.4.2.3. Clinical Laboratory Tests

Observed values and changes from baseline in clinical chemistry, hematology, and urinalysis will be summarized descriptively by treatment group at baseline and at each postbaseline time point separately for each disease cohort. 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.

9.4.2.4. Electrocardiograms

By-participant data listings of ECG parameters will be provided separately for each disease cohort. Electrocardiograms will be evaluated and summarized as normal, abnormal not clinically significant, or abnormal clinically significant. A shift from baseline to worst on-study ECG table will be presented for ECG results. Observed values and change from baseline in ECG intervals (PR, RR, QT, and QTc) will be summarized descriptively at baseline and each postbaseline time point. The QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

9.4.3. Pharmacokinetic/Pharmacodynamic Analyses

Graphs of mean serum ravulizumab concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual participants may also be provided. Actual dose administration and sampling times will be used for all calculations. 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

The incidence and titers for ADAs to ravulizumab will be presented at each postbaseline time point in tabular format separately for each disease cohort. Additionally, any confirmed ADA positive samples will be tested for the presence of neutralizing antibodies to ravulizumab.

9.4.5. Exploratory Analyses

9.4.5.1. Exploratory Efficacy Endpoints

The exploratory efficacy analyses will be descriptive in nature and will be based on the FAS. Full details regarding the exploratory efficacy analyses will be described in the SAP.

For continuous endpoints, data will be summarized at baseline and each postbaseline time point by treatment group using descriptive statistics for the observed value as well as the change from baseline.

For categorical endpoints, data will be summarized by treatment group by calculating the point estimate and two-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method.

For the LN cohort, time to CRR, time to PRR, and time to UPCR > 50% decrease from baseline will be summarized using spot urine samples. Participants will be assigned as responders at the time of their CRR, PRR, or UPCR > 50% decrease from baseline, respectively, or censored at the

earliest of their discontinuation time, receipt of additional standard of care therapy, or at Week 50 if they have not responded or received additional standard of care therapy by then. Kaplan-Meier cumulative distribution curves will be generated for each treatment group, and a log-rank test comparing the curves will be performed. A corresponding summary table will present the CDF estimate, the number of participants at risk, the number of participants responding, and the number of participants censored at each postbaseline time point by treatment group. The table will also present first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of time to response.

Slope of eGFR for the IgAN cohort will be computed using a mixed effect model including data through Week 26 or Week 50, respectively. The model will include eGFR as the response variable, random patient effects for intercepts and slopes, fixed categorical effects of treatment group, visit, randomization stratification factor, and treatment group by visit interaction as well as a fixed, continuous effect of baseline eGFR.

9.4.5.2. Biomarkers

Analyses of exploratory biomarkers will be described in a separate SAP.

9.4.5.3. Quality of Life

The following quality of life assessments will be summarized by treatment group at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline:

- EQ-5D-5L
- SF-36 score
- FACIT-Fatigue (LN cohort only)

Additional details will be described in the SAP.

9.5. Planned Analyses

9.5.1. Dose Confirmation Analysis

To ensure the adequacy of the dose regimen, an interim PK/PD analysis for dose confirmation will be conducted by an independent clinical pharmacologist. The interim PK confirmation analysis will be conducted using masked PK/PD data from the first 10 participants treated with ravulizumab (a minimum of 3 participants in each disease-specific cohort), using data cut when the tenth participant reaches 2 weeks post first dose (ie, at Day 15). The PK dataset for review will include:

- Day 1 C_{max}, Day 15 C_{trough}, and C_{max} for all 10 participants.
- Pharmacokinetics data beyond Day 15 C_{max} timepoint (eg, Day 29 PK) may be included in the dataset (availability depending upon the enrollment rate).
- Free and total C5 data associated with above timepoints and ADA data will be included in the dataset as supportive evidence.

If observed Day 1 C_{max}, Day 15 C_{max} and C_{trough} values, and other available PK/PD data are within the expected range, the study will proceed unchanged. If the totality of the available PK/PD data are not within the expected range, a dose regimen adjustment may be necessary for all participants or for a subset of participants. If all participants require a dose regimen adjustment, enrollment will be paused until a new regimen is determined. If dose regimen adjustment is only required for a subset of participants, enrollment may continue in the subset not requiring dose adjustment. In the event of dose adjustments, the participants treated with the previous dose will switch over to the new dose and continue treatment on study but will be excluded from the primary efficacy analysis. Replacement participants may be enrolled to preserve study power.

9.5.2. Interim Analysis for Primary Endpoint

The primary efficacy analysis will be performed for each disease-specific cohort at the end of the 26-week Initial Evaluation Period after all participants in the disease-specific cohort have completed or withdrawn from the 26-week Initial Evaluation Period. This analysis will allow for evaluation of the primary endpoint and Phase 3 planning and will have no impact on the progression of this study.

In addition, an early interim analysis may be conducted for either disease cohort at the discretion of Alexion (based on feasibility) when at least 50% of participants have been randomly assigned to study treatment and have had the opportunity to complete the 26-week Initial Evaluation Period. These interim analyses, if performed, will be conducted by a separate unblinded team to preserve the integrity of the study design and minimize risk of bias. The interim analysis for the IgAN cohort will be for Phase 3 planning purposes only with no impact on the progression of the study. The interim analysis for the LN cohort will not include hypothesis testing and will not impact the progression of the study.

9.5.3. Interim Analysis for Extension Period

An interim efficacy analysis will be performed for each disease-specific cohort at the end of the 50-week Extension Period after all participants in the disease-specific cohort have completed or withdrawn from the 50-week Extension Period.

9.5.4. Final Analysis

The final study analysis will be conducted at the end of the study (Section 4.5). The SAP will describe the planned analysis in greater detail.

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 with 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, substantial protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC and regulatory authority before the study is initiated.
- Any substantial 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.
- The Investigator will be responsible for the following, as applicable:
  - 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
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European clinical trial regulation (CTR) 536/2014 for clinical studies (if applicable), 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 Trials 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.
  - Alexion 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 information technology (IT) security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
  - Both Alexion and the study 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 (Alexion or respectively the study 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 Alexion 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 Alexion, so that Alexion 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 Alexion, the processor under contractual obligations with Alexion promptly and in due course after discovering the breach notifies Alexion and provides full cooperation with the investigation. In these cases, to the extent Alexion 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 Alexion, so that Alexion 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 Alexion with all of the information needed for notification of the breach, without disclosing data that allows Alexion directly or indirectly to identify the participants. The notification will be done by Alexion 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 Alexion, so that Alexion has no access to the identifying personal information of the participants. The contract between Alexion and the Study Monitor shall expressly specify these conditions.
- The contract between the study site and Alexion 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.

- The Coordinating Investigator will be identified among the enrolling Investigators during the course of the study and will be responsible for reviewing the clinical study report (CSR) and confirming that it accurately describes the conduct and results of the study.

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 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, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent or a certified translation if applicable, 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 any screening procedures were performed 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, as applicable.
- 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. This document may require translation into the local language. 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 are required to sign a new ICF (see 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 Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed about the uses of their personal study-related and coded (pseudonymized) data, who will have access to their personal data, how and how long it will be used, and that it will be used by Alexion in accordance with local data protection law. In addition, multiple local laws require that participants must also be informed of any individuals 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 are provided with the appropriate legal basis for which a controller processes their personal data. The level of disclosure, the security controls used to protect their data, and information regarding any transfer of their personal data outside of their country or region must also be explained to the participant.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, any third parties acting on behalf of Alexion ,and by inspectors from regulatory authorities.

- Alexion and the site 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.
- 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 EU GDPR 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, it 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. 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.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic 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.
- 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.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification 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.
  - Remote source data verification may be employed where permitted by local regulations.
  - The scope of the source data verification will be described in detail in the Monitoring Plan.
- 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 during the retention period 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 trial master file (TMF) are archived and stored by Alexion for at least 30 years.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site activation and will be the study start date.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the EoS or ED Visit, all data have been collected and entered into electronic data capture (EDC) system, all required documents and study supplies have been collected and reconciled, and a study-site closure visit has been performed.

The Investigator must initiate study-site closure if there is reasonable cause; sufficient notice must be given in advance of the intended termination.

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

- 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 recruitment of participants by the Investigator
- Discontinuation of further study intervention development
- Withdrawal of the local ethics committee/health authority favorable opinion or approval

Alexion or health authority have the ability to 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 drug to patients enrolled or continuing in the study
- Sponsor decision to suspend or discontinue testing, evaluation, or development of the study drug in IgAN and LN indications

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IECs/IRBs, the 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.

10.1.10. Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

10.1.11. COVID-19 Risk Assessment

Proliferative LN and IgAN can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. Given that treatment for these conditions does involve immunosuppression, there is a 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. 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 might lead to other serious infections including viral infections in patients treated with ravulizumab remains unclear. The site Investigator will therefore balance the benefit/risk considerations for the study participant taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 11.

Table 11: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Potentially higher risk population for SARS-CoV-2 infection	Participants in this study will receive allowed concomitant therapy that may include immunosuppressants. Participants in this study may receive meningococcal vaccination and prophylactic antibiotics prior to treatment with a C5 inhibitor. It is unknown how this may impact their risk for SARS-CoV-2 infection.	During the time that the COVID-19 pandemic is active, Alexion will recommend that sites in a position to start the study and enroll participants follow the national and institutional guidances regarding prevention of SARS-CoV-2 infection. Additionally, during that time period, it is encouraged that Investigators and their staff follow all possible precautions and monitoring recommended by national/local health authority guidelines in order to minimize a participant's potential exposure to COVID-19 and identify SARS-CoV-2 infection. Depending on the site, this will consist of measures such as social distancing, temperature screening, enhanced cleaning, use of personal protective equipment for participants, staff, and caregivers, and COVID-19 testing as necessary. Physical exams and vital signs monitoring

Table 11: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		are also required at each study visit for all sites.
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 non-urgent 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 investigational product 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, participants eligibility as well as 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 reason the data is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

Abbreviations: C5 = complement component 5; COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

10.1.12. COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant ravulizumab administration, based on ravulizumab's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ravulizumab.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, patients 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 12.

Table 12: Potential 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 eCRF 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; eCRF = electronic case report form

10.1.13. Remote Source Data Verification During COVID-19 Pandemic

To ensure the rights, safety, and well-being of trial participants, as well as the integrity of the trial and its data during the COVID-19 pandemic, when onsite study monitoring activities are restricted, remote source data verification (rSDV) may be employed wherever permitted by local regulations.

ALXN1210-NEPH-202 is a Phase 2 trial in patients with LN and IgAN. Alexion has assessed that the inability to complete ongoing source data verification (SDV) could pose a risk to the robustness of the study data. Delaying ongoing verification of key efficacy (primary and secondary) endpoints and important safety endpoints could result in late identification of incorrect or missing data, which could impact the integrity of the study data.

Remote SDV will be carried out in written agreement with the Investigator and, if applicable, the institution, under conditions ensuring adequate data protection and participants' rights. Depending on local regulation and agreement with the site Investigator and institution preference, rSDV may be conducted through direct and controlled read-only monitor access to institution electronic medical records systems, passive access to source documents via live image transmission, and/or sharing of redacted copies of source documents via a secure, validated, and access-restricted system. Regarding the electronic sharing of redacted copies of source documents, the following requirements must be followed:

- Scanned or electronic documents to be uploaded (as PDF, jpeg, or other image format) that are of sufficient resolution to ensure readability, in black and white or color.
- To ensure completeness of the shared content, the monitor will prepare a written request to the investigative site listing the source data needed to conduct rSDV and will perform a quality check on the list of documents shared by the site against the list of requested source data.
- Site staff must perform a quality check ensuring source documents are redacted before making them available to monitors. A data breach management policy and a security team will be in place to identify violations and to ensure correct and timely action.
- To prevent loss of or unauthorized access to source data, investigative site personnel will need to actively grant access to their specific monitor. The monitor will only have viewing rights, thereby preventing loss, alteration, or download of source data.
- Traceability of pseudonymized documents reviewed remotely will be kept by the monitor for verification onsite.

The detailed scope of rSDV will be outlined in supporting study plans (eg, Clinical Monitoring Plan). Conduct of rSDV will only be performed during the COVID-19 pandemic.

10.2. Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the study central laboratory, unless otherwise noted.
- Local laboratory results are required in the event that the central laboratory results are not available in time for either 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 either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: WOCBPs should only be enrolled after a negative serum pregnancy test result at Screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the time points specified in the Schedule of Activities (Section 1.3).
- Investigators must document their review of each laboratory safety report.

Table 13: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters

Hematology	• Red blood cell count
	• Hemoglobin
	• Hematocrit
	• RBC indices
	  ○ Mean corpuscular volume
	  ○ Mean corpuscular hemoglobin
	  ○ Percentage of reticulocytes
	  ○ Corpuscular hemoglobin content
	• White blood cell count with differential (including early progenitors):
	  ○ Neutrophils, segmented
	  ○ Lymphocytes
	  ○ Monocytes
	  ○ Eosinophils
	  ○ Basophils
	  ○ Platelet count
	  ○ Mean platelet volume

Table 13: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
Coagulation panel	• INR • PT • APTT • D-Dimer • Fibrinogen
Clinical chemistry	• Liver function tests: o ALT o AST o ALP o Albumin o Total protein o Bilirubin (total, direct and indirect) o GGT o Glucose • Renal function: o Blood urea nitrogen o Calcium o Chloride o Creatinine and eGFR calculated using CKD-EPI formula o Magnesium o Phosphate o Potassium o Sodium o Total carbon dioxide o Urea
24-h urine	• Total protein, total creatinine, total albumin, total sodium, creatinine clearance, and protein to creatinine ratio, albumin to creatinine ratio.
Spot urine studies	• Protein, albumin, creatinine, and protein to creatinine and albumin/creatinine ratio
Routine urinalysis and urine sediment	• Albumin • Bilirubin • Blood • Erythrocytes • Glucose • Ketones • Leukocyte esterase

Table 13: Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters
	• Nitrite • pH • Protein • Specific gravity • Urobilinogen • Urine sediment: number of RBCs/high-power field and number of RBC casts [b]
PK/PD and immunogenicity	• Serum PK • Serum PD (free and total C5) • Immunogenicity (ADA)
Other study-specific tests	• HCV PCR viral load, HBV antigen and serology panel • HIV-1 and HIV-2 antibody • Serum follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Serum or urine human chorionic gonadotropin pregnancy test (as needed for WOCBPs)[a] • Complement: C3, C4, and CH50 • Autoantibody profile: ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, anti-C1q, anti-phospholipid antibodies (LN cohort only)
	• Anti-ds-DNA antibody: to be measured by ELISA at all visits as part of SLEDAI Assessment (LN cohort only)

[a] Serum pregnancy test at Screening and End of Study Visit/Early Discontinuation Visit, and local urine pregnancy test at all other times as specified in Schedule of Assessments.

[b] For participants in the IgAN cohort, eligibility for hematuria can be determined via the local laboratory.

Abbreviations: ADA = antidrug antibody; ALP =alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibody; anti-C1q = anti-complement component C1q; anti-La = anti-small RNA binding exonuclease protection factor La; anti-Ro = anti-Sjögren's-syndrome-related antigen A; anti-Sm= anti-Smith antibody; APTT =activated partial thromboplastin time; AST = aspartate aminotransferase; C3, C4, and C5 = complement components 3, 4, and 5; CH50 = 50% hemolytic complement activity; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; dsDNA = double-stranded DNA; eGFR = estimated glomerular filtration rate; ELISA = enzyme-linked immunosorbent assay; GGT = gamma-glutamyltransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgAN = immunoglobulin A nephropathy; INR = international normalized ratio; LN = lupus nephritis; RNP = ribonucleoprotein; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; WOCBP = women 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 participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- 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 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.
- "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.

Events Not Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. 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 drug 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).

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:
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.
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

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

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.

An SUSAR is defined as:

A serious event that is not listed in the IB and that the Investigator identifies as related to investigational product or procedure. United States Title 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs 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 AE/SAE CRF page.
- 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 from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, 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 CRF 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.
- 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 he/she has 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.

Follow-up of AEs and SAEs
• 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 Tool
• All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness. • The primary mechanism for reporting an SAE to Alexion will be the electronic data collection tool. • If the electronic system is unavailable 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 fax or email. Facsimile transmission or email may 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. • When further information becomes available, the EDC should be updated within 24 hours with the new information and an updated SAE report should be submitted to Alexion global drug safety (GDS). • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form.

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 536/2014 (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 study intervention or that would lead to changes in the administration of the study intervention or in overall conduct of a clinical trial 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 536/2014 (49), where unexpected events require an urgent modification of a clinical trial, 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 trial, Alexion should apply for a substantial modification before restarting the clinical trial.

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 drug, 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 CTCAE v5.0 or higher.

If anaphylaxis occurs according to the criteria listed in Table 14, 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 14: 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: o Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) o Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
• 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 a 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 study intervention, but rather a human or process related failure while the intervention is under the 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 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 at room temperature
- Wrong participant received the medication (excluding IRT/Randomization and Trial Supply Management [RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM - 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 [refer to Section 8.6 for information on 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 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 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 in 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 post-menopausal 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 drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBPs.

1. Premenarchal
2. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented 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.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement may be required.
   - 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.

10.6.2. Contraception Guidance

10.6.2.1. Guidance for Female Participants

Female participants of non-childbearing potential are exempt from contraception requirements. Non-childbearing potential for female participants is defined as any of the following:

1. Prior to first menses

2. Postmenopausal, as documented by amenorrhea for at least 1 year prior to the Day 1 Visit. Confirmatory FSH serum levels consistent with postmenopausal status may be obtained by the Investigator at Screening. In the absence of 12 months of amenorrhea, multiple elevated FSH levels will be required. The reason for not obtaining an FSH should be documented by the Investigator at the time of Screening
3. Permanent sterilization at least 6 weeks prior to the Day 1 Visit
4. Hysteroscopic sterilization
5. Bilateral tubal ligation or bilateral salpingectomy
6. Hysterectomy
7. Bilateral oophorectomy

Female participants of child-bearing potential must use a highly effective method of contraception, including at least 1 of the following until at least 8 months after the final dose of study drug:

1. Intrauterine device in place for at least 6 weeks prior to first dose.
2. Progestogen-only hormonal contraception (either oral, injectable, or implantable) for at least 6 weeks prior to first dose.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose).
7. Sexual abstinence for female 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 female participants who wish to initiate a highly effective method of contraception during the study must refrain from heterosexual intercourse for at least 8 months after the final dose of study drug.
    - Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods) is not considered a highly effective method of contraception for female participants.

Other methods of contraception that are not considered highly effective for female participants:

1. Barrier methods, such as male or female condoms, diaphragm, or cervical cap, used alone or in combination, are not acceptable.
2. Spermicides or spermicidal sponges, used alone or in combination with barrier methods, are not acceptable.

Withdrawal (coitus interruptus) is not acceptable.

Lactational amenorrhea is not acceptable.

Female participants must not donate ova from the Day 1 visit until 8 months after the final dose of study drug.

10.6.2.2. Guidance for Male Participants

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

Male participants who have had a vasectomy > 6 months prior to first dose must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to first dose must use a condom and spermicide during heterosexual intercourse.

Male participants who have not had a vasectomy must use a condom and spermicide during heterosexual intercourse 8 months after their final dose of study drug.

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 participants' s preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom and spermicide 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.

Male participants must not donate sperm from the Day 1 visit until 8 months after their final dose of study drug.

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 the signing of the ICF until 8 weeks after last dose of the study drug is administered. Any female participant who becomes pregnant while participating in the study will be discontinued from the study drug. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study drug via semen following paternal exposure. If a female participant or a male participant's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

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

Pregnancy is not regarded as an AE unless there is a suspicion that the study drug 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.

Any female participant who becomes pregnant while participating in the study will be discontinued from study drug.

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 drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate Pregnancy Outcome/Breastfeeding 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 estimated 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 initial Information will be recorded on the appropriate form and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- The participant will be followed up to determine the outcome of the pregnancy. 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 post-study pregnancy related SAE considered reasonably related to the study drug by the Investigator will be reported to Alexion as described in Section 8.4.4. 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.
- Any female participant who becomes pregnant while participating in the study will discontinue study drug.

10.7. Handling of Human Biological Samples

All research and biological samples, including those for possible future research, are subject to national regulations and will only be conducted in a specified country if approved in that country.

Handling, storage, and shipment of biological samples are detailed in the laboratory manual.

10.7.1. Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each site keeps full traceability of collected biological samples from the participants while in storage at the site until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

Alexion or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the Alexion-assigned biobanks or other sample archive facilities and will be tracked by the appropriate Alexion team for the remainder of the sample life cycle.

All appropriately consented samples will be retained for a maximum of 25 years from study completion or other period as per local requirements.

10.7.2. Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, Alexion is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is communicated immediately to Alexion or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and Alexion are informed about the sample disposal.

Alexion ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, the action is documented, and study site is notified.

10.8. Biomarkers

- Blood, urine, and kidney tissue samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to ravulizumab, or LN, IgAN, and related diseases. The samples may also be used to develop methods, assays, prognostics and/or companion diagnostics related to the study drug target, disease process, pathways associated with disease state, and/or mechanism of action of ravulizumab.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to ravulizumab to understand study disease or related conditions.
- The results of biomarker analyses may be reported in the CSR or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ravulizumab continues but no longer than 5 years after termination of the study or other period as per local requirements.

10.9. Systemic Lupus Erythematosus Diagnosis Classification Criteria

The 2019 European League Against Rheumatism / American College of Rheumatology Classification Criteria for SLE (Aringer, 2019) will be used for eligibility of the LN Cohort.

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

10.10. Revised 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) Classification

Category	Recommendation
Class II	Definition for mesangial hypercellularity adjusted: Four or more nuclei fully surrounded by matrix in the mesangial area not including the hilar region
Class III and IV	The term endocapillary proliferation is replaced by endocapillary hypercellularity
	The term crescent is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. Fibrin and fibrous matrix may be present; 10% or more of the circumference of Bowman's capsule should be involved.
	Cellular crescent: more than 75% cells and fibrin and less than 25% fibrous matrix
	Fibrous crescent: more than 75% fibrous matrix and less than 25% cells and fibrin
	Fibrocellular crescent: 25% to 75% cells and fibrin and the remainder fibrous matrix
	Adhesion: an area of isolated continuity of extracellular matrix material between the tuft and capsule even when the underlying segment does not have overt sclerosis
	Fibrinoid necrosis: fibrin associated with glomerular basement membrane disruption and/or lysis of the mesangial matrix; this lesion does not require the presence of karyorrhexis
	Elimination of segmental and global subdivisions of Class IV
	Modification of the NIH lupus nephritis activity and chronicity scoring system to be used instead of the currently used A, C, and A/C parameters
Tubulointerstitial lesions	Indicate whether interstitial inflammation occurs in presence or absence of interstitial fibrosis

Source: Bajema, 2018

10.11. IgAN Diagnosis Classification Criteria

2016 Oxford Classification from the IgA Nephropathy Classification Working Group

Detailed description of the features present on:

- Light microscopy
- Immunohistochemistry or immunofluorescence
- Electron microscopy

Summary of 5 key pathologic features

- Mesangial score < 0.5 (M0) or > 0.5 (M1)
- Endocapillary hypercellularity absent (E0) or present (E1)
- Segmental glomerulosclerosis absent (S0) or present (S1); presence or absence of podocyte hypertrophy/tip lesions in biopsy specimens with S1
- Tubular atrophy/interstitial fibrosis #25% (T0), 26% to 50% (T1), or > 50% (T2)
- Cellular/fibrocellular crescents absent (C0), present in at least 1 glomerulus (C1), in > 25% of glomeruli (C2)

Quantitative data

- Total number of glomeruli
- Number of glomeruli with endocapillary hypercellularity, necrosis, extracapillary hypercellularity (cellular/fibrocellular crescents), global glomerulosclerosis, and segmental glomerulosclerosis

Source: Trimarchi, 2017

10.12. Systemic Lupus Erythematosus Disease Activity Index SELENA Modification (SLEDAI–2K)

The SLEDAI–2K is used to define Extrarenal SLE Flare defined by ≥ 4 points that is not accounted for by proteinuria, hematuria, urinary casts, hypocomplementemia, pyuria, or an increase in anti-dsDNA antibody level (ie, the shaded sections below).

Physicians Global Assessment: _____

0	1	2	3
None	Mild	Med	Severe

SLEDAI SCORE

Check box: If descriptor is present at the time of visit or in the proceeding 30 days

Wt	Present	Descriptor	Definition
8	□	Seizure	Recent onset. Exclude metabolic, infectious or drug cause
8	□	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8	□	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	□	Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	□	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	□	Lupus Headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.
8	□	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8	□	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4	□	Arthritis	More than 2 joints with pain and signs of inflammation (ie, tenderness, swelling, or effusion).
4	□	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	□	Urinary Casts	Heme-granular or red blood cell casts
4	□	Hematuria	> 5 red blood cells/high power field. Exclude stone, infection or other cause.

Wt	Present	Descriptor	Definition
4	□	Proteinuria	> 0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4	□	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	□	New Rash	New onset or recurrence of inflammatory type rash
2	□	Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.
2	□	Mucosal Ulcers	New onset or recurrence of oral or nasal ulcerations
2	□	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening
2	□	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram confirmation.
2	□	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	□	Increased DNA binding	> 25% binding by Farr assay or above normal range for testing laboratory.
1	□	Fever	> 38°C. Exclude infectious cause
1	□	Thrombocytopenia	< 100,000 platelets/mm^3
1	□	Leukopenia	< 3000 White blood cell/mm^3. Exclude drug causes.

_____ TOTAL SCORE (Sum of weights next to descriptors marked present)

10.13. Short Form Health Survey (SF-36)

Header to be completed by Study Site

Study Number: ALXN1210-ALS-308 Subject ID: _____

Date Completed: _____ Time Completed: _____

Completed by: ☐ Patient

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.

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

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

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Short Form Health Survey (SF-36) (Continued)

3. 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
a. <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

Short Form Health Survey (SF-36) (Continued)

4. 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?

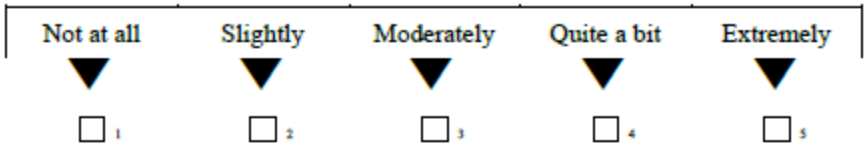
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

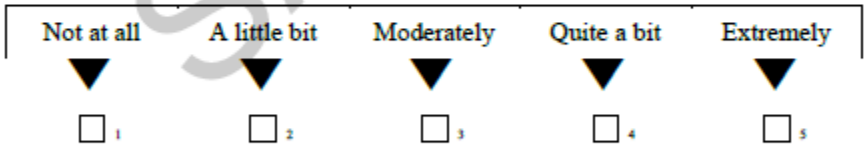
Short Form Health Survey (SF-36) (Continued)

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

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



Short Form Health Survey (SF-36) (Continued)

9. 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
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. 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

Short Form Health Survey (SF-36) (Continued)

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

10.14. 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

Health Questionnaire

English version for the USA

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

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 ❑

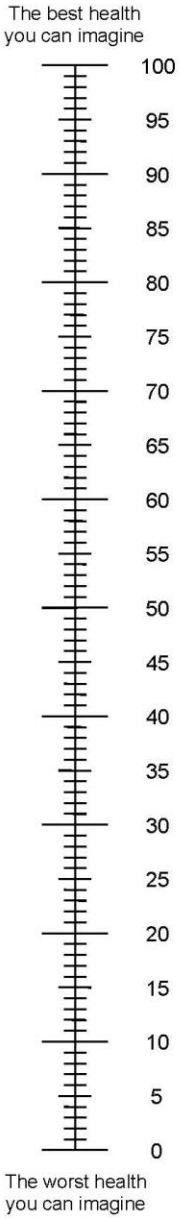
ANXIETY / DEPRESSION

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 ❑

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

- 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 = ☐



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10.15. 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

16 November 2007
Page 1 of 1

10.16. Abbreviations

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
ANCOVA	analysis of covariance
anti-ds DNA	anti-double-stranded DNA
ANA	antinuclear antibody
ARB	angiotensin II receptor blocker
C1q	complement component C1q
C3	complement component 3
C4	complement component 4
C5	complement component 5
C5a	complement component 5a
C5b-9	terminal complement complex
CDF	cumulative distribution function
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum (peak) serum concentration observed after drug administration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRR	complete renal response
CSR	clinical study report
CTIS	Clinical Trials Information System
CTCAE	Common Terminology Criteria for Adverse Events
CTR	clinical trial regulation

Abbreviation	Definition
C_{trough}	concentration at the end of the dosage interval
DPIA	data protection impact assessment
dsDNA	double-stranded DNA
ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EoS	End of Study
EQ-5D-5L	European Quality of Life Health 5-item questionnaire dimensions 5 level
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESRD	end-stage renal disease
EU CTR	European Union Clinical Trials Regulation
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FSGS	focal segmental glomerulosclerosis
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDS	global drug safety
GDPR	General Data Protection Regulation
GMR	geometric mean ratio
HBV	hepatitis B virus
HCV	hepatitis C virus
H/E	hematoxylin and eosin stain
Hib	*Haemophilus influenzae type b*
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hpf	high power field
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IC	immune complex

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgA	immunoglobulin A
IgA1	immunoglobulin A1
IgAN	immunoglobulin A nephropathy
IgG	immunoglobulin G
IgM	immunoglobulin M
IMG	idiopathic membranous glomerulopathy
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN/RPS	International Society of Nephrology/renal Pathology Society
IT	information technology
IV	intravenous(ly)
K2EDTA	dipotassium ethylenediaminetetraacetic acid
KDIGO	Kidney Disease Improving Global Outcomes
LN	lupus nephritis
MedDRA	Medical Dictionary for Regulatory Activities
MEST-C	mesangial and endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy, and the presence of crescents
MMF	mycophenolate mofetil
MMRM	mixed effect model for repeated measures
MPS	mycophenolic acid sodium
M&S	modeling and simulation
N-GAL	neutrophil gelatinase-associated lipocalin
NKF	National Kidney Foundation
NSAID	nonsteroidal anti-inflammatory drug
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria

Abbreviation	Definition
PRR	partial renal response
q8w	every 8 weeks
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	rheumatoid arthritis
RAS	renin-angiotensin system
rSDV	remote source data verification
RBC	red blood cell
RTCA	Real Time Complement Activity
RTSM	Randomization and Trial Supply Management
sC5b-9	soluble C5b-9
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SDV	source data verification
SELENA	Safety of Estrogen in Lupus Erythematosus National Assessment
SF-36	Short Form (36) Health Survey
SGLT-2	sodium-glucose cotransporter-2
SLE	systemic lupus erythematosus
SLEDAI–2K	Systemic Lupus Erythematosus Disease Activity Index SELENA Modification
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMF	trial master file
UACR	albumin to creatinine ratio
UPCR	urine protein to creatinine ratio
USPI	US Prescribing Information
WOCBP	woman of childbearing potential

10.17. Protocol Amendment History

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

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 3.0	Global	21 Nov 2023	• Modifications have been added to address the requirements for transitioning a clinical study under the EU CTR. Further modifications include non-substantial changes, minor corrections, and harmonized terminology.
Amendment 2.1	SGP, KOR, TWN	28 Apr 2022	• The primary purpose of this amendment is to provide clarification for the exclusion criterion regarding history of hepatitis B. Patients with active hepatitis B or C infection are excluded. Patients with previous exposure to hepatitis B characterized by positive core antibody (anti-HBc) with a positive surface antibody (anti-HBs) and patients with past hepatitis C effectively treated with documented sustained virologic response at the time of Screening may be included. Enrollment in the study is not a safety risk to the patients based on the specified exclusion criteria. Potential inclusion of such patients does not have anticipated effects on efficacy or safety endpoints.

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 2.0	Global	02 Nov 2021	• Addressed feedback from local regulatory authorities, Institutional Review Boards, and Ethics Committees • Modified and clarified the inclusion and exclusion criteria and minor requirements throughout the protocol to allow for expanded participant recruitment • Added a secondary efficacy endpoint to assess suboptimal response in the LN cohort • Increased the visit windows for specified visits for the IgAN cohort • Increased the maximum dose of MMF a LN participant can receive, allow for additional corticosteroid taper following Week 26 • Updated the criteria to determine valid 24-hour urine collections • Removed the option of home infusion visits • Clarified the process for unblinding a participant's treatment assignment for safety reasons • Added clarification for the statistical analyses • Provided additional COVID-19 related mitigation and monitoring guidance.
Amendment 1.5	UK	29 Jun 2021	• To provide COVID-19 vaccine risk assessment
Amendment 1.4	DEU	17 Jun 2021	• To reimplement recommendations from the EC that were removed from Amendment 1.3
Amendment 1.3	DEU	13 May 2021	• To clarify entry criteria, as done in Amendment 1.2, but remove the changes in Amendment 1.2 that included recommendations from the EC.
Amendment 1.2	DEU	07 May 2021	• To clarify entry criteria, remove legally authorized representative/legal guardian from the informed consent process, and provide additional COVID-19 related mitigation and monitoring guidance

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 1.1	FRA	11 Feb 2021	• To exclude participants from enrollment who have hypersensitivity to any ravulizumab excipient, and to clarify the process for unblinding a participant's treatment assignment for safety reasons
Amendment 1	Global	24 Sep 2020	• To clarify allowed and disallowed medications, to provide information on COVID-19 related risk mitigations, and to clarify other procedural items
Original protocol	Not applicable	28 Jul 2020	Not applicable

11. REFERENCES

Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12(5):825-835.

Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2009;20(5):1103-1112.

Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71(9):1400-1412.

Arriens C, Polyakova S, Adzerikho I, Randhawa S, Solomons N. OP0277 AURORA phase 3 study demonstrates voclosporin statistical superiority over standard of care in lupus nephritis (LN). Annals of the Rheumatic Diseases. 2020;79(Suppl 1):172-173.

Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int. 2018;93(4):789-796.

Bao L, Cunningham PN, Quigg RJ. Complement in lupus nephritis: new perspectives. Kidney Dis. 2015;1(2):91-99.

Barbour SJ, Coppo R, Zhang H, et al. Evaluating a new international risk-prediction tool in IgA nephropathy. JAMA Int Med. 2019;179(7):942-952.

Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71:1771-1782.

Biesecker G, Katz S, Koffler D. Renal localization of the membrane attack complex in systemic lupus erythematosus nephritis. J Exp Med. 1981;154(6):1779-1794.

Birmingham DJ, Hebert LA. The complement system in lupus nephritis. Semin Nephrol. 2015;35(5):444-454.

Chen YE, Korbet SM, Katz RS, Schwartz MM, Lewis EJ; Collaborative Study Group. Value of a complete or partial remission in severe lupus nephritis. Clin J Am Soc Nephrol. 2008;3(1):46-53.

Coresh J, Heerspink HJL, Sang Y, et al. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. Lancet Diabetes Endocrinol. 2019;7(2):115-127.

Dall'Era M, Stone D, Levesque V, Cisternas M, Wofsy D. Identification of biomarkers that predict response to treatment of lupus nephritis with mycophenolate mofetil or pulse cyclophosphamide. Arthritis Care Res. 2011;63(3):351-357.

Fellstrom BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. Lancet. 2017;389(10084):2117-2127.

Fogueri U, Cheungapasitporn W, Bourne D, Fervenza FC, Joy MS. Rituximab exhibits altered pharmacokinetics in patients with membranous nephropathy. Ann Pharmacother. 2019;53(4):357-363.

Furie R, Rovin BH, Houssiau F, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020;383(12):1117-1128.

Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005;353(21):2219-2228.

Haas M. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. Am J Kidney Dis. 1997;29(6):829-842.

Hebert LA, Wilmer WA, Falkenhain ME. Renoprotection: One or many therapies? Kid Int. 2001;59(4):1211-1226.

Holtkamp F, Gudmundsdottir H, Maciulaitis R, et al. Change in albuminuria and estimated GFR as end points for clinical trials in early stages of CKD: a perspective from European regulators. Am J Kidney Dis. 2020;75(1):6-8.

Hoover PJ, Costenbader KH. Insights into the epidemiology and management of lupus nephritis from the US rheumatologist's perspective. Kidney Int. 2016;90(3):487-492.

Ix JH, Wassel CL. Stevens LA, Beck GJ, Froissart M, Navis G, et al. Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. Clin J Am Soc Nephrol. 2011;6(1):184-191.

KDIGO 2021 Executive Summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. 2021;100:753-779.

Kim AHJ, Strand V, Sen DP, et al. Association of blood concentrations of complement split product iC3b and serum C3 with systemic lupus erythematosus disease activity. Arthritis Rheumatol. 2019;71(3):420-430.

Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. Am J Kidney Dis. 2000;35(5):904-914.

Lai KN, Leung JC, Tang SC. Recent advances in the understanding and management of IgA nephropathy. F1000Research. 2016;5:161.

Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. Am J Kidney Dis. 2020;75(1):84-104.

Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. Adv Exp Med Biol. 2019;1165:3-15.

Mageau A, Timset J-F, Perrozziello A, et al. The burden of chronic kidney disease in systemic lupus erythematosus: A nationwide epidemiologic study. Autoimmun Rev. 2019;18(7):733-737.

Maillard N, Wyatt RJ, Julian BA, et al. Current understanding of the role of complement in IgA nephropathy. J Am Soc Nephrol. 2015;26(7):1503-1512.

Markowitz GS, D'Agati VD. The ISN/RPS 2003 classification of lupus nephritis: An assessment at 3 years. Kidney Int. 2007;71(6):491-495.

Oortwijn BD, Eijgenraam JW, Rastaldi MP, et al. The role of secretory IgA and complement in IgA nephropathy. Semin Nephrol. 2008;28(1):58-65.

Pakchotanon R, Gladman DD, Su J, Urowitz MB. Sustained complete renal remission is a predictor of reduced mortality, chronic kidney disease and end-stage renal disease in lupus nephritis. Lupus. 2018;27(3):468-474.

Parikh SV, Rovin BH. Current and emerging therapies for lupus nephritis. J Am Soc Nephrol. 2016;27(10):2929-2939.

Pickering MC, Walport MJ. Links between complement abnormalities and systemic lupus erythematosus. Rheumatology (Oxford). 2000;39(2):133-141.

Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. N Engl J Med. 2015;373(23):2225-2236.

Reich HN, Troyanov S, Scholey JW, Cattran DC. Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18(12):3177-3183.

Rizk DV, Maillard N, Julian BA, et al. The emerging role of complement proteins as a target for therapy of IgA nephropathy. Front Immunol. 2019;10:504.

Roberts BV, Susano I, Gipson DS, Trachtman H, Joy MS. Contribution of renal and non-renal clearance on increased total clearance of adalimumab in glomerular disease. J Clin Pharmacol. 2013;53(9):919-924.

Rovin BH, Solomons N, Pendergraft WF, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int. 2019;95(1):219-231.

Sahelijo L, Mujeebuddin A, Mitchell D, et al. First in human single-ascending dose study: safety, biomarker, pharmacokinetics and exposure-response relationships of ALXN1210, a humanized monoclonal antibody to C5, with marked half-life extension and potential for significantly longer dosing intervals. Blood. 2015;126(23):4777.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.

Schur PH. Systemic lupus erythematosus and complement. Nephrologie. 1988;9(2):53-60.

Sheridan D, Yu ZX, Zhang Y, et al. Design and preclinical characterization of ALXN1210: A novel anti-C5 antibody with extended duration of action. PLoS One. 2018;13(4):e0195909.

Thurman JM. Complement in kidney disease: core curriculum 2015. Am J Kidney Dis. 2015;65(1):156-168.

Trimarchi H, Barratt J, Cattran DC, Cook HT, Coppo R, Haas M, et al. Oxford classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. Kidney Int. 2017;91(5):1014-1021.

Wilmer WA, Rovin BH, Hebert CJ, et al. Management of glomerular proteinuria: a commentary. J Am Soc Nephrol. 2003;14:3217-3232.

Wilson HR, Medjeral-Thomas NR, Gilmore AC, et al. Glomerular membrane attack complex is not a reliable marker of ongoing C5 activation in lupus nephritis. Kidney Int. 2019;95(3):655-665.

Zwirner J, Burg M, Schulze M, et al. Activated complement C3: a potentially novel predictor of progressive IgA nephropathy. Kidney Int. 1997;51(4):1257-64.

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