TITLE PAGE

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Efficacy and Safety of ALXN2050 in Adult Participants with Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)

Alexion Protocol Number: ALXN2050-NEPH-201

AstraZeneca D Code: D7845C00001

Amendment Number: 3.0

Compound: ALXN2050

Study Phase: 2

Brief Title: Phase 2 Study of ALXN2050 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)

IND: 153068

EudraCT: 2021-001426-22

NCT: NCT05097989

EU CT: 2023-504825-38-00

Release Date: 21 Feb 2024

Sponsor Signatory:

[redacted]

Date

[redacted]
Alexion Pharmaceuticals, Inc.

The document has been e-signed in Veeva. Please refer to last page for signature details.

Medical Monitor Contact Information can be found in the Study Contact List.

INVESTIGATOR'S AGREEMENT

I have read the study protocol amendment and agree to conduct the study in accordance with this protocol amendment, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline for Good Clinical Practice (GCP), 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 amendment.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2.0	31 May 2023
Amendment 1.0	17 May 2022
Original Protocol	03 Jun 2021

Amendment 3.0 (21 Feb 2024)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU) and in the EU Clinical Trials Regulation (CTR) 536/2014 Article 2, 2 (13).

Overall Rationale for the Amendment:

The primary reason for this amendment is to address the requirements for transitioning a clinical study under the EU CTR. Further modifications include nonsubstantial changes, minor corrections, and harmonized terminology.

Section # and Name	Description of Change	Brief Rationale
Throughout protocol	Updated document date and version. Made minor editorial and document formatting revisions including change in section numbering in Section 8. Updated Global Drug Safety (GDS) to Global Patient Safety (GPS).	Administrative changes. For clarity.
	Updated the format of the author reference citation.	To align with the Alexion Style Guide
TITLE PAGE and Section 1.1. Synopsis	Changed AstraZeneca Protocol Number to AstraZeneca **D Code**, and Short Title to **Brief Title**. Added Regulatory Agency identifier numbers in the synopsis.	To align with EU CTR requirements.
Section 4.4. End of Study Definition	Updated end of study definition.	To align with EU CTR requirements.
Section 6.1. Study Intervention(s) Administered	Removed "NIMP" from Table 10.	To align with EU CTR requirements.
Section 6.4 Study Intervention Compliance	Added "and in the eCRF".	Administrative change to correct error in PA 2.0.
Section 6.5.3. Allowed Concomitant Therapy (formerly: Background Therapies) Throughout protocol	Change of terminology: "background therapy" to "**allowed concomitant therapy**".	To align with EU CTR requirements.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.4. Additional Standard of Care Therapy (formerly: Rescue Therapy for LN Cohort) Throughout protocol	Change of terminology: "rescue therapy" to "**additional standard of care therapy**".	To align with EU CTR requirements.
Section 6.8. Treatment of Overdose (formerly: Section 8.4)	Transposed the reporting details for an event of overdose or suspected overdose.	To align with EU CTR requirements.
Section 8.3.4. Regulatory Reporting Requirements for SAEs	Described reporting requirements	To align with EU CTR requirements.
Section 8.3.5.1. Timelines	Deleted the following text: The designated Alexion representative works with the Investigator to ensure that all relevant information is completed within 1 (initial fatal/life threatening or follow-up fatal/life threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the event of medication error, drug abuse, or misuse and within 30 days for all other events.	To align with the current Alexion processes.
Section 10.1.1. Regulatory and Ethical Considerations	Added details on serious breach (including personal data breach) prevention, identification, notification, and impact mitigation.	To align with EU CTR requirements.
Section 10.1.5. Data Protection	Updated and described data protection measures to ensure patient identity remains secure.	To align with EU CTR requirements.
Section 10.1.7. Data Quality Assurance	Specified document retention period at investigative site and at Alexion.	To align with EU CTR requirements.
Section 10.4. Medication Error, Drug Abuse, and Drug Misuse	Updated text in Medication Error and added reference to Section 6.8 for information on treatment of overdose.	To align with EU CTR requirements.

Abbreviations: CTR = Clinical Trials Regulation; eCRF = electronic case report form; EU = European Union; LN = lupus nephritis; NIMP = non-investigational medicinal product; PA = protocol amendment

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LIST OF ABBREVIATIONS

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

Abbreviation or Term	Explanation
ACEi	angiotensin-converting enzyme inhibitor
ACR	American College of Rheumatology
AE	adverse event
ANCOVA	analysis of covariance
anti-dsDNA	anti-double-stranded DNA
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ARB	angiotensin II receptor blocker
AP	alternative pathway
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AxMP	auxiliary medicinal product
Bb	Bb fragment of complement factor B
bid	twice daily
C1q	complement component C1q
C3	complement component 3
C3a	complement component 3a
C4	complement component 4
C5	complement component 5
C5a	complement component 5a
C5b-9	terminal complement complex
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) plasma concentration observed after drug administration
CNI	calcineurin inhibitor
COVID-19	coronavirus disease 2019
CP	classical pathway

Abbreviation or Term	Explanation
CRR	complete renal response
CSR	clinical study report
CTR	Clinical Trials Regulation
CYP3A	cytochrome P450, family 3, subfamily A
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EQ-5D-5L	European Quality of Life Health 5-item questionnaire dimensions 5 level
ESRD	end-stage renal disease
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FB	complement factor B
FD	complement factor D
FH	complement factor H
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GPS	Global Patient Safety
GMR	geometric mean ratio
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hpf	high-power field
HRT	hormone replacement therapy
IB	Investigator's brochure
IC	immune complex
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation or Term	Explanation
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgA1	immunoglobulin A1
IgAN	immunoglobulin A nephropathy
IgG	immunoglobulin G
IRB	Institutional Review Board
IRT	interactive response technology
ISN/RPS	International Society of Nephrology/Renal Pathology Society
IV	intravenous(ly)
LN	lupus nephritis
LP	lectin pathway
KDIGO	Kidney Disease Improving Global Outcomes
MAC	membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MMRM	mixed-effect model for repeated measures
MPS	mycophenolic acid sodium
NKF	National Kidney Foundation
NOAEL	no observed adverse effect level
OLE	Open-label Extension
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRR	partial renal response
QoL	quality of life
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 using Fridericia's formula
RAS	renin-angiotensin system
RBC	red blood cell
rSDV	remote source data verification
RTSM	Randomization and Trial Supply Management
sC5b-9	soluble C5b-9

Abbreviation or Term	Explanation
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDV	source data verification
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 2000 Safety of Estrogens in Lupus Erythematosus National Assessment (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
UACR	urine albumin to creatinine ratio
UPCR	urine protein to creatinine ratio
ULN	upper limit of normal
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Efficacy and Safety of ALXN2050 in Adult Participants with Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)

Brief Title: Phase 2 Study of ALXN2050 in Proliferative Lupus Nephritis (LN) or Immunoglobulin A Nephropathy (IgAN)

Regulatory Agency Identifier Number(s)

IND: 153068

EudraCT: 2021-001426-22

NCT: NCT05097989

EU CT: 2023-504825-38-00

Rationale: ALXN2050 is a potent, reversible, oral small molecule inhibitor of complement factor D (FD), which is an essential component of the complement alternative pathway (AP). The complement system is involved in the pathophysiology of proliferative LN and immunoglobulin A nephropathy (IgAN). The objectives of this study are to evaluate the efficacy and safety of oral ALXN2050 compared to placebo, demonstrate proof of concept for efficacy of FD inhibition, and establish a dose in patients with LN or IgAN.

Objectives and Endpoints

Objectives	Endpoints
Primary (Both Cohorts)	
To evaluate the efficacy of ALXN2050 to reduce proteinuria in participants with LN or IgAN	Percentage change in proteinuria from baseline to Week 26 (based on 24-hour urine collection[s])
Secondary (Both Cohorts)	
To evaluate the efficacy of ALXN2050 to improve measures of kidney function in participants with LN or IgAN	Percentage change in proteinuria from baseline to Week 50 (based on 24-hour urine collection[s])
	Achieving > 30% and > 50% reduction in proteinuria at Week 26 and Week 50 compared to baseline (based on 24-hour urine collection[s] at each time point)
	Change from baseline in eGFR at Week 26 and Week 50
Secondary (LN Cohort Only)	
To evaluate the efficacy of ALXN2050 on measures of kidney function in participants with LN	Meeting the criteria for CRR at Week 26 and Week 50 (as defined in Section 8.1.10)
	Meeting the criteria for PRR at Week 26 and Week 50 (as defined in Section 8.1.10)

Objectives	Endpoints
	Time to the first occurrence of UPCR ≤ 0.5 g/g as measured by spot urine sample
	Achieving corticosteroid taper to 7.5 mg/day at Weeks 12, 26, and 50
	Experience of a Renal Flare (as defined in Section 8.1.6) through Week 50
	Experience of an Extrarenal SLE Flare (as defined in Section 8.1.7) through Week 50
	Meeting the criteria for Treatment Failure (as defined in Section 8.1.9) through Week 50
	Meeting the criteria for 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 ALXN2050 on measures of kidney function in participants with IgAN	Meeting the criteria for Partial Remission at Week 26 and Week 50 (as defined in Section 8.1.11)
PK/PD (Both Cohorts)	
To characterize the PK and PD of ALXN2050 in participants with LN or IgAN	Observed plasma concentrations of ALXN2050 over time
	Absolute values and change from baseline in plasma Bb concentration and serum AP activity over time
Safety (Both Cohorts)	
To characterize the safety and tolerability of ALXN2050 in participants with LN or IgAN	Incidence of TEAEs and TESAEs over time
	Changes from baseline in laboratory assessments
Exploratory (Both Cohorts)	
To assess the efficacy of ALXN2050 in exploratory efficacy endpoints	Percentage change in proteinuria from baseline to Week 102 and Week 154 (based on 24-hour urine collection[s])
	Change from baseline in eGFR at Week 102 and Week 154
To evaluate the efficacy of ALXN2050 on hematuria in 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 • Achieving < 10 RBC/hpf

Objectives	Endpoints
To assess quality of life based on participant-reported outcomes in participants with LN or IgAN based on treatment with ALXN2050	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 biomarkers such as complement, autoimmune, and renal in participants with LN or IgAN	Absolute values and change from baseline in levels of biomarkers in blood and urine over time
Exploratory (LN Cohort Only)	
To assess the efficacy of ALXN2050 in exploratory efficacy endpoints	Time to the first CRR or PRR (using spot UPCR)
	Meeting the criteria for Overall Renal Response (CRR or PRR) at Week 26 and Week 50
	Time to the first occurrence of UPCR > 50% decrease from baseline (using spot UPCR)
To assess quality of life based on participant-reported outcomes	Change from baseline in FACIT-Fatigue total score at Week 26 and Week 50
To assess the efficacy of ALXN2050 in other exploratory endpoints	Histology changes from baseline to Week 50, if tissue is available
	Absolute values and change from baseline in anti-dsDNA and anti-C1q antibodies at Week 26 and Week 50
Exploratory (IgAN Cohort Only)	
To assess the efficacy of ALXN2050 in exploratory efficacy endpoints	Slope of eGFR computed from baseline to Week 26 and Week 50

Abbreviations: AP = alternative pathway; anti-C1q = anti-C1q complement component ; anti-dsDNA = anti-double-stranded DNA; Bb = Bb fragment of complement factor B; CRR = complete renal response; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; FACIT = Functional Assessment of Chronic Illness Therapy; hpf = high-power field; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PRR = partial renal response; RBC = red blood cell; SLE = systemic lupus erythematosus; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; SF-36 = Short Form (36) Health Survey; UPCR = urine protein to creatinine ratio

Overall Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study of ALXN2050 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.

- Participants in the LN cohort must have a diagnosis of LN with an active flare based on kidney biopsy, estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m^2, and proteinuria (defined as urine protein to creatinine ratio [UPCR] ≥ 1 g/g from one 24-hour urine collection).
- Participants in the IgAN cohort must have a diagnosis of IgAN based on kidney biopsy, eGFR > 30 mL/min/1.73 m^2, and proteinuria defined as mean protein ≥ 1 g/24 hours from 2 valid 24-hour urine collections (Section 8.1.1). Participants 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.

All participants will continue to receive allowed concomitant therapy consistent with the standard of care for participants with LN and IgAN throughout the study. 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 and after Week 26, for Suboptimal Response. Approved novel treatments for LN can be used per the Investigator's discretion. However, if additional standard of care therapy is initiated, the Investigator should consult the list of disallowed medications (Section 6.5.2). If additional standard of care therapy is a prohibited medication, study intervention should be discontinued at least 3 days prior to initiation of the additional standard of care therapy.

Blinded Initial Evaluation Period

- For each disease cohort, participants will be randomly assigned in a 3:1:3 ratio on Day 1 to receive ALXN2050 180 mg twice daily (bid), ALXN2050 120 mg bid, or placebo bid throughout the Blinded Initial Evaluation Period (26 weeks).
- For the IgAN cohort, participants assigned to the placebo group on Day 1 will also be assigned to their study treatment for the Blinded Extended Treatment Period (ALXN2050 180 mg bid or ALXN2050 120 mg bid) in a 1:1 allocation ratio at the time of randomization.

Blinded Extended Treatment Period

After completion of the Blinded Initial Evaluation Period (Week 26), participants will continue to receive study intervention during a Blinded Extended Treatment Period for 24 weeks as follows:

- Participants in the LN cohort will continue to receive their randomized allocation of study intervention (ALXN2050 180 mg, ALXN2050 120 mg, or placebo) bid. 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.

- Participants in the IgAN cohort randomized to the ALXN2050 180 mg bid or ALXN2050 120 mg bid groups will continue to receive their randomized allocation of study intervention bid.
- Participants in the IgAN cohort randomized to the placebo group will receive either ALXN2050 180 mg bid (n = 12) or ALXN2050 120 mg bid (n = 12) as assigned at the time of randomization.

Open-Label Extension Period

After completion of all assessments at the end of the Blinded Extended Treatment Period (Week 50 Visit), all participants will have the opportunity to enter the Open-label Extension (OLE) Period for up to 2 years (104 weeks) if no relevant side effects (in the opinion of the Investigator) are present.

During the OLE Period:

- Participants in both cohorts receiving ALXN2050 during the Blinded Initial Evaluation Period and the Blinded Extended Treatment Period will continue their active treatment at the same dose level. Once an optimal dose is identified (based on the 26 weeks primary analysis) for each cohort, all participants in that cohort with at least 50 weeks of study treatment will receive the optimal dose of ALXN2050.
- Participants in the LN cohort randomized to the placebo group will no longer receive placebo and will continue to receive allowed concomitant therapy. These participants will have the option to receive ALXN2050 180 mg bid or the optimal dose (if already identified) if the participant has a Renal Flare as defined in Section 8.1.6 or Suboptimal Response as defined in Section 8.1.8.
- Percentage change in proteinuria from baseline and change from baseline in eGFR at Weeks 102 and Week 154 will be assessed as exploratory efficacy endpoints. Safety and tolerability will also be evaluated continually throughout the OLE Period.

Disclosure Statement: This is a parallel-group treatment study with 3 arms that is participant and Investigator blinded during the 26-week Blinded Initial Evaluation Period and the 24-week Blinded Extended Treatment Period.

Number of Participants:

Approximately 70 participants in the LN cohort and approximately 56 participants in the IgAN cohort will be randomly assigned to study intervention.

Intervention Groups and Duration:

The study consists of an up to 6-week Screening Period, a 26-week Blinded Initial Evaluation Period, a 24-week Blinded Extended Treatment Period, and an OLE Period of up to 2 years. In addition, all participants will be followed for safety for 30 days after the last dose of study intervention. Thus, the total treatment duration is 154 weeks, and the total study duration is up to 164 weeks.

Data Monitoring Committee: Yes

Ethical Considerations and Benefit-Risk Assessment

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

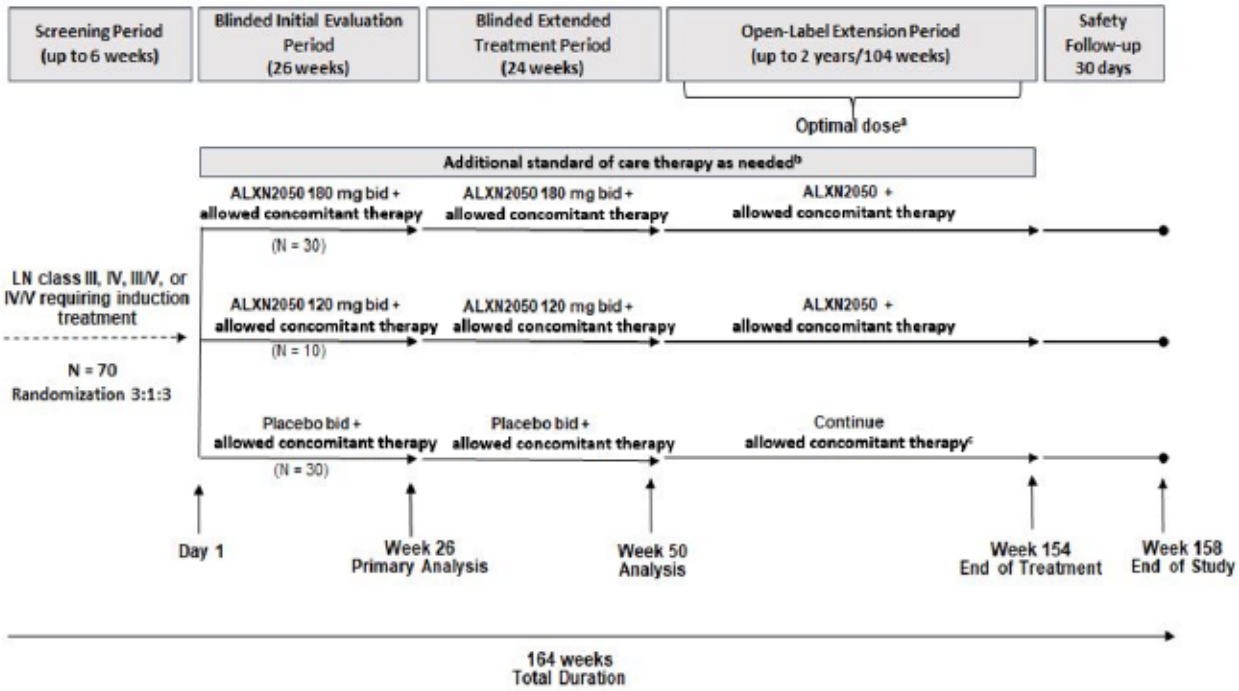
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

A thorough benefit-risk assessment has been performed for ALXN2050. Measures will be taken to minimize risk to study participants. The potential risks identified in association with ALXN2050 are justified by the anticipated benefits that may be afforded to participants with LN or IgAN (ALXN2050 Investigator's Brochure [IB]).

1.2. Schema

The study design schematic for the LN cohort is provided in Figure 1 and for the IgAN cohort in Figure 2.

Figure 1: Study Design Schematic (LN Cohort)



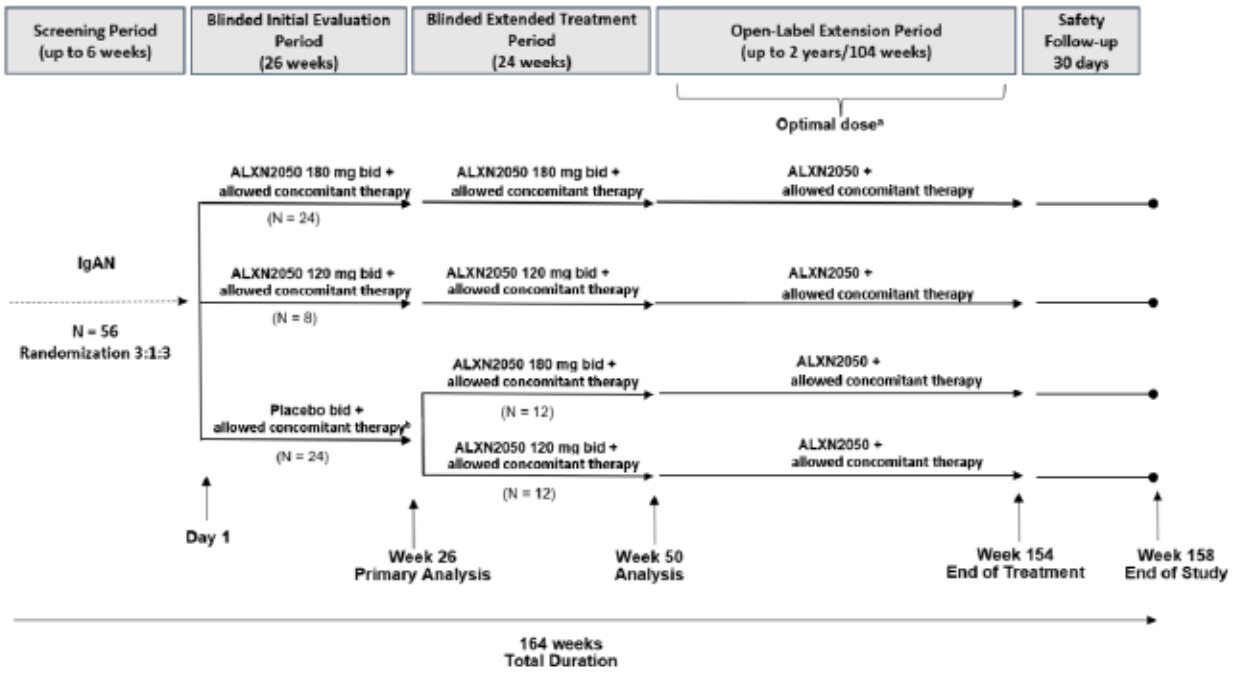
[a] The optimal dose level will be identified based on the results of the Week 26 Primary Analysis for each cohort. Once identified, all participants on active treatment in that cohort who have at least 50 weeks of treatment will receive the selected optimal dose for the remainder of the study.

[b] Participants will receive additional standard of care therapy in the event of a protocol-defined Renal Flare, or severe Extrarenal SLE Flare. Approved novel treatments for LN can be used per the Investigator's discretion. 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. However, if a CNI is used, ALXN2050 will need to be discontinued 3 days prior to CNI administration.

[c] After completion of the Blinded Extended Treatment Period, participants in the placebo group will only receive allowed concomitant therapy during the Open-label Extension Period and will have the option to receive ALXN2050 180 mg bid or the optimal dose (if already identified) if the participant has a Renal Flare as defined in Section 8.1.6 or Suboptimal Response as defined in Section 8.1.8.

Abbreviations: bid = twice daily; CNI = calcineurin inhibitor; LN = lupus nephritis; SLE = systemic lupus erythematosus

Figure 2: Study Design Schematic (IgAN Cohort)



[a] The optimal dose level will be identified based on the results of the Week 26 Primary Analysis for each cohort. Once identified, all participants in that cohort who have at least 50 weeks of treatment will receive the selected optimal dose for the remainder of the study.

[b] At randomization, participants assigned to the placebo group will also be assigned to their study treatment for the Blinded Extended Treatment Period (ALXN2050 120 mg bid or ALXN2050 180 mg bid) in a 1:1 allocation ratio. After completion of the Blinded Initial Evaluation Period (Week 26), these participants will continue on ALXN2050 treatment during the Blinded Extended Treatment Period.

Abbreviations: bid = twice daily; IgAN = immunoglobulin A nephropathy

1.3. Schedule of Activities

The Schedule of Activities (SoA) is provided as follows:

- Screening Period and Blinded Initial Evaluation Period: Screening to Week 26 (Day 183) Visit (LN cohort in Table 1 and IgAN cohort in Table 2)
- Blinded Extended Treatment Period (LN cohort in Table 3 and IgAN cohort in Table 4)
- Open-label Extension Period and Safety Follow-up Period (both LN and IgAN cohorts in Table 5)

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

Period	Screen-ing	Initial Evaluation Period									Notes
Visit	1	2	3	4	5	6	7	8	9	Evaluation for Renal Flare and Extrarenal SLE Flare Assessment Visit[a]	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	Up to 6 W		W2	W4	W8	W12	W16	W20	W26/ ED[b]		
Days and Window	D -42 to -1	D1	D15 ± 3	D29 ± 3	D57 ± 5	D85 ± 5	D113 ± 5	D141 ± 5	D183 ± 5		
General Assessments/Procedures											
Informed consent	X										
Inclusion/exclusion	X	X									Confirm eligibility prior to first dose of study intervention at Day 1; participants may be rescreened.
Demographics	X										
Medical history	X										
LN history/diagnosis	X										
Documentation of kidney biopsy	X										Biopsy obtained ≤ 6 months prior to Screening or during Screening. Send local pathology report and microscopy slides to Central Pathology Laboratory (Section 8.12.5).
Vaccination or confirmation of vaccination against *Neisseria meningitidis*[c]	X										Prophylactic antibiotics for at least 2 weeks post vaccination if < 2 weeks prior to first dose. (Section 6.5.5).
Prior LN therapy	X										Record corticosteroid and MMF usage (Section 6.5.3.1).
Weight	X	X							X		
Height	X										
Pregnancy test (WOCBP only)	X	X	X	X	X	X	X	X	X		Serum tests required at Screening and ED; urine tests at all other visits. (Section 8.2.6)

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

Period	Screen-ing	Initial Evaluation Period									Notes
Visit	1	2	3	4	5	6	7	8	9	Evaluation for Renal Flare and Extrarenal SLE Flare Assessment Visit[a]	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	Up to 6 W		W2	W4	W8	W12	W16	W20	W26/ ED[b]		
Days and Window	D -42 to -1	D1	D15 ± 3	D29 ± 3	D57 ± 5	D85 ± 5	D113 ± 5	D141 ± 5	D183 ± 5		
FSH test[d]	X										Only for females who are not WOCBP (Section 8.2.4.4).
HIV, HCV, and HBV	X										
Dispense participant safety card	X										Instruct participants to carry safety card at all times and bring it to scheduled visits (Section 8.2.7).
Efficacy Assessments											
24-hour urine collection[e]	X								X	X	One collection is needed as soon as possible during Screening. Two separate collections must be obtained within 2 weeks prior to the Week 26 Visit. (Section 8.1.1.1).
Morning spot urine sample	X	X	X	X	X	X	X	X	X	X	Two consecutive spot urine samples at Week 16 (Section 8.1.2).
eGFR (measured by serum creatinine)	X	X	X	X	X	X	X	X	X	X	At Week 26, the first creatinine sample for eGFR will be obtained within 2 weeks prior to Week 26 study visit and the second creatinine sample will be obtained on the study visit day (Section 8.1.3).
Predose blood sample for serum clinical complement tests	X	X	X		X		X		X	X	Section 10.2.

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

Period	Screen-ing	Initial Evaluation Period									Notes
Visit	1	2	3	4	5	6	7	8	9	Evaluation for Renal Flare and Extrarenal SLE Flare Assessment Visit[a]	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	Up to 6 W		W2	W4	W8	W12	W16	W20	W26/ ED[b]		
Days and Window	D -42 to -1	D1	D15 ± 3	D29 ± 3	D57 ± 5	D85 ± 5	D113 ± 5	D141 ± 5	D183 ± 5		
Monitor for Renal Flare and/or Extrarenal SLE Flare[a]		Continuous monitoring								X	Refer to Section 8.1.6 and Section 8.1.7 for definitions. Document use of additional standard of care therapy and/or repeat biopsy, if applicable (Section 6.5.4).
Safety Assessments											
Physical examination, including neurological assessments[f]	X	X							X		Section 8.2.1.
Abbreviated PE			X	X	X	X	X	X			
Vital signs	X	X	X	X	X	X	X	X	X	X	Vital signs to be taken predose at clinic visits (Section 8.2.2).
ECG for LN patients on hydroxychloroquine	X	X	X	X	X	X	X	X	X	X	Section 8.2.3.
ECG for LN patients not on hydroxychloroquine	X	X							X		
Prior medications and procedures	X										Section 8.2.5.
Concomitant medications and NPTP		Continuous monitoring								X	Section 6.5 and Section 8.2.5.
Allowed concomitant LN therapy		Continuous monitoring								X	See details on corticosteroid taper in Section 6.5.3.1.
Adverse events		Continuous monitoring								X	Section 10.3.

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

Period	Screening	Initial Evaluation Period									Notes
Visit	1	2	3	4	5	6	7	8	9	Evaluation for Renal Flare and Extrarenal SLE Flare Assessment Visit[a]	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	Up to 6 W		W2	W4	W8	W12	W16	W20	W26/ ED[b]		
Days and Window	D -42 to -1	D1	D15 ± 3	D29 ± 3	D57 ± 5	D85 ± 5	D113 ± 5	D141 ± 5	D183 ± 5		
Predose blood sample for clinical chemistry, hematology, and coagulation	X	X	X	X	X	X	X	X	X	X	Section 8.2.4.2 and Section 10.2.
Urinalysis and urine sediment	X	X	X	X	X	X	X	X	X	X	Section 8.2.4.3 and Section 10.2.
Participant safety card review		X	X	X	X	X	X	X	X	X	Confirm participants carry safety card at all times (Section 8.2.7).
PK and PD Assessments[5]											
Predose blood sample for PK		X	X	X	X	X	X		X	X	See footnote for sampling timepoints.
Predose blood sample for Bb and AP activity		X	X	X	X	X	X		X	X	
Postdose blood sample for PK		X	X								
Postdose blood sample for Bb and AP activity		X	X								
Exploratory Assessments											
EQ-5D-5L		X			X		X		X		If possible, complete the PROs prior to procedures and intervention administration (Section 8.10).
SF-36		X			X		X		X		
FACIT-Fatigue		X			X		X		X		
SLEDAI-2K		X							X	X	Required at Day 1 and Week 26/ED; perform as needed for evaluation of Extrarenal SLE Flare (Section 8.1.7).
Blood and urine samples for biomarkers	X	X	X		X		X		X	X	Collect predose on in-clinic dosing days (Section 10.2).

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

Period	Screening	Initial Evaluation Period									Notes
Visit	1	2	3	4	5	6	7	8	9	Evaluation for Renal Flare and Extrarenal SLE Flare Assessment Visit[a]	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	Up to 6 W		W2	W4	W8	W12	W16	W20	W26/ ED[b]		
Days and Window	D -42 to -1	D1	D15 ± 3	D29 ± 3	D57 ± 5	D85 ± 5	D113 ± 5	D141 ± 5	D183 ± 5		
Blood sample for autoantibodies	X	X							X	X	Section 10.2.
Optional kidney biopsy[h]										X	Send local pathology report and microscopy slides to the Central Pathology Laboratory (Section 8.12.5.3).
Study Intervention											
Randomization		X									Review eligibility prior to randomization.
Morning dose administered in-clinic		X	X	X	X	X	X	X	X[i]		Administer after all other required tests/procedures.
Study intervention compliance and accountability		X	X	X	X	X	X	X	X		Participants on study intervention should bring all unused study intervention at each clinic visit for tablet counting.
Study intervention dispensing		X	X	X	X	X	X	X	X		Participants on study intervention will be provided with sufficient study intervention to last until their next study visit (except at ED).

[a] Renal Flare (as defined in Section 8.1.6) and/or severe Extrarenal SLE Flare (as defined in Section 8.1.7) may occur at any time during the study. Evaluation of Renal Flare requires that UPCR from the morning spot urine collection is confirmed by a central lab UPCR based on 24-hour urine collected within 2 weeks, as well as 2 serum creatinine samples obtained within a 2 week period. Evaluation of Renal and Extrarenal SLE Flares 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 occurs 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.

[b] For participants who discontinue study intervention prior to Week 50, every effort should be made to have the participant continue the study visits as per the SoA through the Week 50. A Safety Follow-up Visit should be performed 30 days after the last dose of study intervention. If the participant does not agree to continue with the study visits after study intervention is discontinued, the ED Visit should be performed as soon as possible, and a Safety Follow-up Visit should be performed 30 days after the last dose of study intervention (refer to Table 5 for the Safety Follow-up Visit procedures.

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

[c] To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all participants must be vaccinated against meningococcal infection within 3 years or before the administration of study intervention on Day 1. Participants who initiate study intervention less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination (Section 6.5.5).

[d] FSH test need not be done if documentation confirming postmenopausal status is available (Section 8.2.4.4).

[e] Renal Flare requires a 24-hour urine collection for confirmation (Section 8.1.1).

[f] Perform a symptom based neurologic examination if participant has complaints or clinical findings attributable to the CNS and if positive for findings, full neurologic examination to be performed at each assessment timepoint.

[g] **Predose:** collect within 0.5 h predose on indicated in-clinic dosing days. **Postdose:** approximately 50% participant in each treatment arm will be assigned to PK/PD sample collection at 2 ± 0.5 h, 4 ± 0.5 h, and 6 ± 0.5 h postdose on Day 1 and at 2 ± 0.5 h, 4 ± 0.5 h, 6 ± 0.5 h postdose at Week 2. For the other approximate 50% of participant, samples will be collected at 2 ± 0.5 h postdose on Day 1 and 2 ± 0.5 h postdose at Week 2 (Section 8.4 and Section 8.5)

[h] Participants may receive a kidney biopsy for clinical reasons or for evaluation of a Renal Flare (as defined in Section 8.1.6) 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 26 should also be sent to the Central Pathology Laboratory for review as soon as possible.

[i] The primary efficacy endpoint assessment will be obtained prior to dosing on Day 183. Dosing on Day 183 is the start of the Blinded Extended Treatment Period.

Note: If possible, all assessments should be performed prior to administration of study intervention on in-clinic dosing days, unless otherwise specified.

Abbreviations: AP = alternative pathway; Bb = Bb fragment of complement factor B; CNS = central nervous system; 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; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LN = lupus nephritis; MMF = mycophenolate mofetil; NPTP = nonpharmacologic therapies and procedures; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; PRO = participant-reported outcome; SLE = systemic lupus erythematosus; SF-36 = Short Form (36) Health Survey; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000 Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) Modification; SoA = Schedule of Activities; UPCR = urine protein to creatinine ratio; W = week(s); WOCBP = women of childbearing potential

Table 2: Schedule of Activities During Screening and the Blinded 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**	**Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.**
Week	**Up to 6 W**		**W2**	**W6**	**W12**	**W18**	**W26/ ED[a]**	
Days and Window	**D -42 to -1**	**D1**	**D15 ± 3**	**D43 ± 5**	**D85 ± 5**	**D127 ± 5**	**D183 ± 5**	
General Assessments/Procedures								
Informed consent	X							
Inclusion/exclusion	X	X						Confirm eligibility prior to first dose of study intervention at Day 1; participants may be rescreened.
Demographics	X							
Medical history	X							
IgAN history/diagnosis	X							
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 (Section 8.12.5).
Prior IgAN therapy	X							Record ACEi/ARB usage (Section 8.2.5).
Vaccination or confirmation of vaccination against *N meningitidis*[b]	X							Prophylactic antibiotics for at least 2 weeks post vaccination if < 2 weeks prior to first dose. (Section 6.5.5).
Weight	X	X					X	
Height	X							
HIV, HCV, and HBV	X							
Pregnancy test (WOCBP only)	X	X	X	X	X	X	X	Serum tests required at Screening and ED; urine tests at all other visits (Section 8.2.6).
FSH test[c]	X							Only for females who are not WOCBP (Section 8.2.4.4).
Dispense participant safety card	X							Instruct participants to carry safety card at all times and bring to scheduled visits (Section 8.2.7).

Table 2: Schedule of Activities During Screening and the Blinded 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	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	Up to 6 W		W2	W6	W12	W18	W26/ ED[a]	
Days and Window	D -42 to -1	D1	D15 ± 3	D43 ± 5	D85 ± 5	D127 ± 5	D183 ± 5	
Efficacy Assessments								
24-hour urine collection	X						X	Two separate, complete, and valid 24-hour urine collections are required during Screening and within 2 weeks prior to the Week 26 Visit. (Section 8.1.1.2).
Morning spot urine sample	X	X	X	X	X	X	X	Two consecutive spot urine samples at Week 18 (Section 8.1.2).
eGFR (measured by serum creatinine)	X	X	X	X	X	X	X	
Predose blood sample for serum clinical complement tests	X	X	X		X	X	X	Section 10.2.
Safety Assessments								
Physical examination, including neurological assessments[d]	X	X					X	Section 8.2.1.
Abbreviated PE			X	X	X	X		
Vital signs	X	X	X	X	X	X	X	Vital signs to be taken prior to dosing at clinic visits (Section 8.2.2).
ECG	X	X					X	Section 8.2.3.
Prior medications and procedures	X							Section 8.2.5.
Concomitant medications and NPTP		Continuous monitoring						Section 6.5 and Section 8.2.5.
Allowed concomitant IgAN therapy		Continuous monitoring						Section 6.5.3.2.

Table 2: Schedule of Activities During Screening and the Blinded 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**	**Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.**
Week	**Up to 6 W**		**W2**	**W6**	**W12**	**W18**	**W26/ ED[a]**	
Days and Window	**D -42 to -1**	**D1**	**D15 ± 3**	**D43 ± 5**	**D85 ± 5**	**D127 ± 5**	**D183 ± 5**	
Adverse events	Continuous monitoring							Section 10.3.
Predose blood sample for clinical chemistry, hematology, and coagulation	X	X	X	X	X	X	X	Section 8.2.4.2 and Section 10.2.
Urinalysis and urine sediment	X[e]	X	X	X	X	X	X	Section 8.2.4.3 and Section 10.2.
Participant safety card review		X	X	X	X	X	X	Confirm participants carry safety card at all times (Section 8.2.7).
PK and PD Assessments[f]								
Predose blood sample for PK		X	X	X	X	X	X	See footnote for sampling timepoints.
Predose blood sample for Bb and AP activity		X	X	X	X	X	X	
Postdose blood sample for PK		X	X					
Postdose blood sample for Bb and AP activity		X	X					

Table 2: Schedule of Activities During Screening and the Blinded 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**	**Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.**
Week	**Up to 6 W**		**W2**	**W6**	**W12**	**W18**	**W26/ ED[a]**	
Days and Window	**D -42 to -1**	**D1**	**D15 ± 3**	**D43 ± 5**	**D85 ± 5**	**D127 ± 5**	**D183 ± 5**	
Exploratory Assessments								
EQ-5D-5L		X		X	X		X	If possible, complete the PROs prior to procedures and intervention administration (Section 8.10).
SF-36		X		X	X		X	
Blood and urine samples for biomarkers	X	X	X		X	X	X	Collect predose on in-clinic dosing days (Section 10.2).
Study Intervention								
Randomization		X						Review eligibility prior to randomization.
Morning dose administered in-clinic		X	X	X	X	X	X[g]	Administer dose after all other required tests/procedures.
Study intervention compliance and accountability		X	X	X	X	X	X	Participants on study intervention should bring all unused study intervention at each clinic visit for tablet counting.
Study intervention dispensing		X	X	X	X	X	X	Participants on study intervention will be provided with sufficient study intervention to last until their next study visit (except at ED).

[a] For participants who discontinue study intervention prior to Week 50, every effort should be made to have the participant continue the study visits as per the SoA through the Week 50. A Safety Follow-up Visit should be performed 30 days after the last dose of study intervention. If the participant does not agree to continue with the study visits after study intervention is discontinued, the ED Visit should be performed as soon as possible, and a Safety Follow-up Visit should be performed 30 days after the last dose of study intervention. Refer to Table 5 for the Safety Follow-up Visit procedures.

[b] To reduce the risk of meningococcal infection (*N meningitidis*), all participants must be vaccinated against meningococcal infection within 3 years or before the administration of study intervention on Day 1. Participants who initiate study intervention less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination (Section 6.5.5).

[c] FSH test need not be done if documentation confirming postmenopausal status is available (Section 8.2.4.4).

[d] Perform a symptom based neurologic examination if participant has complaints or clinical findings attributable to the CNS and if positive for findings, full neurologic examination to be performed at each assessment timepoint.

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

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

[f] **Predose**: collect within 0.5 h predose on indicated in-clinic dosing days. **Postdose:** approximately 50% participant in each treatment arm will be assigned to PK/PD sample collection at 2 ± 0.5 h, 4 ± 0.5 h, 6 ± 0.5 h postdose on Day 1 and at 2 ± 0.5 h, 4 ± 0.5 h, 6 ± 0.5 h postdose at Week 2. For the other approximately 50% of participant, samples will be collected at 2 ± 0.5 h postdose on Day 1 and 2 ± 0.5 h postdose at Week 2 (Section 8.4 and Section 8.5).

[g] The primary efficacy endpoint assessment will be obtained prior to dosing on Day 183. Dosing on Day 183 is the start of the Blinded Extended Treatment Period.

Note: If possible, all assessments should be performed prior to administration of study intervention on in-clinic dosing days, unless otherwise specified.

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; AP = alternative pathway; ARB = angiotensin II receptor blocker; Bb = Bb fragment of complement factor B; CNS = central nervous system; 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; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgAN = immunoglobulin A nephropathy; NPTP = nonpharmacologic therapies and procedures; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; PRO = participant-reported outcome; SF-36 = Short Form (36) Health Survey; SoA = Schedule of Activities; W = week(s); WOCBP = women of childbearing potential

Table 3: Schedule of Activities During the Blinded Extended Treatment Period: Week 34 to Week 50 Visits (LN Cohort)

Period	Extended Treatment Period				Notes
Visit	10	11	12	Evaluation for Renal Flare, Extrarenal SLE Flare, and Suboptimal Response Assessment Visit[a]	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	W34	W42	W50/ED[b]		
Days and Window	D239 ± 7	D295 ± 7	D351 ± 7		
General Assessments/Procedures					
Weight			X		
Pregnancy test (WOCBP only)	X	X	X		Serum pregnancy test required at ED; urine pregnancy tests at all other visits (Section 8.2.6).
Efficacy Assessments					
24-hour urine collection			X	X[a]	Two separate 24-hour urine collections required within 2 weeks prior to the Week 50 Visit (Section 8.1.1). Renal Flare and Suboptimal Response require a 24-hour urine collection for confirmation (Section 8.1.6 and Section 8.1.8)
Morning spot urine sample	X	X	X	X	Section 8.1.2
eGFR (measured by serum creatinine)	X	X	X	X	At Week 50, the first creatinine sample for eGFR will be obtained within 2 weeks prior to Week 50 study visit and the second creatinine sample will be obtained on the study visit day (Section 8.1.3).
Predose blood sample for serum clinical complement tests	X	X	X	X	Section 10.2
Monitor for Renal Flare and/or Extrarenal SLE Flare and/or Suboptimal Response[a]	Continuous monitoring			X	Refer to Section 8.1.6, Section 8.1.7, and Section 8.1.8 for definitions. Document use of additional standard of care therapy and/or repeat biopsy, if applicable (Section 6.5.4).
Safety Assessments					
Physical examination, including neurological assessments[c]			X		Section 8.2.1.
Abbreviated PE	X	X			
Vital signs	X	X	X	X	Vital signs to be taken predose at clinic visits (Section 8.2.2).

Table 3: Schedule of Activities During the Blinded Extended Treatment Period: Week 34 to Week 50 Visits (LN Cohort)

Period	Extended Treatment Period				Notes
Visit	10	11	12	Evaluation for Renal Flare, Extrarenal SLE Flare, and Suboptimal Response Assessment Visit[a]	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	W34	W42	W50/ED[b]		
Days and Window	D239 ± 7	D295 ± 7	D351 ± 7		
ECG for LN patients on hydroxychloroquine	X	X	X	X	Section 8.2.3.
ECG for LN patients not on hydroxychloroquine			X		
Concomitant medications and NPTP	Continuous monitoring			X	Section 6.5 and Section 8.2.5.
Allowed concomitant LN therapy	Continuous monitoring			X	See details on corticosteroid taper in Section 6.5.3.1.
Adverse events	Continuous monitoring			X	Section 10.3.
Predose blood sample for clinical chemistry, hematology, and coagulation	X	X	X	X	Section 8.2.4.2 and Section 10.2.
Urinalysis and urine sediment	X	X	X	X	Section 8.2.4.3 and Section 10.2.
Participant safety card review	X	X	X	X	Confirm participants carry safety card at all times (Section 8.2.7).
PD and PK Assessments					
Predose blood samples for PK	X	X	X	X	Section 8.4.
Predose blood sample for Bb and AP activity	X	X	X	X	Section 8.5.
Exploratory Assessments					
SF-36	X	X	X		PROs to be performed as early as possible during visits (Section 8.10).
EQ-5D-5L	X	X	X		
FACIT-Fatigue	X	X	X		
SLEDAI-2K			X	X	Required at Week 50/ED, perform as needed for evaluation of Extrarenal SLE Flare (Section 8.1.7).
Blood and urine samples for biomarkers	X	X	X	X	Collect predose on in-clinic dosing days (Section 10.2).
Blood sample for autoantibodies			X	X	Section 10.2.

Table 3: Schedule of Activities During the Blinded Extended Treatment Period: Week 34 to Week 50 Visits (LN Cohort)

Period	Extended Treatment Period				Notes
Visit	10	11	12	Evaluation for Renal Flare, Extrarenal SLE Flare, and Suboptimal Response Assessment Visit[a]	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	W34	W42	W50/ED[b]		
Days and Window	D239 ± 7	D295 ± 7	D351 ± 7		
Optional kidney biopsy[d]			X	X	Send local pathology report and microscopy slides to the Central Pathology Laboratory (Section 8.12.5.3).
Study Intervention[e]					
Morning dose administered in-clinic	X	X	X		Administer after all other required tests/procedures.
Study intervention compliance and accountability	X	X	X		Participants on study intervention should bring all unused study intervention at each clinic visit for tablet counting.
Study intervention dispensing	X	X	X		Participants on study intervention will be provided with sufficient study intervention to last until their next study visit (except at ED).

[a] Renal Flare (as defined in Section 8.1.6), and Extrarenal SLE Flare (as defined in Section 8.1.7) may occur at any time during the study. Suboptimal Response (as defined in Section 8.1.8) may occur after Week 26. Evaluation of Renal Flare requires a UPCR from a spot urine sample that is confirmed on a 24-hour urine collection, as well as 2 serum creatinine samples obtained within a 2-week period. Evaluation of Renal and Extrarenal SLE Flares must be performed as soon as possible upon notification to the Investigator of symptom onset or lack of response (after Week 26). If Renal Flare or Extrarenal SLE Flare or Suboptimal Response (after Week 26) occurs between scheduled visits, only the assessments for the Renal Flare/Extrarenal SLE Flare/Suboptimal Response (after Week 26) Visit are needed. If Renal Flare or Extrarenal SLE Flare or Suboptimal Response (after Week 26) occurs 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 (after Week 26).

[b] For participants who discontinue study intervention prior to Week 50, every effort should be made to have the participant continue the study visits as per the SoA through the Week 50. A Safety Follow-up Visit should be performed 30 days after the last dose of study intervention. If the participant does not agree to continue with the study visits after study intervention is discontinued, the ED Visit should be performed as soon as possible, and a Safety Follow- -up Visit should be performed 30 days after the last dose of study intervention. Refer to Table 5 for the Safety Follow -up Visit procedures.

[c] Perform a symptom based neurologic examination if participant has complaints or clinical findings attributable to the CNS and if positive for findings, full neurologic examination to be performed at each assessment timepoint.

[d] Participants will be asked to undergo an optional repeat kidney biopsy after completion of the Blinded Extended Treatment 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).

[e] During the Blinded Extended Treatment Period, participants in the LN cohort will continue to receive their randomized allocation of study intervention.

Note: If possible, all assessments should be performed prior to administration of study intervention on in-clinic dosing days, unless otherwise specified.

Table 3: Schedule of Activities During the Blinded Extended Treatment Period: Week 34 to Week 50 Visits (LN Cohort)

Abbreviations: AP = alternative pathway; Bb = Bb fragment of complement factor B; CNS = central nervous system; 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; FACIT = Functional Assessment of Chronic Illness Therapy; LN = lupus nephritis; NPTP = nonpharmacologic therapies and procedures; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; PRO = participant-reported outcome; SF-36 = Short Form (36) Health Survey; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000 Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) Modification; SoA = Schedule of Activities; UPCR = urine protein to creatinine ratio; W = week; WOCBP = women of childbearing potential

Table 4: Schedule of Activities During the Blinded Extended Treatment Period: Week 28 to Week 50 Visits (IgAN Cohort)

Period	Extended Treatment Period					Notes
Visit	8	9	10	11	12	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.
Week	W28	W32	W38	W42	W50/ ED[a]	
Days and Window	D197 ± 7	D225 ± 7	D267 ± 7	D295 ± 7	D351 ± 7	
General Assessments/Procedures						
Weight					X	
Pregnancy test (WOCBP only)	X	X	X	X	X	Serum pregnancy test required at ED; urine pregnancy tests at all other visits (Section 8.2.6).
Efficacy Assessments						
24-hour urine collection					X	Two separate 24-h urine collections required within 2 weeks prior to the Week 50 Visit (Section 8.1.1.2).
Morning spot urine sample	X	X	X	X	X	Section 8.1.2.
eGFR (measured by serum creatinine)	X	X	X	X	X	
Predose blood sample for serum clinical complement tests	X	X	X	X	X	Section 10.2.
Safety Assessments						
Physical examination, including neurological assessments[b]					X	Section 8.2.1.
Abbreviated PE	X	X	X	X		
Vital signs	X	X	X	X	X	Vital signs to be taken predose at clinic visits (Section 8.2.2).
ECG					X	Section 8.2.3.
Concomitant medications and NPTP		Continuous monitoring				Section 6.5 and Section 8.2.5.
Allowed concomitant IgAN therapy		Continuous monitoring				Section 6.5.3.2.
Adverse events		Continuous monitoring				Section 10.3.
Predose blood sample for clinical chemistry, hematology, and coagulation	X	X	X	X	X	Section 8.2.4.2 and Section 10.2.

Table 4: Schedule of Activities During the Blinded Extended Treatment Period: Week 28 to Week 50 Visits (IgAN Cohort)

Period	Extended Treatment Period					Notes
Visit	**8**	**9**	**10**	**11**	**12**	**Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early.**
Week	**W28**	**W32**	**W38**	**W42**	**W50/ ED[a]**	
Days and Window	**D197 ± 7**	**D225 ± 7**	**D267 ± 7**	**D295 ± 7**	**D351 ± 7**	
Urinalysis and urine sediment	X	X	X	X	X	Section 8.2.4.3 and Section 10.2.
Participant safety card review	X	X	X	X	X	Confirm participants carry safety card at all times (Section 8.2.7).
PK and PD Assessments						
Predose blood samples for PK	X	X	X	X	X	Section 8.4.
Predose blood sample for Bb and AP activity	X	X	X	X	X	Section 8.5.
Exploratory Assessments						
SF-36			X		X	PROs to be performed as early as possible during visits.
EQ-5D-5L			X		X	
Blood and urine samples for biomarkers	X	X	X	X	X	Collect predose on in-clinic dosing days (Section 10.2).
Study Intervention[c]						
Morning dose administered in-clinic	X	X	X	X	X	Administer dose after all other required tests/procedures.
Study intervention compliance and accountability	X	X	X	X	X	Participants on study intervention should bring all unused study intervention at each clinic visit for tablet counting.
Study intervention dispensing	X	X	X	X	X	Participants on study intervention will be provided with sufficient study intervention to last until their next study visit (except at ED).

[a] For participants who discontinue study intervention prior to Week 50, every effort should be made to have the participant continue the study visits as per the SoA through the Week 50. A Safety Follow-up Visit should be performed 30 days after the last dose of study intervention. If the participant does not agree to continue with the study visits after study intervention is discontinued, the ED Visit should be performed as soon as possible, and a Safety Follow-up Visit should be performed 30 days after the last dose of study intervention. Refer to Table 5 for the Safety Follow-up Visit procedures.

[b] Perform a symptom based neurologic examination if participant has complaints or clinical findings attributable to the CNS and if positive for findings, full neurologic examination to be performed at each assessment timepoint.

[c] During the Blinded Extended Treatment Period, participants in the IgAN placebo group will switch to receive either ALXN2050 180 mg bid or ALXN2050 120 mg bid. Participants in the IgAN cohort randomized to active treatment will continue to receive their randomized allocation of study intervention.

Note: If possible, all assessments should be performed prior to administration of study intervention on in-clinic dosing days, unless otherwise specified.

Table 4: Schedule of Activities During the Blinded Extended Treatment Period: Week 28 to Week 50 Visits (IgAN Cohort)

Abbreviations: AP = alternative pathway; Bb = Bb fragment of complement factor B; bid = twice daily; CNS = central nervous system; 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; NPTP = nonpharmacologic therapies and procedures; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; PRO = participant-reported outcome; SF-36 = Short Form (36) Health Survey; SoA = Schedule of Activities; W = week (s); WOCBP = women of childbearing potential

Table 5: Schedule of Activities During the Open-label Extension Period and Safety Follow-up Period (Both LN and IgAN Cohorts)

Period	Adhoc visit[a]	Open-label Extension Period									Safety Follow-up Period	Notes
Week	After W50	W63	W76	W89	W102	W115	W128	W141	W154/ ED[b]	Evaluation for Renal Flare, Extrarenal SLE Flare, and Suboptimal Response Assessment Visit (LN only)[c]	4 weeks post last dose	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early
Days and Window		D442 ± 14	D533 ± 14	D624 ± 14	D715 ± 14	D806 ± 14	D897 ± 14	D988 ± 14	D1079 ± 14		30 (± 3) days post last dose	
General Assessments/Procedures												
Weight									X			
Pregnancy test (WOCBP only)		X	X	X	X	X	X	X	X		X	Serum test required at ED; urine tests at all other visits (Section 8.2.6).
Efficacy Assessments												
24-hour urine collection					X				X	X		Obtain one 24-hour urine collection; Section 8.1.1
Morning spot urine sample		X	X	X	X	X	X	X	X	X		Section 8.1.2.
Monitor for Renal Flare and/or Extrarenal SLE Flare and/or Suboptimal Response (LN only)		Continuous monitoring								X		Refer to Section 8.1.6, Section 8.1.7, and Section 8.1.8 for definitions. Document use of additional standard of care therapy and/or repeat biopsy, if applicable (Section 6.5.4).
Blood samples for autoantibodies (LN only)										X		Section 10.2.

Table 5: Schedule of Activities During the Open-label Extension Period and Safety Follow-up Period (Both LN and IgAN Cohorts)

Period	Adhoc visit[a]	Open-label Extension Period									Safety Follow-up Period	Notes
Week	After W50	W63	W76	W89	W102	W115	W128	W141	W154/ ED[b]	Evaluation for Renal Flare, Extrarenal SLE Flare, and Suboptimal Response Assessment Visit (LN only)[c]	4 weeks post last dose	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early
Days and Window		D442 ± 14	D533 ± 14	D624 ± 14	D715 ± 14	D806 ± 14	D897 ± 14	D988 ± 14	D1079 ± 14		30 (± 3) days post last dose	
Safety Assessments												
Physical examination, including neurological assessments[d]									X			Section 8.2.1.
Abbreviated PE		X	X	X	X	X	X	X			X	
ECG (only for LN patients receiving hydroxychloroquine)	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.3
Vital signs		X	X	X	X	X	X	X	X	X	X	Vital signs to be taken prior to dosing at clinic visits (Section 8.2.2).
Concomitant medications and NPTP		Continuous monitoring								X	X	Section 6.5 and Section 8.2.5.
Allowed concomitant LN or IgAN therapy		Continuous monitoring								X	X	Section 6.5.3.1 and Section 6.5.3.2.
Adverse events		Continuous monitoring								X	X	Section 10.3.
Blood sample for clinical chemistry, hematology, and coagulation		X	X	X	X	X	X	X	X	X		Section 8.2.4.2 and Section 10.2.

Table 5: Schedule of Activities During the Open-label Extension Period and Safety Follow-up Period (Both LN and IgAN Cohorts)

Period	Adhoc visit[a]	Open-label Extension Period									Safety Follow-up Period	Notes
Week	After W50	W63	W76	W89	W102	W115	W128	W141	W154/ ED[b]	Evaluation for Renal Flare, Extrarenal SLE Flare, and Suboptimal Response Assessment Visit (LN only)[c]	4 weeks post last dose	Unscheduled visits can be performed as needed. An ED Visit is required if participant discontinues study early
Days and Window		D442 ± 14	D533 ± 14	D624 ± 14	D715 ± 14	D806 ± 14	D897 ± 14	D988 ± 14	D1079 ± 14		30 (± 3) days post last dose	
Urinalysis and urine sediment		X	X	X	X	X	X	X	X	X		Section 8.2.4.3 and Section 10.2.
Participant safety card review		X	X	X	X	X	X	X	X	X		Confirm participants carry safety card at all times (Section 8.2.7).
Study Intervention[a]												
Study intervention compliance and accountability		X	X	X	X	X	X	X	X			Participants on study intervention should bring all unused study intervention at each clinic visit for tablet counting.
Study intervention dispensing		X	X	X	X	X	X	X				Participants on study intervention will be provided with sufficient study intervention to last until their next study visit (except at W154 and ED).

[a] Adhoc visit is only applicable for LN patients who are receiving hydroxychloroquine: When patients are switched from 120 mg to 180 mg after Week 50, or when placebo patients who are on allowed concomitant therapy initiate ALXN2050 at any dose due to a Renal Flare, additional ECG needs to be obtained at an adhoc visit 2 weeks (± 7 days) after the dose initiation or dose escalation.

[b] For participants who discontinue study intervention prior to the end of the Open-label Extension Period, the ED Visit should be performed as soon as possible and a Safety Follow-up Visit should be performed 30 days after the last dose of study intervention.

Table 5: Schedule of Activities During the Open-label Extension Period and Safety Follow-up Period (Both LN and IgAN Cohorts)

[c] Renal Flare (as defined in Section 8.1.6), Extrarenal SLE Flare (as defined in Section 8.1.7) may occur at any time during the study and Suboptimal Response (as defined in Section 8.1.8) after Week 26. Evaluation of Renal Flare requires a UPCR from a spot urine sample that is confirmed on a 24-hour urine collection, as well as 2 serum creatinine samples obtained within a 2-week period. Evaluation of Renal and Extrarenal SLE Flares or 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 occurs 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] Perform a symptom based neurologic examination if participant has complaints or clinical findings attributable to the CNS and if positive for findings, full neurologic examination to be performed at each assessment timepoint.

[e] In the LN cohort, placebo patients will receive only allowed concomitant therapy. For all other patients in both cohorts, see Figure 1 and Figure 2.

Note: If possible, all assessments should be performed prior to administration of study intervention on in-clinic dosing days, unless otherwise specified.

Abbreviations: CNS = central nervous system; D = day; ECG = electrocardiogram; ED = early discontinuation; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis; NPTP = nonpharmacologic therapies and procedures; PE = physical examination; SLE = systemic lupus erythematosus; UPCR = urine protein to creatinine ratio; W = week; WOCBP = women of childbearing potential

2. INTRODUCTION

2.1. Study Rationale

ALXN2050 is a potent, reversible, oral small molecule inhibitor of FD, which is an essential component of the complement AP. The complement system is involved in the pathophysiology of proliferative LN and IgAN. The objectives of this study are to evaluate the efficacy and safety of oral ALXN2050 compared to placebo, demonstrate proof of concept for efficacy of FD inhibition, and establish an effective dose that addresses ongoing unmet medical need in patients with LN or IgAN who are treated with allowed concomitant therapy consistent with the standard of care.

2.2. Background

2.2.1. Lupus Nephritis and Immunoglobulin A Nephropathy

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 adverse outcomes, including end-stage renal disease (ESRD) (Lv, 2019). Despite advances in immunosuppressive treatments, certain types of glomerulonephritis such as LN and IgAN continue to respond poorly to treatment, resulting in CKD over time. There has been some progress in terms of approved treatments for patients with LN with 2 recent approvals in the US, ie, belimumab and voclosporin. At 2 years, belimumab showed a complete renal response (CRR) of 30.0% vs 20.0% compared to placebo (Furie, 2020). At 1 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.

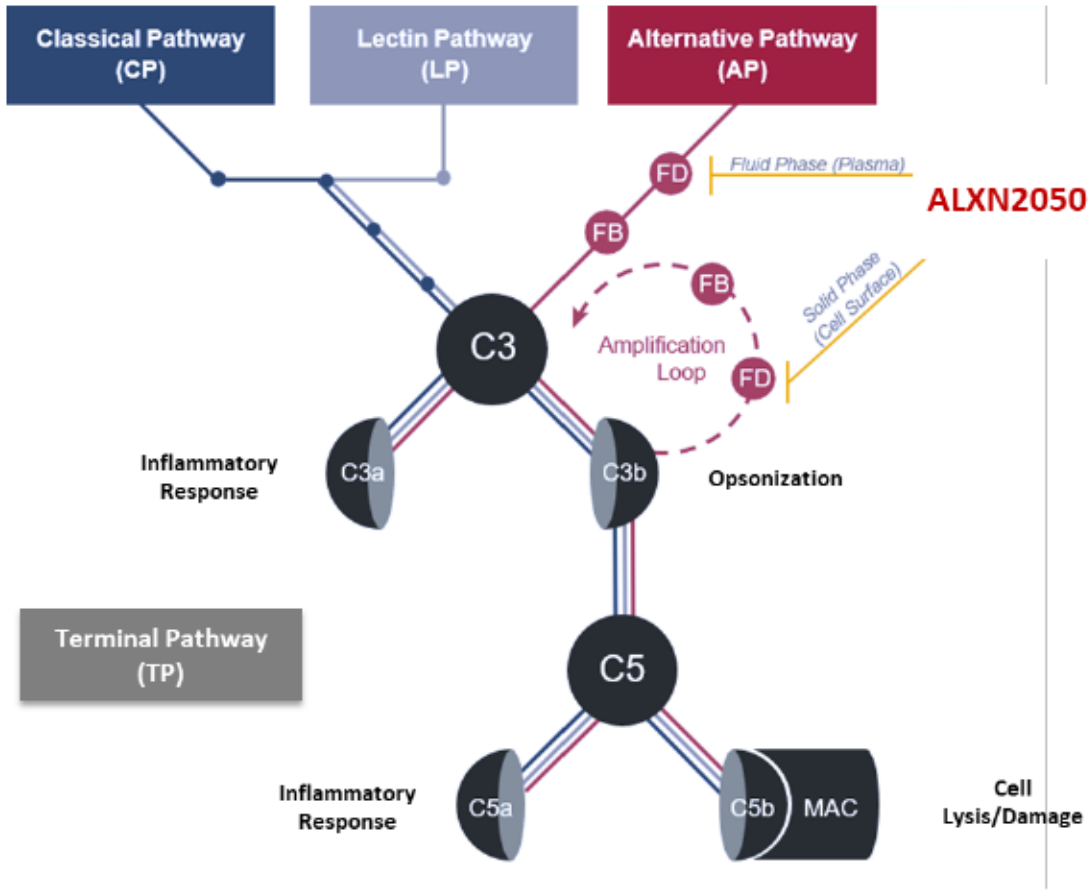
The pathophysiology of glomerular diseases such as LN and IgAN involves a complex overlap of abnormal cellular immune response, loss of humoral immune tolerance, aberrant coagulation, and systemic inflammation. Dysregulation of the AP of complement, either by direct AP activation or via the AP-mediated amplification of complement classical pathway (CP) and lectin pathway (LP), has emerged as an additional driving factor that interplays with these pathways in LN and IgAN (Lukawska, 2018; Thurman, 2006). The narrow vessels and high perfusion in the kidney make this organ particularly susceptible to immune complex (IC) deposition and consequent complement-mediated injury. Histologic evidence of complement deposition observed in kidney biopsy samples from patients with either LN or IgAN suggests a pathological role. Serum/plasma levels of complement components within and downstream of the AP (eg, complement component 3 [C3] and the membrane attack complex [MAC]) correlate with disease activity and response to treatment, particularly in patients with LN (Galindo-Izquierdo, 2021; Thurman, 2015).

2.2.2. ALXN2050

ALXN2050 is an orally active, small molecule, complement FD inhibitor that is in development for the treatment of complement-mediated diseases. A serine protease, FD catalyzes the cleavage

of complement factor B (FB) to produce the Bb fragment of complement factor B (Bb), an enzymatic component of AP C3 and complement component 5 (C5) convertases. ALXN2050 acts by binding reversibly to FD, blocking its serine protease activity and thereby inhibiting AP activation and the resulting production of C3 cleavage fragments, anaphylatoxins of complement components 3a and 5a (C3a and C5a), and downstream MAC complex (Figure 3). In addition, although FD inhibition does not inhibit components specific to the CP or LP of complement, it will reduce the production of C3 cleavage fragments and downstream MAC formation initiated through these 2 pathways via inhibition of the amplification of activation (Harboe, 2004).

Figure 3: Complement Pathways



Abbreviations: C = complement component; FB = complement factor B; FD = complement factor D; MAC = membrane attack complex
Source: Adapted from (Merle, 2015a; Merle, 2015b; Yuan, 2017)

A detailed description of the chemistry, pharmacology, efficacy, and safety of ALXN2050 is provided in the Investigator's Brochure (IB).

2.2.3. Rationale for Evaluating ALXN2050 in Participants with Lupus Nephritis

Lupus nephritis occurs in approximately 50% of patients with SLE (Almaani, 2019; Morales, 2021), an autoimmune disorder caused by loss of tolerance to self-antigens, the production of autoantibodies, and deposition of complement-fixing 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. Lupus nephritis leading to CKD is an independent major risk factor for overall mortality and morbidity attributed to cardiovascular diseases (Gasparotto, 2020). 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 (Tektonidou, 2016). Recurrence of LN after treatment (Renal Flare) occurs within 1 year in up to 25% of patients and is associated with 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). Immune complexes can activate the complement CP by direct interaction with complement component 1q (C1q) in the C1 complex; further activation by the AP-mediated amplification loop contributes to the overall accumulation of complement activation products and the resulting inflammatory response and tissue injury. 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 (Thurman, 2020). 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, 2010; Dall'Era, 2011). Decreases in C3, complement component 4 (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; Song, 2017). In fact, the pharmacodynamic (PD) marker of ALXN2050, plasma complement factor Bb, is significantly elevated in patients with active LN when compared to patients with LN in clinical remission, active SLE without LN, and normal controls. Lastly, plasma Bb level significantly correlates with kidney disease activity indices and is a risk factor for adverse kidney outcomes (Song, 2017).

Restoring complement regulation may improve renal responses through acute anti-inflammatory effects and lasting effects on IC deposition-mediated injury in the kidney. The contribution of AP activity to LN pathophysiology has been demonstrated in mouse models (Elliott, 2004; Grossman, 2016; Watanabe, 2000) and further supported by soluble biomarker profiles and the composition of renal deposition in patients with LN (Birmingham, 2017; Kim, 2020; Lukawska, 2018; Song, 2017). Restoring AP regulation may improve renal responses through acute anti-inflammatory effects and lasting effects on IC deposition-mediated injury in the kidney. Hence, FD inhibition is promising for both induction treatment for active proliferative LN and maintenance treatment of chronic LN (Lukawska, 2018; Thurman, 2006).

The American College of Rheumatology (ACR) and jointly 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 MMF or low-dose cyclophosphamide. For maintenance therapy, the guidelines agree on MMF or azathioprine, with or without low dose glucocorticoids (Bertsias, 2012). In patients with LN, the main goal of therapy is prevention of CKD progression, prevention of ESRD, and improved survival. Lack of achievement of remission, in particular complete remission, is one of the major risk factors for the progression of renal

disease. Hence, short-term CRR and partial renal response (PRR) are used to assess the efficacy of standard of care and novel therapies. After 6 to 12 months of treatment, only 10% to 40% of patients achieve a CRR with standard of care (Parikh, 2016).

Recent approvals in the US of belimumab and voclosporin represent progress in the treatment of LN. Results at 2 years showed a CRR of 30.0% for belimumab vs 20.0% for placebo (Furie, 2020). For voclosporin, CRR was 40.8% compared to 22.5% for placebo at one year (Arriens, 2020). However, a significant need exists for therapies that yield fast and durable responses, with high complete response rates, along with reduced need for steroids and/or immunosuppressants in patients with LN.

2.2.4. Rationale for Evaluating ALXN2050 in Participants with Immunoglobulin A Nephropathy

Immunoglobulin A nephropathy (IgAN), also known as Berger's disease, is the most common global primary glomerulonephropathy that can progress to renal failure. Immunoglobulin A 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 immunoglobulin A (IgA) immunofluorescence in the glomeruli, usually codominant with C3 according to the Oxford Classification nomenclature (KDIGO, 2017; 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 AP and LP complement pathways may be activated, leading to generation of anaphylatoxins of C3a and C5a, and the MAC C5b-9, with subsequent promotion of inflammatory mediators (Lukawska, 2018; Maillard, 2015; Thurman, 2006). 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 of these products, 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. Evidence for AP involvement has been established in the codeposition with IgA of properdin and of regulators of AP C3 convertase stability including complement factor H (FH) and factor H-related protein-5 (FHR5) (Medjeral-Thomas, 2014; Rizk, 2019). Further support has arisen from the association of IgAN pathogenesis with circulating levels of the FHR proteins, and with the identification of both protective and pathogenic variants in the *CFH* locus which affect expression or activity of FH and FH-related proteins (Tortajada, 2019). Together these findings suggest a role of complement in the pathophysiology and the prognostic value of complement biomarkers in IgAN (Rizk, 2019). Animal studies demonstrate that aberrantly glycosylated IgA complexes with C3b and FB are codeposited in glomeruli (Hashimoto, 2012). This is supported in humans through data demonstrating elevated messenger ribonucleic acid (mRNA) transcript expression of FD and properdin in glomeruli relative to other kidney fractions (Song, 1998).

Factor D inhibition is a potential target for treatment of patients with IgAN at high risk of progression to kidney disease (Rizk, 2019) (ie, significant proteinuria despite optimal RAS blockade) (Reich, 2007). Factor D inhibition blocks complement AP activation directly and tempers complement activation via other pathways through inhibition of the amplification loop, leading to prevention of the downstream molecular and cellular consequences, and subsequently has potential for therapeutic efficacy in patients with IgAN.

Treatments for IgAN include RAS blocking agents, such as angiotensin-converting enzyme (ACE) inhibitors (ACEis) or angiotensin II receptor blockers (ARBs). These therapies are aimed at controlling blood pressure and preserving kidney function through decreasing intraglomerular pressure, which in turn reduces proteinuria. These treatments are insufficient in preserving renal function in patients with IgAN, as a high proportion still suffer from progressive CKD and ESRD (KDIGO, 2020). Patients with baseline hypertension (Pugh, 2019) and proteinuria > 1 g/day (Reich, 2007) are at increased risk for renal disease progression.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Potential risks associated with participation in this study and risk mitigation measures are presented in Table 6.

Table 6: Potential Risks and Mitigation Strategies

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention		
Meningococcal infection	Participants receiving Factor D complement inhibitor therapy may have an increased risk of infections, particularly *Neisseria meningitidis*.	All participants must be vaccinated against meningococcal disease within 3 years prior to, or at the time of, initiating the study intervention. Participants who initiate study intervention less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination. Participants must carry the Patient Safety Card dispensed at the Day 1 Visit at all times to promote rapid recognition of any potential signs or symptoms of infection.
Seizure	Convulsions and/or electroencephalogram abnormalities have been observed during nonclinical repeat-dose toxicology studies. Refer to	Participants with history of seizures are excluded. Procedures specified in Section 10.14 are to be followed if a suspected seizure occurs.

Table 6: Potential Risks and Mitigation Strategies

Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Section 4.3 for information on the safety margin.	
Other		
Pregnancy exposure/lactation	No studies of ALXN2050 have been conducted in pregnant women. There are no data available on excretion of ALXN2050 in breast milk.	Pregnancy testing will be conducted as specified in the Schedule of Activities (Section 1.3). A negative serum pregnancy test (Screening Visit) and a negative urine pregnancy test (Day 1) are required prior to randomization. If a pregnancy is reported during the study, safety follow-up will be performed (Section 10.5). Pregnant or nursing women are excluded from participating in this clinical study. Participants must use a highly effective or acceptable method of contraception during the study and following the final dose of study intervention (Section 10.5).

2.3.1.1. Coronavirus Disease 2019

The 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 10.11. The risk assessment for COVID-19 vaccination is described in Section 10.12.

2.3.2. Benefit Assessment

LN and IgAN are lifelong 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 (belimumab and voclosporin) and IgAN (budesonide), there remains a significant unmet need for novel interventions which would allow more definitive treatments for LN as well as disease-specific treatments for patients with IgAN, particularly in patients who are at risk of progressive kidney disease.

Based on its mechanism of action (Section 2.2.2), ALXN2050 may provide an efficacious treatment to patients with LN or IgAN, rare diseases with a large unmet clinical need. Potential benefits of participating in this clinical study include:

- More frequent routine assessments/procedures (eg, physical examinations and vital signs assessments) at prespecified study visits
- Potential clinical improvement and decreased risk of kidney disease progression

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the high unmet need for effective therapies for patients with LN or IgAN, the outcomes of these patient populations with currently available care, along with the measures taken to minimize risk to participants in this study, the potential risks of participating in the study are justified by the anticipated benefits.

More detailed information about the potential benefits and potential risks of ALXN2050 may be found in the ALXN2050 IB.

3. OBJECTIVES AND ENDPOINTS

Table 7: Mapping Objectives to Endpoints

Objectives	Endpoints
Primary (Both Cohorts)	
To evaluate the efficacy of ALXN2050 to reduce proteinuria in participants with LN or IgAN	Percentage change in proteinuria from baseline to Week 26 (based on 24-hour urine collection[s])
Secondary (Both Cohorts)	
To evaluate the efficacy of ALXN2050 to improve measures of kidney function in participants with LN or IgAN	Percentage change in proteinuria from baseline to Week 50 (based on 24-hour urine collection[s])
	Achieving > 30% and > 50% reduction in proteinuria at Week 26 and Week 50 compared to baseline (based on 24-hour urine collection[s] at each time point)
	Change from baseline in eGFR at Week 26 and Week 50
Secondary (LN Cohort Only)	
To evaluate the efficacy of ALXN2050 on measures of kidney function in participants with LN	Meeting the criteria for CRR at Week 26 and Week 50 (as defined in Section 8.1.10)
	Meeting the criteria for PRR at Week 26 and Week 50 (as defined in Section 8.1.10)
	Time to the first occurrence of UPCR ≤ 0.5 g/g as measured by spot urine sample
	Achieving corticosteroid taper to 7.5 mg/day at Weeks 12, 26, and 50
	Experience of a Renal Flare (as defined in Section 8.1.6) through Week 50
	Experience of an Extrarenal SLE Flare (as defined in Section 8.1.7) through Week 50
	Meeting the criteria for Treatment Failure (as defined in Section 8.1.9) through Week 50
	Meeting the criteria for 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 ALXN2050 on measures of kidney function in participants with IgAN	Meeting the criteria for Partial Remission at Week 26 and Week 50 (as defined in Section 8.1.11)

Table 7: Mapping Objectives to Endpoints

Objectives	Endpoints
PK/PD (Both Cohorts)	
To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of ALXN2050 in participants with LN or IgAN	Observed plasma concentrations of ALXN2050 over time
	Absolute values and change from baseline in plasma Bb concentration and serum AP activity over time
Safety (Both Cohorts)	
To characterize the safety and tolerability of ALXN2050 in participants with LN or IgAN	Incidence of TEAEs and TESAEs over time
	Changes from baseline in laboratory assessments
Exploratory (Both Cohorts)	
To assess the efficacy of ALXN2050 in exploratory efficacy endpoints	Percentage change in proteinuria from baseline to Week 102 and Week 154 (based on 24-hour urine collection[s])
	Change from baseline in eGFR at Week 102 and Week 154
To evaluate the efficacy of ALXN2050 on hematuria in 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 • Achieving < 10 RBC/hpf
To assess quality of life based on participant-reported outcomes in participants with LN or IgAN based on treatment with ALXN2050	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 biomarkers such as complement, autoimmune, and renal in participants with LN or IgAN	Absolute values and change from baseline in levels of biomarkers in blood and urine over time
Exploratory (LN Cohort Only)	
To assess the efficacy of ALXN2050 in exploratory efficacy endpoints	Time to the first CRR or PRR (using spot UPCR)
	Meeting the criteria for Overall Renal Response (CRR or PRR) at Week 26 and Week 50
	Time to the first occurrence of UPCR > 50% decrease from baseline (using spot UPCR)
To assess quality of life based on participant-reported outcomes	Change from baseline in FACIT-Fatigue total score at Week 26 and Week 50
To assess the efficacy of ALXN2050 in other exploratory endpoints	Histology changes from baseline to Week 50, if tissue is available

Table 7: Mapping Objectives to Endpoints

Objectives	Endpoints
	Absolute values and change from baseline in anti-dsDNA and anti-C1q antibodies at Week 26 and Week 50
Exploratory (IgAN Cohort Only)	
To assess the efficacy of ALXN2050 in exploratory efficacy endpoints	Slope of eGFR computed from baseline to Week 26 and Week 50

Abbreviations: AP = alternative pathway; anti-C1q = anti-C1q complement component ; anti-dsDNA = anti-double-stranded DNA; Bb = Bb fragment of complement factor B; CRR = complete renal response; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life Health 5-item questionnaire dimensions 5 level; FACIT = Functional Assessment of Chronic Illness Therapy; hpf = high-power field; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PRR = partial renal response; RBC = red blood cell; SLE = systemic lupus erythematosus; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; SF-36 = Short Form (36) Health Survey; UPCR = urine protein to creatinine ratio

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study of ALXN2050 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.

- Participants in the LN cohort must have a diagnosis of LN with an active flare based on kidney biopsy, eGFR > 30 mL/min/1.73 m^2, and proteinuria defined as UPCR ≥ 1 g/g from one 24-hour urine collection.
- Participants in the IgAN cohort must have a diagnosis of IgAN based on kidney biopsy, eGFR > 30 mL/min/1.73 m^2, and proteinuria defined as mean protein ≥ 1 g/24 hours from 2 valid 24-hour urine collections (Section 8.1.1). Participants 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 Blinded Initial Evaluation Period, a 24-week Blinded Extended Treatment Period, and an OLE Period of up to 2 years. Upon completion of the OLE Period or if a participant decides to withdraw from the study, all participants will be followed for safety for 30 days after the last dose of study intervention. Thus, the total treatment duration is 154 weeks, and the total study duration is up to 164 weeks.

All participants will continue to receive allowed concomitant therapy consistent with the standard of care for participants with LN and IgAN throughout the study. Participants in the LN cohort will receive additional standard of care therapy in the event of a protocol-defined Renal Flare or Extrarenal SLE Flare and after Week 26, for Suboptimal Response. Approved novel treatments for LN can be used per the Investigator's discretion. However, if additional standard of care therapy is initiated, the Investigator should consult the list of disallowed medications (Section 6.5.2). If the additional standard of care therapy is a prohibited medication, study intervention should be discontinued at least 3 days prior to initiation of the additional standard of care therapy.

See study design schematics in Figure 1 and Figure 2 for LN and IgAN cohorts, respectively.

4.1.1. Screening

Participants will be screened for eligibility for up to 6 weeks during the Screening Period. 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.

4.1.2. Blinded Initial Evaluation Period

Approximately 126 adult participants with either LN or IgAN will be randomized into the study on Day 1 (approximately 70 participants in the LN cohort and approximately 56 participants in the IgAN cohort), as follows:

- For each disease cohort, participants meeting eligibility criteria will be randomly assigned in a 3:1:3 ratio to receive ALXN2050 180 mg bid, ALXN2050 120 mg bid, or placebo bid (Table 8).
- For the IgAN cohort, participants assigned to the placebo group will also be assigned to their study treatment for the Blinded Extended Treatment Period (ALXN2050 180 mg bid or ALXN2050 120 mg bid) in a 1:1 allocation ratio at the time of randomization.

Table 8: Summary of Participants in Each Treatment Group During the Blinded Initial Evaluation Period

Treatment Group	LN Cohort	IgAN Cohort
	Approximate Number of Participants	Approximate Number of Participants
ALXN2050 180 mg bid	30	24
ALXN2050 120 mg bid	10	8
Placebo bid	30	24

Abbreviations: bid = twice daily; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis

Stratification will be performed as follows:

- For the LN cohort: by whether corticosteroid induction treatment was initiated prior to Screening versus during the Screening Period.
- For the IgAN cohort: by mean proteinuria (1 to 2 g/day versus > 2 g/day) from 2 valid 24-hour urine collections during the Screening Period.

After completion of the Day 1 Visit assessments, participants will receive the first dose of study intervention prior to leaving the clinic. Participants will continue to receive bid doses of study intervention throughout the Blinded Initial Evaluation Period (Table 11).

4.1.3. Blinded Extended Treatment Period

After completion of the Blinded Initial Evaluation Period (Week 26 Visit), participants will continue to receive study intervention during a Blinded Extended Treatment Period for 24 weeks as follows:

- Participants in the LN cohort will continue to receive their randomized allocation of study intervention (ALXN2050 180 mg, ALXN2050 120 mg, or placebo) bid. 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.
- Participants in the IgAN cohort randomized to active treatment will continue to receive their randomized allocation of study intervention (ALXN2050 180 mg or ALXN2050 120 mg) bid.

- Participants in the IgAN cohort randomized to the placebo group will receive either ALXN2050 180 mg bid or ALXN2050 120 mg bid as assigned at the time of randomization.

4.1.4. Open-label Extension Period

After completion of all assessments at the end of the Blinded Extended Treatment Period (Week 50 Visit), all participants will have the opportunity to enter an OLE Period and receive ALXN2050 for up to 2 years (104 weeks) if no relevant side effects (in the opinion of the Investigator) and no Treatment Failure (LN cohort) are present. During the OLE Period:

- Participants in the LN cohort randomized to the active treatment groups will continue to receive the same dosing regimen as assigned during the Blinded Extended Treatment Period.
- Participants in the LN cohort randomized to the placebo group will no longer receive placebo and will continue to receive allowed concomitant therapy alone. These participants will have the option to receive ALXN2050 180 mg bid or the optimal dose (if already identified) if the participant has a Renal Flare as defined in Section 8.1.6 or Suboptimal Response as defined in Section 8.1.8.
- Participants in the IgAN cohort will continue to receive the same dosing regimen as assigned during the Blinded Extended Treatment Period.
- Participants in both cohorts receiving ALXN2050 who complete at least 50 weeks of treatment will receive the optimal dose level of ALXN2050 (180 mg or 120 mg bid) once an optimal dose is identified based on results of the primary analysis at Week 26 and/or Data Monitoring Committee (DMC) review of the safety and efficacy data.
- Percentage change in proteinuria from baseline and change from baseline in eGFR at Weeks 102 and Week 154 will be assessed as exploratory efficacy endpoints. Safety and tolerability will also be evaluated continually throughout the OLE Period.

After completion of the study or after ED, a Safety Follow-up Visit will be conducted 30 days after the last dose of study intervention.

4.1.5. 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.

Remote visit options may be available at the Investigator's discretion and oversight, in accordance with the local regulations. Remote visit options may include visits conducted at the participant's home, 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 SoA (Section 1.3), whenever possible. Information about adverse events (AEs), concomitant medications, allowed concomitant therapies, and disease-related signs or symptomatology must be sent to the Investigator for evaluation on the day of the remote visit. In case of any signs or symptoms indicating a serious adverse event (SAE), the participant will need to be evaluated at the study site.

4.2. Scientific Rationale for Study Design

Justification for specific design elements is provided in Table 9.

Table 9: Scientific Rationale for the Design of Study ALXN2050-NEPH-201

Design Element	Rationale
Target populations	Glomerular diseases such as LN and IgAN continue to respond poorly to treatment, resulting in CKD over time. While there has been some progress in terms of approved treatments with 2 recent approvals in some countries for patients with LN (ie, belimumab and voclosporin) and IgAN (budesonide), there remains a significant unmet need for novel interventions which would allow more definitive treatments for LN as well as disease-specific treatments for patients with IgAN, particularly in patients who are at risk of progressive kidney disease. See Section 2.2.3 and Section 2.2.4.
Randomized, double-blind, placebo-controlled	A randomized, double-blind, placebo-controlled study design in addition to allowed concomitant therapy consistent with the standard of care is selected to provide the most robust evidence of the efficacy of ALXN2050 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 true treatment effect of ALXN2050 by minimizing the risk of selection bias.
Randomization stratum	A single randomization stratum was selected for each cohort to ensure equal distribution of baseline characteristics that may impact the endpoints. See Section 6.3.1.
Selection of 2 dose levels (ALXN2050 180 mg bid and ALXN2050 120 mg bid)	The optimal dose of ALXN2050 in glomerular diseases is not known. Thus, participants will be randomized to a high-dose group (180 mg bid), a low-dose group (120 mg bid), or a placebo group in a 3:1:3 allocation ratio. The primary analysis will compare the high-dose treatment group to the placebo treatment group. A smaller number of participants will be randomized to the low-dose treatment group to collect supportive data that will be summarized descriptively. Given the unknown degree of AP inhibition required to achieve clinical efficacy in these indications and to ensure robust AP inhibition in a majority of patients, 180 mg bid was chosen for the high-dose group. See Section 4.3.
Primary endpoint (proteinuria)	Change in proteinuria is considered a valid surrogate endpoint for kidney survival in glomerular diseases. See Section 4.2.1.
Safety endpoints	The safety parameters being evaluated are commonly used in clinical studies per ICH and GCP guidelines.

Table 9: Scientific Rationale for the Design of Study ALXN2050-NEPH-201

Design Element	Rationale
Duration of study	The 26-week initial 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 Extended Treatment Period and OLE Period will facilitate collection of longitudinal efficacy and additional safety data of ALXN2050 for all participants.

Abbreviations: AP = alternative pathway; bid = twice daily; CKD = chronic kidney disease; GCP = Good Clinical Practice; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis; OLE = Open-label Extension

4.2.1. Rationale for Primary Endpoint

The primary endpoint for the study is percent change from baseline to Week 26 in 24-hour 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 (NKF) in collaboration with the US Food and Drug Administration (FDA) and the European Medicines Agency (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% to 30% relative treatment effect over standard of care in change in proteinuria is considered clinically relevant (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 ALXN2050 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 ALXN2050 will provide participants who respond to FD inhibition sufficient time to achieve reduction of proteinuria.

Currently, the most precise method for measuring proteinuria is a complete 24-hour urine collection.

Proteinuria is further justified as an endpoint in this Phase 2 study because ALXN2050 has potential for 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 an eGFR of > 30 mL/min/1.73 m^2 is required for both disease cohorts. Finally, although treatment response in patients with LN is traditionally defined by stratification into complete and partial response, there is no consensus definition across guidelines, and proteinuria is the most important clinical variable used to define response (Parikh, 2016). In fact, a retrospective analysis of 1-year clinical response metrics from the Euro Lupus Nephritis Trial demonstrated proteinuria < 800 mg/day at 1 year to be the best predictor of good long-term renal outcome. The addition of serum creatinine level and microscopic hematuria did not improve the prediction model (Parikh, 2020).

4.3. Justification for Dose

Clinical pharmacokinetics (PK) and PD data have been generated for ALXN2050 in single-ascending and multiple-ascending dose studies in healthy volunteers (Studies ACH228-001 and ACH228-002). In these clinical studies, ALXN2050 demonstrated a dose-proportional increase in systemic exposure following single-dose administration and a greater than dose-proportional increase following multiple-dose administration at steady state (Days 7 and 14) over the dosing range of 40 mg bid to 200 mg bid. Large intersubject variability was observed.

Following multiple-dose administration of ALXN2050 ranging from 40 mg bid to 200 mg bid in healthy participants, PD activity (determined by AP inhibition in the AP Wieslab assay) increased with increasing dose. The 120 mg bid dosing regimen provided sustained AP inhibition (AP activity < 10%) in healthy participants whose ALXN2050 concentrations achieved the 90% inhibitory concentration (IC_{90}) threshold through the 12-hour dosing periods. Therefore, 120 mg bid is selected as the minimum therapeutic dose. Intersubject variability in PK and PK-PD relationship indicated that a dose higher than 120 mg bid (such as 180 mg bid) may be required to ensure more participants reach and maintain ALXN2050 concentration above the threshold for 90% AP inhibition. In addition, it is expected that FD baseline levels will be elevated in patients who exhibit reduced kidney function, which would raise the ALXN2050 threshold concentration required for 90% inhibition of AP activity in patients with either LN or IgAN. Therefore, the 180 mg bid is selected as the likely therapeutic dose.

In a multiple ascending dose study, the 120 and 200 mg bid dose regimens were safe and effective, showing an approximately 10-fold or greater safety margin in both maximum plasma concentration observed after study intervention administration (C_{max}) and the area under the concentration-time curve from time zero to 24 hours (AUC_{0-24}) over the exposures achieved at the no observed adverse effect level (NOAEL) from nonclinical chronic toxicology studies (see ALXN2050 IB). In addition, both dosage regimens provided complete (> 90%) and sustained inhibition of AP activity throughout the 12-hour dosing interval. Therefore, 120 mg bid is selected as the minimum therapeutic dosage.

Based on the favorable clinical safety and tolerability data from these studies, and the PK and PD characterization of ALXN2050, the dosing regimens of 120 mg bid and 180 mg bid are proposed for this dose-finding study in participants with LN or IgAN. The exposure range generated by the proposed ALXN2050 120 mg bid and 180 mg bid dosing is expected to be adequate to establish the PK-PD relationship in participants with LN or IgAN, thereby setting up the basis for dose selection in the planned Phase 3 study.

The optimal dose will be identified as the dose with the best benefit to risk ratio based on PK/PD modeling, safety, and efficacy data.

4.4. Definition of Study Periods and End of Study

The Screening Period is up to 6 weeks (Table 1 [LN cohort] and Table 2 [IgAN cohort]).

The Blinded Initial Evaluation Period is from Day 1 to Week 26 (Table 1 [LN cohort] and Table 2 [IgAN cohort]).

The Blinded Extended Treatment Period starts with dosing of study intervention at the Week 26 (Day 183) Visit and continues through the Week 50 (Day 351) Visit (Table 3 [LN cohort] and Table 4 [IgAN cohort]).

The OLE Period begins after the Week 50 Visit and continues up to 2 years (Table 5).

The Safety Follow-up Period is 4 weeks after the last dose of study intervention and includes a Safety Follow-up Visit 30 (± 3) days after the last dose.

A participant is considered to have completed the study:

- If he/she has completed all periods of the study, including the OLE Period and the last scheduled procedure shown in the SoA
- In the event the study is stopped early, the participant has completed all applicable periods of the study, including the Early Discontinuation (ED) and Safety Follow-up Visits
- The participant completes the study early because the study intervention is registered or approved (in accordance with country-specific regulations)

Early termination or discontinuation: A participant is considered to terminate early from the study if the participant is discontinued from the study during the Blinded Initial Evaluation Period, Blinded Extended Treatment Period, or OLE Period.

End of study: The end of study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

Refer to the SoA in 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

A participant must meet all inclusion criteria to be eligible to participate in the study.

5.1.1. Inclusion Criteria for Both Cohorts

Age

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

Sex

2. Male or female participant.
3. Female participants of childbearing potential and male participants must follow protocol-specified contraception guidance as described in Section 10.5.2.

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. Vaccinated against meningococcal infection (*Neisseria meningitidis*) within 3 years prior to, or at the time of randomization. Participants who initiate study intervention < 2 weeks after receiving a meningococcal vaccine must receive appropriate prophylactic antibiotics until at least 2 weeks after the vaccination.

Disease Characteristics

6. Local pathology report from the kidney biopsy (Section 8.12.5) used for eligibility must be available.

Prior/Concomitant Therapy

7. 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 Blinded Treatment Periods (through Week 50).

5.1.2. Inclusion Criteria Specific for LN Cohort

Disease Characteristics

8. Clinical diagnosis of SLE by 2019 ACR and EULAR criteria (Section 10.7).
9. Diagnosis of 2018 Revised ISN/RPS classification (active focal or diffuse proliferative LN Class III or IV; Section 10.8) 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.

10. Clinically active LN at Screening requiring/receiving immunosuppression induction treatment in the opinion of the Investigator.
11. Proteinuria with UPCR ≥ 1 g/g based on one 24-hour urine collection during the Screening Period.

5.1.3. Inclusion Criteria Specific for IgAN Cohort

12. Established diagnosis of primary IgAN based on kidney biopsy (Section 10.9) obtained any time prior to or during the Screening Period.
13. Mean proteinuria ≥ 1 g/day on 2 complete and valid 24-hour urine collections during the Screening Period.
14. For participants with a kidney biopsy performed > 1 year prior to Screening that was used for eligibility:
    - Presence of hematuria as defined by a positive result for blood on urine dipstick or ≥ 10 red blood cells (RBCs)/high-power field (hpf) microscopy on urine sediment (documented by the local laboratory) during Screening Period. Presence of hematuria documented by the central laboratory may also be acceptable.
15. Compliance with stable and optimal dose of RAS inhibitor treatment including maximum allowed or tolerated ACE inhibitor and/or ARB dose for ≥ 3 months prior to Screening with no expected change in dose during the Blinded Treatment Periods (through Week 50) (participants with established intolerance to RAS inhibitors may be included).
16. Controlled and stable blood pressure (defined as < 140/90 mmHg) over the past 3 months prior to randomization.

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria for Both Cohorts

A participant will be excluded from the study if any of the following criteria apply.

Disease Characteristics

1. Estimated GFR ≤ 30 mL/min/1.73 m^2 during Screening calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)
2. For participants 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 to 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 solid organ (kidney, heart, lung, small bowel, pancreas, or liver) or bone marrow transplant, or planned transplant during the Blinded Extended Treatment Period (50 weeks)

Medical Conditions

5. Splenectomy or functional asplenia
6. History of seizure
7. Known or suspected complement deficiency, unless attributable to underlying disease (ie, LN and IgAN)
8. History or presence of any risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of Long QT Syndrome), a screening QT interval corrected using Fridericia's formula (QTcF) > 450 msec for males and > 470 msec for females, or receiving medications known to significantly prolong the corrected QT interval (QTc), except for hydroxychloroquine in patients with LN
9. Laboratory abnormalities at Screening, including:
   - Alanine aminotransferase (ALT) > 2 × the upper limit of normal (ULN)
   - Direct bilirubin > 2 × ULN
10. Hemoglobin A1C at Screening > 7.0%
11. Any other clinically significant laboratory abnormality that, in the opinion of the Investigator, would make the participant inappropriate for the study or put the participant at undue risk
12. 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
13. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of the Screening Period
14. History of hypersensitivity to any ingredient contained in the study intervention, including inability to take or tolerate the allowed concomitant therapies consistent with the standard of care (Section 6.5.3), with the exception of RAS inhibitors for the IgAN cohort (inclusion criterion 15).
15. History of malignancy within 5 years prior to Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence
16. Evidence of hepatitis B (positive hepatitis surface antigen [HBsAg] or positive core antibody (anti-HBc) with negative surface antibody [anti-HBs]) or hepatitis C viral infection (hepatitis C virus [HCV] antibody positive, except for patients with documented successful treatment and documented sustained virologic response [SVR]) at Screening
17. Evidence of human immunodeficiency virus (HIV antibody positive) infection at Screening

18. Bone marrow insufficiency with absolute neutrophil count < $1.3 \times 10^3/\mu L$; thrombocytopenia (platelet count < $50,000/mm^3$)
19. Active systemic bacterial, viral, or fungal infection within 14 days prior to first dose of study intervention
20. Presence of fever as documented by a temperature ≥ 38°C (100.4°F) within 7 days prior to administration of study intervention on Day 1
21. History of *Neisseria meningitidis* infection

Prior/Concomitant Therapy

22. Current treatment with a biologic medication that may affect immune system functioning, or has stopped treatment with a biologic medication that may affect immune system functioning, and 5 terminal half-lives of the biologic medication have not elapsed by the time of the Screening Visit, or treatment with belimumab or rituximab ≤ 6 months prior to Screening
23. Any previous or current treatment with complement inhibitors (eg, eculizumab, ravulizumab)
24. Use of known cytochrome P450, family 3, subfamily A (CYP3A) sensitive substrates, moderate or strong CYP3A inducers, and/or moderate or strong CYP3A inhibitors from 2 weeks or 5 half-lives, whichever is longer, prior to the first administration of study intervention on Day 1 (randomization). The full list provided in Section 10.16)
25. Use of selected medications known to lower the seizure threshold and/or cause seizure. See Section 10.15 for list of medications

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

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

5.2.2. Exclusion Criteria Specific for LN Cohort

28. Participants who have initiated any of the following treatments for the current active LN flare:
    a. Cyclophosphamide ≤ 6 months prior to Screening
    b. CNIs ≤ 1 month prior to Screening
    c. A cumulative dose of intravenous (IV) methylprednisolone > 3 g
    d. Mycophenolate mofetil > 2 g/day (or equivalent) for ≥ 8 consecutive weeks prior to Screening
    e. Prednisone or prednisone equivalent ≥ 0.5 mg/kg/day for ≥ 8 consecutive weeks prior to Screening
29. Uncontrolled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg) on 2 or more measurements during the Screening Period

30. Prior history or clinically active SLE related cerebritis, seizures, stroke, or stroke syndrome requiring treatment or clinically active pericarditis
31. Inability to take or tolerate the allowed concomitant therapies consistent with the standard of care.

5.2.3. Exclusion Criteria Specific for IgAN Cohort

32. Diagnosis of rapid progressive glomerulonephritis as measured by eGFR loss ≥ 30% over a period of 3 months prior to or during the Screening Period
33. Secondary etiologies of IgAN (eg, SLE, cirrhosis, celiac disease)
34. Clinically active Henoch-Schonlein purpura (IgA vasculitis) requiring treatment
35. 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
36. Blood pressure of ≥ 140/90 mmHg during the Screening Period confirmed on 2 measures > 30 minutes apart
37. Body mass index ≥ 38 kg/m^2 during Screening

5.3. Lifestyle Considerations

Certain foods such as grapefruit have been shown to be inhibitors of CYP3A4 enzyme activity. Participants should refrain from consuming these foods and beverages from 2 weeks prior to the first administration of study intervention on Day 1 until 2 weeks after the final dose of study intervention.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor.

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.

6.1. Study Intervention(s) Administered

The interventions in this study are ALXN2050 and matching placebo. Study interventions are presented in Table 10. Allowed concomitant therapies are discussed in Section 6.5.3.1 and Section 6.5.3.2 for the LN and IgAN cohorts, respectively.

Table 10: Study Interventions

Study Intervention Name	ALXN2050	Placebo
Dose formulation	Tablet	Tablet
Physical description	Round, white to off-white film coated tablet	Round, white to off-white film coated tablet
Unit dose strength(s)	60 mg	Placebo
Dosage levels	120 mg bid or 180 mg twice daily	Not applicable
Route of administration	Oral	Oral
IMP or AxMP	IMP	IMP
Use	Experimental	Placebo comparator
Former Name	ACH-0145228	Not applicable
Sourcing	Alexion Pharmaceuticals, Inc.	Alexion Pharmaceuticals, Inc.

Abbreviations: AxMP = auxiliary medicinal product; bid = twice daily; IMP = investigational medicinal product

Participants will take study intervention bid (a dose of 3 tablets in the morning and a second [evening] dose of 3 tablets approximately 12 hours after the morning dose). Doses should be taken at approximately the same time each day. If a dose is missed, it should be taken within 6 hours of the originally scheduled time. After 6 hours, the missed dose should be skipped. In either case, the next dose should be taken according to the original dosing schedule. Information on missed doses should be recorded in the electronic case report form (eCRF).

Most doses will be taken outside of the clinic. Participants will be provided with sufficient study intervention to last until their next study visit.

For study visits that require PK sample collection, participants will be instructed to abstain from taking their ALXN2050 dose on the mornings of their study visits so that they can be dosed in the clinic following the protocol-required assessments. At the clinic visit, participants will first have blood drawn for clinical laboratory and other evaluations as outlined in the SoA (Section 1.3), then take the morning dose of ALXN2050 assigned for that day.

6.1.1. Blinded Treatment

ALXN2050 and placebo tablets will be identical in appearance. The blinded study interventions are shown in Table 11.

Table 11: Blinded Study Intervention from Week 1 to Week 50 in Addition to Allowed Concomitant Therapy

Timing	Dose Group		
	ALXN2050 120 mg bid	ALXN2050 180 mg bid	Placebo
Morning dose	60 mg	60 mg	Placebo
	60 mg	60 mg	Placebo
	Placebo	60 mg	Placebo
Approximately 12 hours interval			
Evening dose	60 mg	60 mg	Placebo
	60 mg	60 mg	Placebo
	Placebo	60 mg	Placebo

Abbreviation: bid = twice daily

6.1.2. Study Intervention(s) Packaging and Labeling

Study intervention will be provided in tamper proof containers that will be labeled according to country-specific regulations. At a minimum, the container will be labeled with:

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

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Preparation

The study intervention will be provided by Alexion; no specific preparation instructions are required.

6.2.2. Storage and Handling

ALXN2050 and matching placebos must be stored at room temperature (15°C to 30°C; 59°F to 86°F).

Study intervention will be shipped directly to each investigational site. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before dispensation of the study intervention.

Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

6.2.3. Accountability and Disposal

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

- This responsibility includes the reporting of any temperature excursions and product complaints to AlexionIMPTE@alexion.com and productcomplaints@alexion.com within 1 business day of awareness.

  A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.

- The Investigator must maintain adequate records of drug dispensation throughout the study. At a minimum, drug dispensation activities must include recording the date, lot number, quantity of tablets administered to each participant, and information about any used, unused, or expired containers that are destroyed at the site or returned to Alexion.

- At the conclusion or termination of the study, after final accountability for study intervention inventory has been performed by Alexion or designee, the Investigator must ensure used, unused, or expired containers at the site are returned to Alexion or designee in accordance with Alexion instructions or destroyed if the site has appropriate facilities and written procedures to dispose of study intervention.

- 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, and accountability and information for the final disposition of unused study intervention is provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization and Stratification

All participants will be randomized on Day 1 using a centralized interactive response technology (IRT) after the Investigator has verified that they are eligible to participate in the study. After Screening, eligible participants will be assigned to a treatment arm by stratified randomization. For each disease cohort, participants meeting eligibility criteria will be randomly assigned in a 3:1:3 ratio to receive ALXN2050 180 mg bid, ALXN2050 120 mg bid, or placebo bid, respectively (Table 8) during the Blinded Initial Evaluation Period. The LN cohort will continue with the same treatment allocation during the Blinded Extended Treatment Period. For the IgAN cohort, participants assigned to the placebo group will also be assigned to their active study treatment for the Blinded Extended Treatment Period (ALXN2050 120 mg bid or ALXN2050 180 mg bid) in a 1:1 allocation ratio at the time of initial randomization.

The randomization stratum for the LN cohort is as follows:

- Corticosteroid induction treatment initiated (prior to screening, during Screening Period)

The randomization stratum for the IgAN cohort is as follows:

- Mean proteinuria from 2 valid 24-hour urine collections (1 to 2 g/day versus > 2 g/day)

6.3.2. Blinding

All investigational site personnel, other staff directly associated with the conduct of the study, and all participants will be blinded to treatment assignment during the Blinded Initial Evaluation Period and the Blinded Extended Treatment Period. The double-blind will be maintained by using identical study treatment kits and labels for all participants. The placebo tablet will have an identical appearance to that of ALXN2050. The randomization code will be maintained by the IRT provider. Select Alexion staff will be unblinded for the primary analysis at Week 26. All participants, Investigators, and site personnel will remain blinded to treatment assignment from Day 1 through the end of the Blinded Extended Treatment Period (ie, Week 50). After completion of all assessments at the end of the Blinded Extended Treatment Period, participants will begin receiving open-label treatment during the OLE Period and therefore, participants, Investigators, and site personnel will no longer be blinded to the initial treatment assignment. Knowledge of the initial treatment assignment during the OLE Period is not expected to impact the data integrity as the primary and key secondary endpoints have already been collected and due to the objective nature of these endpoints.

6.3.3. Unblinding

During the Blinded Initial Evaluation Period and the Blinded Extended Treatment Period, unblinding should only be considered for the safety of the participant. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator will be able to unblind the participant's treatment allocation directly using the IRT. If a participant'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.

In the event of a suspected unexpected serious adverse reaction (SUSAR), 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 (eg, monitors, Investigators) and those responsible for data analysis and interpretation of results, such as biometrics personnel.

Unblinded information will only be accessible to those who are involved in safety reporting to Health Authorities, IECs, and/or IRBs.

Any participant who is unblinded during the blinded periods will be withdrawn from the study.

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

6.4. Study Intervention Compliance

When participants are dosed at the investigational site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and in the eCRF.

When participants self-administer study intervention at home, compliance with the study intervention will be assessed by direct questioning and counting of returned tablets during the next in-clinic visit and recorded in the source documents. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of study intervention dispensed and administered to/taken by each participant must be maintained and reconciled with study intervention records provided to the investigational site. Intervention start and stop dates, including dates for planned and unplanned intervention delays and/or dose reductions will also be recorded.

6.5. Prior and Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), vaccines, or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

Nonpharmacologic treatments and therapies that the participant receives during the clinical study must be recorded along with:

- Reason for use
- Dates of administration, including start and end dates
- Diagnostics administered, if applicable
- Whether the treatment is ongoing

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

6.5.1. Allowed Medications and Therapy

Allowed concomitant therapy is discussed in Section 6.5.3.1 (LN cohort) and Section 6.5.3.2 (IgAN cohort).

Any medication or therapy (including over-the-counter or prescription medicines, vaccines, vitamins, and/or herbal supplements) deemed necessary for the participant's care during the study, or for the treatment of any AE, along with any other medications, other than those listed as disallowed medications in Section 6.5.2, may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF (Section 8.2.5).

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 through Week 50. 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. However, these can be used if indicated for symptomatic relief for a short period of time (up to a maximum of 7 days per the labeled usage; if an increased dose/treatment duration is required, the Investigator must discuss with the Sponsor).

For participants in the LN cohort only:

- *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 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.

6.5.2. 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
- A complement inhibitor (eg, eculizumab, ravulizumab)
- New use or modification of the dose of SGLT-2 inhibitors (up to 50 weeks)
- New use or modification of the dose of RAS inhibitor or direct renin antagonist treatment (up to 50 weeks)
- Known CYP3A sensitive substrates, moderate or strong CYP3A inducers, and/or moderate or strong CYP3A inhibitors are prohibited throughout the study, until 1 week after the final administration of study intervention (see Section 10.16 for a full list of these medications)

- Selected medications known to lower the seizure threshold and/or cause seizure should not be taken concomitantly (see Section 10.15 for a full list of these medications)
- Medications known to significantly prolong the corrected QT interval (QTc), with the exception of hydroxychloroquine in patients with LN

In the event that a participant receives a prohibited medication and/or therapy, the Investigator will consider the discontinuation of study intervention (Section 7.1). SGLT-2 inhibitors, RAS inhibitors, and direct renin antagonists are prohibited but may be considered without discontinuation of study intervention 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)

For participants in the LN cohort, escalation of immunosuppression is allowed for protocol-defined Renal, Extrarenal Flares, and Suboptimal Response (after Week 26). CNIs including, but not limited to voclosporin, are prohibited. If a CNI is used as additional standard of care therapy per the clinical judgment of the Investigator, ALXN2050 will need to be discontinued 3 days prior to CNI administration. However, the participant can remain in the study and continue the study visits as per the SoA.

Any medications not specified in this section, that remain a concern to the Investigator should be discussed with the Medical Monitor.

6.5.3. Allowed Concomitant Therapy

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

6.5.3.1. 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 g 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 12. The starting minimum and maximum doses allowed are

30 mg/day and 60 mg/day, respectively. A corticosteroid taper will commence at Week 2 (Day 14). 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.

  - 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 titrated per the discretion of the Investigator to a cumulative dose up 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 1.5 to 3 g/day of MMF until Week 50, after which it may be decreased or discontinued based on the Investigators' judgment and the KDIGO clinical practice guidelines (KDIGO, 2012).

- For participants who have initiated corticosteroid induction treatment prior to Screening and do not meet Exclusion Criterion 28 (Section 5.2):
  - If the participant already received methylprednisolone IV $\geq$ 1 g or equivalent oral corticosteroid induction and is receiving MMF $\geq$ 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 Blinded Initial Evaluation Period the dose of MMF should be adjusted to achieve 1.5 to 3 g/day no later than Day 28 (Week 4). MMF will be continued at 1.5 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, 2012).
  - If the participant already received methylprednisolone IV $\geq$ 1 g or equivalent oral corticosteroid induction 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 1.5 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 1.5 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, 2012).
  - 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 doses allowed are 30 mg/day and 60 mg/day, respectively) as outlined in Table 12. The prednisone dose will be tapered starting at 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 12: Corticosteroid Taper for Participants with Lupus Nephritis

Study Week	Prednisone Dose or Equivalent Dose (mg/day)			
	≤ 60 kg	61 to 80 kg	81 to 100 kg	≥ 100 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] Weight at Screening will be used for dosing, and this weight category will be used throughout the study. 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.

- An equivalent dose of enteric-coated mycophenolic acid sodium (MPS) may be used instead of MMF (ie, a 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. If the participant's symptoms resolve, the Investigator should attempt to increase MMF (or equivalent) to the goal level of 1.5 to 3 g/day. If symptoms return, then the participant should be continued on the highest tolerable dose.
- Changes to the dose of MMF and the justification will be documented in the eCRF.

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 12). 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 the participant meets the protocol-defined criteria for Renal Flare (Section 8.1.6) and/or severe Extrarenal SLE Flare (Section 8.1.7), in which case these participants will receive additional standard of care therapy and will be included as treatment failures.

6.5.3.2. 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 maximumly tolerated dose of RAS-blocking agents, such as ACEis or ARBs.

The allowed concomitant treatment should be held stable throughout the first 50 weeks of the Treatment Period of the study.

6.5.4. Additional Standard of Care Therapy for LN Cohort

In the LN cohort, participants who meet criteria for protocol-defined Renal Flare (Section 8.1.6) will receive additional standard of care therapy.

Participants in the LN cohort who meet the criteria for Extrarenal SLE Flare (Section 8.1.7) may receive additional standard of care therapy, if considered clinically appropriate by the Investigator. If additional standard of care therapy is administered for an Extrarenal SLE Flare, the event is considered a severe Extrarenal SLE Flare.

After Week 26, additional standard of care therapy for participants with Suboptimal Response (Section 8.1.8) is allowed at the clinical discretion of the Investigator in conversation with the Medical Monitor.

Additional standard of care therapy, all flares, and Suboptimal Response will be documented in the eCRF.

Additional standard of care therapy is defined as intensification of current standard of care or introduction of new immunosuppressive therapies. The specific choice of additional standard of care therapy is generally at the discretion of the Investigator and may include approved medications for LN (eg, voclosporin, belimumab). However, if a CNI is used as additional standard of care therapy, ALXN2050 will need to be discontinued 3 days prior to CNI administration (Section 6.5.2).

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

- Participants with protocol-defined Renal Flare may be treated with oral 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 Extrarenal SLE Flare may be treated with oral 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 8.1.6).
- Other medical conditions or surgery

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

6.5.5. Vaccination and Antibiotic Prophylaxis

To mitigate the potential risk of meningococcal infection, all participants must be vaccinated within 3 years prior to, or at the time of, initiating the study intervention. Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes. Participants who initiate study intervention treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination.

Participants must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors. Vaccination may not be sufficient to prevent meningococcal infection. All participants should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

Any participant without sufficient history of these vaccines may be vaccinated or provided boosters per national or local guidelines.

Given the chronic progression of IgAN, in participants with IgAN, every effort should be made to start the meningococcal vaccination series at least 14 days prior to randomization.

Participants should be vaccinated or revaccinated against other pathogens according to current national vaccination guidelines or local practice for vaccination use as part of standard of care.

6.6. Dose Modification

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

Once the optimal dose of ALXN2050 is determined, participants on ALXN2050 who have completed at least 50 weeks of treatment will be switched to the optimal dose as indicated in Figure 1 (for LN cohort) and Figure 2 (for IgAN).

6.7. Intervention After the End of the Study

After a participant completes the OLE Period or withdraws from the study, study intervention will not be administered.

Upon completion of the last study visit, participants will return to the care of their treating physician.

6.8. Treatment of Overdose

For this study, any blinded dose of investigational medicinal product (IMP) or Alexion auxiliary medicinal product (AxMP) greater than that specified in the protocol will be considered an overdose.

Alexion does not recommend specific treatment for an overdose. General supportive measures are recommended.

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/treating physician should:

1. Capture and forward the event, with or without associated AEs, to Alexion Global Patient Safety (GPS) 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.
2. Contact the Medical Monitor immediately.
3. 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.
4. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
5. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
6. Document the quantity of the excess dose as well as the duration of the overdose.

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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants must be considered for discontinuation from study intervention if any of the following occur during the study:

- Severe hypersensitivity reaction.
- Severe uncontrolled infection.
- Development of seizures (Section 10.14).
- Use of disallowed medication (as defined in Section 6.5.2) to be considered on a case-by-case basis.
- Participants in the LN cohort receiving hydroxychloroquine will be withdrawn if a QT/QTc interval > 500 msec or an increase > 60 msec from baseline occurs and is confirmed on recheck.
- Pregnancy or planned pregnancy. Any female participant who becomes pregnant while participating in the study will discontinue study intervention and will be withdrawn from the study.
- Alexion or the Investigator deems it is necessary for the participant.
- Adverse event that would, in the opinion of the Investigator, make continued treatment with study intervention an unacceptable risk.
- Participants in the LN cohort who have 2 Treatment Failures.

Data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed are provided in the SoA (Section 1.3).

The reason for discontinuation of study intervention will be recorded in the source documents and eCRF.

If the study intervention is definitively discontinued, every effort should be made to have the participant remain in the study and continue the study visits as per the SoA through Week 50 (Section 1.3).

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

- A Safety Follow-up Visit will be performed 30 days following the participant's last dose of study intervention.

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

- ED Visit should be performed as outlined in the SoA (Section 1.3).
- A Safety Follow-up Visit will be performed 30 days following the participant's last dose of study intervention

If a participant discontinues study intervention due to an AE, including SAEs, the event should be followed as described in Section 10.3.3.

7.2. Participant Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.
- The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and eCRF.
- A participant may withdraw from the study at any time at his/her own request.
  - 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 permitted by local requirements.
  - If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- A participant can be withdrawn at any time in the best judgment of the Investigator for safety, behavioral, compliance, or administrative reasons, such as:
  - Pregnancy or planned pregnancy
  - Lack of efficacy
  - Participant noncompliance
  - Intercurrent illness that would affect assessment of clinical status to a significant degree
  - Unacceptable toxicity (including a clinically significant laboratory value) that compromises the participant's ability to continue study specific procedures
  - Any other condition or circumstance that that would jeopardize the welfare of participants were they to continue in the study
- At the time of discontinuing from the study, if possible, an ED Visit should be conducted, as shown in the SoA (Section 1.3). Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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 to reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- 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. Eligibility, study administrative, and screening assessments are further discussed in Section 8.12.
- 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 (Section 1.3).
- See Section 10.2 for the list of clinical laboratory tests (that will be conducted at a central/specialty laboratory).

8.1. Efficacy Assessments

8.1.1. 24-Hour Urine Collection for Proteinuria

For the determination of proteinuria, 24-hour urine collections will be obtained at the time points specified in the SoA (Section 1.3) and will be analyzed by a central laboratory. In addition to protein, albumin, sodium, and creatinine will be quantified in each 24-hour urine collection. Both UPCR as well as urine albumin to creatinine ratio (UACR) will be calculated using an aliquot of the 24-hour urine collections.

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 administration of study intervention 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 eCRF according to the eCRF completion guidelines.

8.1.1.1. 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). Additional 24-hour urine collection is also scheduled for Week 102 and Week 154.

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 8.1.6 and Section 8.1.8).

8.1.1.2. 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). For evaluation of the primary and key secondary endpoints, the two 24-hour urine collections should be obtained within 2 weeks before the Week 26 and Week 50 Visits. Additional 24-hour urine collection is also scheduled for Week 102 and Week 154.

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.

Urine collections will be reviewed by the Medical Monitoring team.

Inadequate collections may need to 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.

8.1.2. Spot Urine Sample (Both Cohorts)

Urinary protein, albumin, and creatinine levels from morning spot urine samples prior to dosing will be measured at the time points specified in the SoA (Section 1.3) to assess the effect of study intervention on UPCR and UACR.

Two consecutive spot urine samples will be obtained for participants in both disease cohorts at Week 16 for the LN cohort and at Week 18 for the IgAN cohort.

The UPCR and UACR results will be recorded in the participant's eCRF.

8.1.3. Estimated Glomerular Filtration Rate (Both Cohorts)

Changes in renal function will be monitored using measurements of eGFR (mL/min/1.73 m^2) and creatinine clearance on a 24-hour urine collection. Serum creatinine will be analyzed as part of the clinical chemistry (Section 10.2) collected predose. The eGFR calculation will be based on the CKD-EPI formula.

For the determination of CRR and PRR in the LN Cohort at Week 26 and Week 50, 2 serum creatinine samples for eGFR will be obtained, the first within 2 weeks prior to each of these study visits and the second on the study visit day. 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 eCRF according to the eCRF completion guidelines.

8.1.4. Hematuria (Both Cohorts)

For participants in both disease cohorts, hematuria from spot urine samples will be evaluated to assess the effect of study intervention 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. Samples should be collected prior to study intervention administration, if applicable.

The local hematuria evaluation by microscopy or urinary dipstick may be used to determine eligibility for the study at Screening for participants with IgAN, if diagnostic biopsy is > 1 year old.

8.1.5. Albumin (LN Cohort Only)

For renal function assessment, samples for serum albumin will be collected as part of the clinical chemistry evaluations described in Section 10.2.

8.1.6. 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 8.1.10), 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 ULN, 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 RBCs/hpf or new RBC casts (based on local laboratory results from at least 2 samples)
    - Kidney biopsy demonstrating LN Class III or IV activity which was conducted since the biopsy used for eligibility
  - Reproducible doubling of the UPCR from a 24-hour urine collection compared with the lowest previous value obtained after the first dose of study intervention.
- **Reproducibility of proteinuria** requires that UPCR from the morning spot urine collection is confirmed by a central lab UPCR based on 24-hour urine collected within 2 weeks.
- **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 (Section 6.5.4). 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 eCRF.

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

The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) is an instrument that assesses the disease activity of SLE. This instrument will be used for the monitoring of Extrarenal SLE Flare in the LN Cohort.

Extrarenal SLE Flare is defined as an increase in SLEDAI-2K Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) Modification ≥ 4 points (see Section 8.11.2) 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. 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 affected participants 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 the Week 26 primary endpoint).
- One corticosteroid treatment will be allowed between Week 26 and Week 46 (4 weeks prior to the Week 50 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).

8.1.8. Suboptimal Response (LN Cohort Only)

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

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

8.1.9. Treatment Failure (LN Cohort Only)

Treatment Failure is defined as the receipt of additional standard of care therapy at any time during the study 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 of 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 intervention and stay in the study. If a participant has 2 Treatment Failures, study intervention discontinuation should be considered (Section 7.1). If a CNI is used for additional standard of care therapy, study intervention will need to be discontinued 3 days prior to CNI administration.

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

Complete Renal Response and 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-hour urine collections obtained within 2 weeks prior to the study visit (Week 26 or Week 50)
- Estimated glomerular filtration rate > 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 8.1.9)

To achieve PRR (Rovin, 2019), participants who did not achieve CRR in the LN cohort must meet all 3 of the following criteria:

- A decrease in UPCR ≥ 50% compared to the baseline value based on mean of two 24-hour urine collections obtained within 2 weeks prior to the study visit (Week 26 or Week 50)
- Estimated glomerular filtration rate > 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 8.1.9)

Overall Renal Response is defined as the composite of CRR and PRR.

8.1.11. Partial Remission (IgAN Cohort Only)

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

8.2. Safety Assessments

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

8.2.1. 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). Height (Screening only) and weight will also be measured and recorded.
- An abbreviated physical examination will include, at a minimum, a body system relevant examination based upon the Investigator's clinical judgment and participant's health status.
- A symptom-based neurologic examination should be performed if the participant has any complaints or clinical findings attributable to the central nervous system, and if positive for findings, a full neurologic examination should be performed as needed (determined by the Investigator) at that assessment time point and at future time points. If a full neurologic examination is required, the Investigator should perform the following evaluations:
  - Mental status
  - Cranial nerve examination
  - Motor examination
  - Gait examination

- Coordination examination
- Sensory examination

8.2.2. Vital Signs

- Body temperature (°C or °F), pulse rate, respiratory rate, systolic and diastolic blood pressure (mmHg), and pulse oximetry will be assessed.
- Blood pressure and heart rate measurements will be assessed with the participant in a seated or supine position using a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and heart rate 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 taken predose at in-clinic dosing visits and before blood collection for laboratory visits and will consist of a single pulse check and a single blood pressure measurement.

8.2.3. Electrocardiograms

- Single 12-lead electrocardiograms (ECGs) will be conducted locally as outlined in the SoA (Section 1.3) to obtain heart rate, PR interval (time from the onset of the P wave to the start of the QRS complex), combination of the Q wave, R wave, and S wave (QRS) interval, QT, and the QTc interval(s). QT interval will be corrected for heart rate using Fridericia's formula.
- Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- The 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.
- Results will be recorded on the eCRF. Clinically significant findings should be recorded on the AE form.

8.2.4. Clinical Safety Laboratory Assessments

- 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 eCRF. 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 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.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be collected in accordance with the Laboratory Manual and the SoA (Section 1.3).
  - Laboratory assessments performed at the institution's local laboratory that require a change in participant management or are considered clinically significant by the Investigator must be recorded in the AE or SAE eCRF. When possible, parameter value outside of the reference range should be entered in a free-text field.
- Repeat laboratory tests may be obtained for safety reasons or for technical issues with the samples

8.2.4.1. 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.

8.2.4.2. Chemistry, Hematology and Coagulation

Blood samples will be collected predose and analyzed for the parameters listed in Section 10.2.

8.2.4.3. Routine Urinalysis and Urine Sediment

Urine samples will be collected at times specified in the SoA and analyzed for the parameters listed in Section 10.2. A microscopic examination of urine samples will be performed if the results of the macroscopic analysis are abnormal. Samples will be obtained from a morning void prior to dosing.

8.2.4.4. Follicle Stimulating Hormone

Follicle stimulating hormone (FSH) may be obtained to confirm postmenopausal status in female participants who are considered postmenopausal. A high FSH level in the postmenopausal range may be used to confirm postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

This test is not needed for men or for women of childbearing potential (WOCBP).

8.2.5. Prior and Concomitant Medications and Procedures

Prior and concomitant medications, including allowed concomitant therapy, will be reviewed as specified in the SoA (Section 1.3).

Prior medications and/or vaccines (including vitamins, herbal preparations, and those discussed in the eligibility criteria [Section 5]) and procedures (eg, surgery, biopsy, physical therapy) that the participant receives or undergoes ≤ 30 days prior to Screening or during the Screening

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

Concomitant medications (including any medication, vitamin, herbal preparation or supplement) and procedures (defined in Section 6.5) are those received on or after the first study intervention 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 nonpharmacologic therapies or changes to concomitant medications and nonpharmacologic therapies since the last visit. Concomitant medications and nonpharmacologic therapies should be recorded in the source documents and the participant's eCRF, 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 6.5.2, 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 eCRF.

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

The Medical Monitor should be contacted if there are any questions regarding concomitant medications or procedures (Section 6.5).

Information on prior use of RAS inhibitors or systemic immunosuppression within 2 years of the Screening Period will be collected. Concomitant use of RAS inhibitors (ACEi and ARB) will be recorded as well. Use of these medications will be recorded in the source documents and the participant's eCRF, including.

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

8.2.6. Pregnancy

A serum or urine pregnancy test will be administered to all female participants of childbearing potential. A negative serum pregnancy test is required at the Screening Visit and a negative urine pregnancy test at Day 1 in order to be considered eligible to continue in the study.

Pregnancy data from female participants and female spouses/partners of male participants will be collected from the first dose of study intervention and at the time points specified in the SoA. Any female participant who becomes pregnant while participating in the study will be discontinued from study intervention (Section 7). If a pregnancy is reported, the Investigator, or designee, must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.5.3.

8.2.7. Participant Safety Card

Before the first dose of the study intervention, a Participant Safety Card will be provided to participants to carry with them at all times. 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. Participants are required to carry the safety card until 30 days after the final dose of study intervention.

8.3. 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, or surrogate).

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

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

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

All AEs and SAEs will be collected from the signing of the ICF until the Safety Follow-up Visit.

All SAEs will be recorded and reported to Alexion 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 the date the investigational site became aware of the event.

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 intervention or study participation, the Investigator must promptly notify Alexion.

8.3.2. 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.

8.3.3. 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.

8.3.4. 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 SUSAR reports (defined in Section 10.3.2) in the format of MedWatch 3500 or Council for International Organizations of Medical Sciences (CIOMS) I Form to health authorities and Investigators as required. Forms submitted to Investigators will be blinded to treatment assignment. In limited circumstances, the blind may be broken in the case of urgent safety issues that could compromise participant safety.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Under the 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.
- In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

8.3.5. Medication Error, Drug Abuse, and Drug Misuse

8.3.5.1. 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 10.4.

8.3.5.2. Medication Error

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

8.3.5.3. Drug Abuse

Drug abuse is the persistent or sporadic intentional, non-therapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired non-therapeutic effect.

8.3.5.4. Drug Misuse

Drug misuse is the intentional and inappropriate use of IMP or Alexion AxMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Alexion AxMP, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

8.4. Pharmacokinetics

- Blood samples will be collected for measurement of concentrations of ALXN2050 before and after administration of study intervention at the time points specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples, including blood volume requirements, will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of ALXN2050. Samples collected for analyses of ALXN2050 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples may be used for research to develop methods, assays for prognosis, diagnostics, and/or treatment monitoring related to LN and/or IgAN, the disease processes, pathways associated with the disease state, and/or mechanism of action of ALXN2050.
- Study intervention concentration information that may unblind the study will not be reported to investigational sites or blinded personnel until the study has been unblinded.

8.5. Pharmacodynamics

- Blood samples for determination of plasma Bb concentration and serum AP activity will be collected before and after administration of study intervention at the time points specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples including blood volume requirements, are provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples will be used to evaluate the PD of ALXN2050. Samples collected for analyses of ALXN2050 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Biomarker information that may unblind the study will not be reported to investigational sites or blinded personnel until the study has been unblinded.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Collection of blood and urine samples for exploratory biomarker research is also part of this study (details provided in Section 10.6). Specific blood and urine biomarkers to be measured are presented in Table 13.

8.7.1. Blood Biomarkers

Blood (serum and 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], Factor Ba)

See Section 10.2 for a list of laboratory tests.

8.7.2. Urine Biomarkers

Urine samples for exploratory research will be collected from all participants during Screening and 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, sC5b-9, Factor Ba)
- Renal injury biomarkers (eg, N-GAL, KIM-1, etc)
- Urinary creatinine

See Section 10.2 for a list of laboratory tests.

8.7.3. Kidney Biopsy Biomarkers

Kidney tissue biopsies will be obtained in the form of unstained tissue slides and stained for the presence of biomarkers which will provide clinical evidence of the disease pathophysiology and response to treatment (Table 13). Some unstained slides may also be used for performing proteomic analysis.

8.7.4. Additional Biomarker Research

Residual blood, urine, and biopsy samples from exploratory biomarkers, PK, and PD as well as residual samples from 24-hour urine collections may be stored for additional method development of assays (eg, prognostic and/or diagnostic tests related to the study intervention

target, disease process, pathways associated with disease state, or other complement-related diseases, and/or mechanism of action of ALXN2050).

Samples may be retained to enable further analysis on ALXN2050 but for no longer than 25 years after termination of the study or other period as per local requirements.

8.8. Immunogenicity Assessments

Immunogenicity is not applicable in this study.

8.9. Health Economics Data and/or Medical Resource Utilization

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

8.10. Participant-reported Outcomes

The following participant-reported outcome (PRO) instruments will be used in this study to capture health-related quality of life (QoL):

- European QoL Health 5-item questionnaire dimensions 5 level (EQ-5D-5L for both cohorts)
- Short Form (SF)-36 Health Survey (for both cohorts)
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (for LN cohort only)

All instruments will be self-reported and administered at visits specified in the SoAs. Information about these instruments and questionnaires, with the correct version and the validated language versions, if needed, will be provided to the sites prior to the start of the study. See Section 10.10.

8.11. Other Exploratory Assessments

8.11.1. Autoantibodies (LN Cohort Only)

Blood samples will be collected for autoantibodies (eg, anti-dsDNA and anti-C1q autoantibodies, among others) during Screening and according to the SoA (Section 1.3).

See Section 10.2 for a list of laboratory tests.

8.11.2. SLEDAI–2K (LN Cohort Only)

The SLEDAI–2K tool 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 and covers a recall period of ≤ 30 days. The SLEDAI–2K assessment will be used for the determination of Extrarenal SLE Flare (Section 8.1.7). For the purpose of assessment for presence of Extrarenal SLE Flare, the following 6 descriptors will not be accounted for: proteinuria, hematuria, urinary casts, hypocomplementemia, pyuria, and increase in the anti-dsDNA antibody level. As a result, the total number of disease activity descriptors assessed is 18 and the total score ranges from 0 to 85.

8.12. General Assessments and Procedures

8.12.1. Informed Consent

Participants must be consented per the informed consent process outlined in Section 10.1.3.

8.12.2. 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.

8.12.3. Demographics

A review of demographic parameters, including age, gender, race, and ethnicity will be performed at Screening, if allowed per country-specific regulations, and documented in the eCRF.

8.12.4. Medical History and LN and IgAN History

The participant's relevant medical history, including prior and concomitant conditions/disorders (including LN and IgAN diagnosis), treatment history, disease status (naïve versus relapse) if available (LN Cohort only), family history of relevant diseases, substance usage, and history of medical conditions and surgeries will be evaluated at Screening by the Investigator, or qualified designee, and documented in the source documents and eCRF. Any changes to medical history occurring during the Screening Period and prior to first dose of study intervention on Day 1 will be documented prior to study intervention administration.

8.12.5. Kidney Biopsy

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

8.12.5.1. Screening Kidney Biopsy

For participants in the LN cohort, the diagnosis of LN must have been confirmed by biopsy obtained ≤ 6 months prior to Screening or during the Screening Period.

The diagnosis of primary IgAN must have been established based on kidney biopsy obtained any time prior to or during the Screening Period.

Eligibility will be determined using the local pathology report according to standardized globally recognized guidelines. The local pathology report must be entered in the eCRF 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, endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy-presence of crescents (MEST-C) score (IgAN cohort only), will be obtained from the local pathology reports, if available, and documented in the eCRF.

The local pathology report and microscopy slides will be sent to the Central Pathology Laboratory to confirm the diagnosis on the kidney biopsy used for eligibility to minimize interpersonal variation in histological scoring.

8.12.5.2. Kidney Biopsy During the Study

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

8.12.5.3. 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 Blinded Extended Treatment 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 8.7.4). 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.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary hypothesis for this study is that ALXN2050 180 mg bid is superior to placebo in decreasing proteinuria.

9.2. Sample Size Determination

This study plans to enroll approximately 126 adult participants with either LN or IgAN in the study (approximately 70 participants in the LN cohort and approximately 56 participants in the IgAN cohort) in a 3:1:3 ratio to ALXN2050 180 mg bid, ALXN2050 120 mg bid, or placebo. All participants will receive standard-of-care treatment in addition to their randomized treatment.

The primary analysis of the primary endpoint will test the hypothesis that ALXN2050 180 mg bid is superior to placebo in decreasing proteinuria. Data from the ALXN2050 120 mg bid treatment group will be summarized descriptively, with no formal statistical testing planned.

In March 2018, an NKF-sponsored workshop on surrogate endpoints for clinical studies in early stages of CKD was held. A 20% to 30% reduction in the geometric mean in proteinuria was decided as a clinically significant treatment effect (Levey, 2020). Sample size calculations are based on a 1-sided 2-sample t-test of log-transformed proteinuria values.

Individual patient data from relevant studies in IgAN was previously used to estimate variability and expected changes in proteinuria for patients on placebo with background 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 from baseline in proteinuria) for the placebo group. In order to target at least a 30% relative treatment effect, (ie 1 minus GMR of ALXN2050 to placebo at Week 26), the GMR is assumed to be 0.55 (ie, a 45% reduction from baseline in proteinuria) for the ALXN2050 180 mg bid group. The log change from baseline in proteinuria is calculated as log (0.85) and log (0.55) for the placebo and ALXN2050 180 mg bid treatment groups, respectively, for the IgAN 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 48 participants (24 participants randomized to ALXN2050 180 mg bid, 24 participants randomized to placebo) in the IgAN cohort will provide approximately 80% power to detect a treatment difference with a 1-sided significance level of 0.05. An additional 8 participants will be enrolled in the ALXN2050 120 mg bid treatment group for a total of 56 participants in the IgAN cohort.

Expected changes in proteinuria and associated variability were not available on the log-scale for LN; however, 2 studies of patients with LN who were treated with MMF showed mean proteinuria values of approximately 4 g/day at baseline and approximately 2 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 from baseline in proteinuria) for the placebo group. In order to target at least a 30% relative treatment effect, (ie, 1 minus GMR of ALXN2050 to placebo at Week 26), the GMR is assumed to be 0.40 (ie, a 60% reduction from baseline in proteinuria) for the ALXN2050 180 mg bid group. The log change from baseline in proteinuria is calculated as log (0.60) and log (0.40) for the placebo and ALXN2050 180 mg bid treatment groups, respectively, for the LN cohort. A common 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 (30 participants randomized to ALXN2050 180 mg bid, 30 participants randomized to placebo) in the LN cohort will provide approximately 80% power to detect a treatment difference with a 1-sided significance level of 0.05. An additional 10 participants will be enrolled in the ALXN2050 120 mg bid treatment group for a total of 70 participants in the LN cohort.

9.3. Populations for Analyses

The population sets used for analysis are defined below.

Analysis Set	Description
Enrolled Set	All consented participants excluding screen failures.
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 intervention. Participants will be analyzed as randomized for reporting efficacy data.
Safety Set	All participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received for reporting exposure and safety data.
Per Protocol Set	All randomized participants who receive at least 1 dose of study intervention and without important protocol deviations.
Pharmacokinetic (PK) Analysis Set	All randomized participants who receive at least 1 dose of study intervention and who have a baseline PK value and at least 1 evaluable postdose PK assessment.
Pharmacodynamic (PD) Analysis Set	All randomized participants who receive at least 1 dose of study intervention and who have a baseline PD value and at least 1 evaluable postdose PD assessment.

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP). The analyses for participants in the LN cohort and participants in the IgAN cohort will be conducted and reported separately.

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

9.4.1. Enrollment and Disposition

The number of participants screened, screen failed, randomized, and treated will be presented. The number of participants discontinued (along with reasons) will be summarized.

9.4.2. Demographics, Baseline Characteristics, Inclusion and Exclusion Criteria, and Protocol Deviations

All demographic information and baseline characteristics will be reported by treatment group for each disease cohort separately.

The number and percentage of participants not meeting a specific inclusion or exclusion criterion will be summarized by treatment group for each disease cohort separately. A similar summary will be provided for important protocol deviations based on prespecified categories.

9.4.3. Medical History

Medical history will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23 or later, System Organ Class (SOC) and Preferred Term by treatment group for each disease cohort separately.

9.4.4. Prior and Concomitant Medications

For analysis and reporting purposes, any medication started prior to first dose of study intervention will be considered prior medication, and medications that started on or after the first dose of study intervention will be considered concomitant medications. All prior and concomitant medications will be summarized by treatment group for each disease cohort separately.

9.4.5. Extent of Drug Exposure

The cumulative and total drug exposure and treatment duration will be summarized descriptively by treatment group for each disease cohort separately.

9.4.6. Efficacy Analyses

9.4.6.1. Analyses of Primary Efficacy Endpoint

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

Proteinuria will be measured and summarized by absolute protein in g/day as well as by UPCR in g/g for each disease cohort.

For the LN cohort, the primary endpoint 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, the primary endpoint 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 ALXN2050 180 mg bid 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. Data from the ALXN2050 120 mg bid treatment group will be summarized descriptively, with no formal statistical

comparisons planned. The point estimate and 2-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 2-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.

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.

9.4.6.2. Analyses of Secondary Efficacy Endpoint(s)

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

For the IgAN cohort, participants initially randomized to the placebo group will receive ALXN2050 in the Blinded Extended Treatment Period. Therefore, analysis of the secondary endpoints during the Blinded Extended Treatment Period will be summarized separately for each treatment group and baseline for the placebo group will be redefined as the last measurement taken before the first dose of ALXN2050 during the OLE Period (ie, the Week 26 measurement).

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

The percent change from baseline in proteinuria at Week 50 will be analyzed using a mixed-effect model for repeated measures (MMRM) including change from baseline in log-transformed proteinuria as the response variable and fixed, categorical effects of treatment group, 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 ALXN2050 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 for the ALXN2050 180 mg bid and placebo treatment groups using a contrast for treatment group-by-visit term at Week 50. Data from the ALXN2050 120 mg bid treatment group will be summarized descriptively, with no formal statistical comparisons planned. The point estimate and 2sided 90% CI for the mean difference of log-transformed proteinuria will be back-transformed (via exponentiation) to obtain the GMR and corresponding 2-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 2-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method.

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

9.4.6.2.2. Secondary Efficacy Analyses for LN Cohort Only

The percentage of participants achieving the following secondary endpoints will be summarized by treatment group by calculating the point estimate and 2-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method:

- Meeting the criteria for CRR as well as individual components of CRR at Week 26 and Week 50
- Meeting the criteria for PRR at Week 26 and Week 50
- Achieving corticosteroid taper to 7.5 mg/day at Week 12, Week 26, and Week 50
- Experience of protocol-defined Renal Flare through Week 50
- Experience of protocol-defined Extrarenal SLE Flare through Week 50
- Meeting the criteria for Treatment Failure through Week 50
- Meeting the criteria for Suboptimal Response through Week 50

Time to the first occurrence of UPCR $\leq$ 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 for ALXN2050 180 mg bid and placebo treatment groups 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 2-sided 95%CI, of time to UPCR $\leq$ 0.5 g/g.

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

9.4.6.2.3. Secondary Efficacy Analyses for IgAN Cohort Only

The percentage of participants meeting the criteria for Partial Remission (defined in Section 8.1.11) at Week 26 and Week 50 will be summarized by treatment group by calculating the point estimate and 2-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method.

9.4.6.3. Multiplicity Adjustment

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

9.4.6.4. Analyses of Exploratory Endpoint(s)

Exploratory analyses will be descriptive in nature and will be based on the FAS. Full details of these analyses will be provided in the SAP.

Exploratory biomarkers will be analyzed if data is available and may be included in the clinical study report (CSR). A separate SAP will be provided for the exploratory biomarkers.

9.4.7. Safety Analyses for Both LN Cohort and IgAN Cohort

The safety and tolerability of ALXN2050 will be assessed based on AEs, clinical laboratory findings, vital sign findings, ECG abnormalities, and physical examination. All safety analyses will be performed on the Safety Set based on the actual treatment received.

9.4.7.1. Adverse Events

The incidence of treatment-emergent adverse events (TEAEs), TEAEs leading to withdrawal from the study, TEAEs leading to study treatment discontinuation, and SAEs will be summarized by treatment group for each disease cohort separately. All AEs will be coded using MedDRA version 23 or higher and will be summarized by SOC and Preferred Term overall, by severity, and by relationship to treatment. Detailed by-participant listings of TEAEs, SAEs, related TEAEs, TEAEs leading to withdrawal from the study, and TEAEs leading to study treatment discontinuation will be provided.

9.4.7.2. 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 each scheduled postbaseline time point and for changes from baseline separately for each disease cohort.

9.4.7.3. 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 scheduled 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.

9.4.7.4. 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 scheduled postbaseline time point. QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

9.4.8. PK/PD Analysis for Both LN Cohort and IgAN Cohort

Descriptive statistics will be calculated for plasma concentration data at each sampling time, as appropriate. Observed trough concentrations (C_{trough}) and serum C_{max} will be summarized.

The PD effects of ALXN2050 will be evaluated by assessing the absolute values and changes and percentage changes from baseline in serum AP activity and plasma Bb concentration over time, as appropriate. Descriptive statistics will be calculated for the PD data at each sampling time, as appropriate.

Population PK modeling will be conducted to characterize the PK of ALXN2050 in participants who are on the active treatment. Covariates (source of variability) that have significant impact on the PK will be identified. Steady state exposure parameters such as the area under the concentration-time curve (AUC) and the C_{max} will be derived from the Population PK model. In addition, a PK-PD model will be developed. Factors contributing to the PK-PD relationship will also be explored. Maximum PD response and the exposure required to achieve 50% of the response will be presented. Actual dose administration and sampling times will be used for Population PK and PK-PD analyses.

Details of Population PK modeling, as well as PK-PD modeling, will be presented in a Population PK/PD Analysis Plan. Results from Population PK/PD analyses will be presented in a separate Population PK/PD Analysis Report.

9.5. Planned Analyses

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

An additional analysis will be performed for each disease-specific cohort at the end of the Blinded Extended Treatment Period after all participants in the disease-specific cohort have completed the Week 50 Visit or withdrawn from the study early.

The final analysis will be performed at the end of the 2-year OLE Period after all participants have completed the Safety Follow-up Visit.

The SAP will describe the planned analyses in greater detail.

9.6. Interim Analysis

An early interim analysis may be conducted at the discretion of Alexion (based on feasibility) when approximately 50% of participants in the IgAN and/or LN disease-specific cohorts have been randomly assigned to study treatment and have had the opportunity to complete the 26-week Primary Evaluation Period or have discontinued from the study treatment before Week 26. This early interim analysis, if performed for either the IgAN cohort and/or LN cohort, will be conducted by a separate unblinded team and will be for Phase 3 planning purposes only with no impact on the progression of the study.

9.7. Data Monitoring Committee

An independent DMC, comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion or designee. In this study, the independent DMC will be responsible for review of efficacy and safety data. The specific responsibilities of the DMC and a schedule of meetings will be described in the DMC Charter.

9.8. Safety Review Committee

A Safety Review Committee will not be used for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments (ie, modifications), ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion, and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC and regulatory/health authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- For studies to be approved by the Medicines and Healthcare products Regulatory Agency: The Investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by applicable law as a serious breach or as required by IRB/IEC procedures.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU CTR 536/2014 for clinical studies, 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 EMA CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
  - A "personal data breach" means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.
- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach, including personal data breaches.
  - A (potential) serious breach is promptly reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion.
- The Coordinating Investigator will be identified among the enrolling Investigators during the course of the study and will be responsible for reviewing the 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 or designee to obtain signed (written or electronic signature) informed consent from all study participants prior to performing any study-related procedures including screening assessments.
- The Investigator or designee will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant, 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 with a participant, 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. Original signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened outside of the Screening window (Table 1) are required to sign a new ICF (Section 5.4).

10.1.4. Recruitment Strategy

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

10.1.5. Data Protection

- Participants will be assigned a unique identifier by Alexion or designee. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related and coded (pseudonymized) data will be used in accordance with applicable data protection law, and participants must also be informed of any 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 will be required to agree to the information contained in the informed consent and provide consent to the processing of their personal data, if required by applicable data protection law.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, and inspectors from regulatory authorities.

- Alexion as a data controller has implemented privacy and security controls designed to help protect participant personal data, including information security controls, firewalls, incident detection, and secure transfer measures.
- The contract between Alexion and study sites specifies responsibilities of the parties related 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 is 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. However, posting of study results per local regulations may be deferred to a later date for one of the following reasons:

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

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed CRF or eCRF 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 eCRF.
- 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 eCRF 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 Clinical 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 (or per local or institutional policy record retention requirements). No records may be destroyed without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion. Clinical study documents and records required as part of the TMF are archived and stored by Alexion for at least 30 years.

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 eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. These eCRFs must be completed by the Investigator or designee as indicated in the site delegation log. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available to Alexion, Alexion delegates, and health authorities, as requested. Source documents are filed at the investigational site.

Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete.

10.1.9. Study and Site Start and Closure

Study Start

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 its sole discretion. 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 End of Study or ED Visit, all data have been collected and entered into the 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

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

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- Primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Alexion will comply with the requirements for publication of study results as defined by the Pharmaceutical Research and Manufacturers of America and the International Committee of Medical Journal Editors and per the Alexion Publication Policy. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.
- Alexion will publish Patient Lay Summaries and include participants and/or caregivers as reviewers for readability and understanding of lay person language.

10.1.11. Good Clinical Practice Compliance

Alexion and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 R2, EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

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

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

10.2. Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the central laboratory or designated ancillary laboratories, unless otherwise noted.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: WOCBP should only be enrolled after a negative serum pregnancy test result at Screening. Serum pregnancy tests should also be done if there is an ED Visit and at the Safety Follow-up Visit. 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 SoA (Section 1.3).
- Investigators must document their review of each laboratory safety report. Clinically significant findings resulting in an assessment of a TEAE should be recorded on the AE eCRF.
- Laboratory/analyte results that could unblind the study will not be reported to investigational sites or other blinded personnel until the study has been unblinded.

Table 13: Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters
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 tests: 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

Table 13: Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters
	○ Total carbon dioxide ○ Creatinine kinase ○ Uric acid • Glycated hemoglobin (HbA1c)
Hematology	• Red blood cell count • Hemoglobin • Hematocrit • Erythrocytes • RBC indices ○ Mean corpuscular volume ○ Mean corpuscular hemoglobin ○ Percentage of reticulocytes ○ Mean corpuscular hemoglobin concentration • White blood cell count with differential (including early progenitors): ○ Neutrophils, segmented ○ Lymphocytes ○ Monocytes ○ Eosinophils ○ Basophils • Platelet count • Mean platelet volume
Coagulation panel	• INR • PT • APTT • D-Dimer • Fibrinogen
Lipid profile	• Cholesterol/HDL ratio • High-density lipoprotein cholesterol • Low-density lipoprotein cholesterol • Non-HDL cholesterol • Total cholesterol • Triglycerides • Very low-density lipoprotein cholesterol
24-h urine	• Total protein, total creatinine, total albumin, total sodium, creatinine clearance, protein to creatinine ratio, and albumin to creatinine ratio

Table 13: Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters
Spot urine studies	• Protein, albumin, creatinine, and protein to creatinine and albumin to creatinine ratios
Routine urinalysis and urine sediment	• Albumin • Bilirubin • Blood • Erythrocytes • Glucose • Ketones • Leukocyte esterase • Nitrite • pH • Protein • Specific gravity • Urobilinogen • Urine sediment: number of RBCs/high-power field and number of RBC casts[a]
Clinical complement tests	Serum samples will include, but are not limited to, assessments of the following: C3, C4, FD, and CH50
PK/PD	• Plasma PK • PD (serum AP activity and plasma Bb concentration)
Exploratory Biomarkers	Exploratory blood samples may include, but are not limited to, assessments of the following: • Complement pathway dysregulation (eg, soluble C5b-9 [sC5b-9], Factor Ba) Exploratory urine biomarkers may include, but are not limited to, assessments of the following: • Complement pathway dysregulation (eg, sC5b-9, Factor Ba) • Renal injury biomarkers (eg, N-GAL, KIM-1) • Urinary creatinine Kidney biopsy tissue exploratory biomarkers: • Unstained kidney tissue microscopy slides (up to 8) will be stained for the presence of biomarkers which may include, but are not limited to, clinical evidence of the disease pathophysiology and/or response to treatment (eg, C5b-9, C3c, C4d, CD68, properdin). The unstained slide(s) may also be used for proteomic profiling.

Table 13: Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters
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 WOCBP)[b] • Serum autoantibodies for LN eg, ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, anti-C1q, anti-phospholipid antibodies (LN cohort only)

[a] For participants in the IgAN cohort, eligibility for hematuria can be determined via the local laboratory.
[b] Serum pregnancy test required at Screening, ED and Safety Follow-up Visits; local urine pregnancy test at all other times as specified in Schedule of Activities (Section 1.3).

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibodies; AP = alternative pathway; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; Bb = Bb fragment of complement factor B; C1q, C3, C3c, C4, C4d = complement components 1q, 3, 3c, 4, 4d; C5b-9 = terminal complement complex; CD68 = cluster of differentiation 68; CH50 = 50% hemolytic complement activity; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; dsDNA = double-stranded DNA; ED = early discontinuation; eGFR = estimated glomerular filtration rate; FD = complement factor D; GGT = gamma-glutamyltransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; INR = international normalized ratio; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; LN = lupus nephritis; PCR = polymerase chain reaction; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PT = prothrombin time; RBC = red blood cell; sC5b-9 = soluble C5b-9; 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 or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A). • **Note**: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease [new or exacerbated] temporally associated with the use of the study intervention, whether or not considered related to the study intervention.

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

Events Not Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before 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. • Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

Events Not Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

10.3.2. Definition of SAE

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

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

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

life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A suspected unexpected serious adverse reaction (SUSAR) is defined as:

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

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

Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable.

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

Recording of AE and/or SAE

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

Recording of AE and/or SAE

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 eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study intervention.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- 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

Follow-up of AEs and SAEs
the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • 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 immediately and within 24 hours of awareness. • The primary mechanism for reporting an SAE to Alexion will be the EDC system. • If the electronic system is unavailable or site staff is unable to process the SAE via the EDC system at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE Reporting via facsimile or email. Facsimile transmission or email may also be used in the event of electronic submission failure. – Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347 • The site will enter the SAE data into the EDC system as soon as it becomes available. • When further information becomes available, the EDC should be updated immediately with the new information and an updated SAE report should be submitted to Alexion GPS within 24 hours of Investigator/site awareness. • After the participant has completed the study, no new data or changes to existing data are expected to be entered in the EDC system. o If a site receives a report of a new SAE from a study participant which the Investigator considers to be related to the study intervention, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via facsimile or email.

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. 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 an IMP or Alexion AxMP 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 GPS 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 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 Interactive Response Technology [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 6.8 for information on treatment of 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, non-therapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired non-therapeutic effect.

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

Examples of drug abuse include but are not limited to:

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

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or Alexion AxMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Alexion AxMPs, 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 GPS 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

10.5. Contraceptive Guidance and Collection of Pregnancy Information

10.5.1. Definitions

Woman of Childbearing Potential (WOCBP)

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

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

Women in the Following Categories Are Not Considered WOCBP

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

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause prior to the Day 1 Visit.
     - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement may be required. In the absence of 12 months of amenorrhea the reason for not obtaining FSH levels should be documented by the Investigator at the time of Screening.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective or acceptable contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
4. Permanent sterilization at least 6 weeks prior to the Day 1 Visit.

10.5.2. Contraception Guidance

Contraceptive use by male or female participants should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner

of a male participant, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.5.3.1). In these cases, follow-up will be conducted on the pregnant partner in the same manner as a female participant who becomes pregnant during the study.

10.5.2.1. Guidance for Female Participants

Female participants of childbearing potential must have a negative serum pregnancy test as required by local regulations at Screening and a negative urine pregnancy test before the first dose of study intervention on Day 1. Additional requirements for pregnancy testing during and after dosing with study intervention are indicated in the SoA (Section 1.3).

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

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

Female participants of childbearing potential must use a highly effective or acceptable methods of contraception, including at least 1 of the following until at least 30 days after the final dose of study intervention. Highly effective methods are:

1. Intrauterine device in place for at least 6 weeks prior to first dose of study intervention.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of study intervention.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of study intervention.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of study intervention.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study intervention.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within the prior 6 months prior to the first dose of study intervention). Male partner is still required to use condom during sexual intercourse.
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 must refrain from heterosexual intercourse for at least 30 days after the final dose of study intervention.

Female participants of childbearing potential may also use the following acceptable methods (considered effective, but not highly effective means failure rate of $\geq$ 1% per year) of contraception:

1. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action

2. Male or female condom with or without spermicide
3. Cervical cap, diaphragm, or sponge with spermicide
4. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods). If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

The following methods of contraception are considered unacceptable (not allowed) in this study:

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

10.5.2.2. Guidance for Male Participants

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

Male participants who have had a vasectomy > 6 months prior to the first dose of study intervention must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to the first dose of study intervention and those who have not had a vasectomy must use a condom (with or without spermicide) during heterosexual intercourse for at least 90 days (ie, 1 spermatogenesis cycle) after their final dose of study intervention.

10.5.2.2.1. Sexual Abstinence for Male Participants

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom with or without spermicide during intercourse.

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

10.5.3. 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 first dose of study intervention until the Safety Follow-up Visit. Any female participant who becomes pregnant during the study will be discontinued from the study intervention and withdrawn from the study. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study intervention via semen following paternal exposure. If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to

Alexion GPS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GPS. If additional follow-up is required, the Investigator will be requested to provide the information.

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

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

10.5.3.1. Male Participants with Partners Who Become Pregnant

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

10.5.3.2. 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.
- For all Alexion products, both in development or postapproval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Pregnancy is not considered as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. While pregnancy itself is not considered to be an AE or SAE, any pregnancy

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

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.6. Exploratory Biomarkers

- Blood and urine samples will be collected for biomarker analyses, and the data will be used for research (eg, exploratory) related to ALXN2050, LN, IgAN, and related diseases. The samples may also be used to develop tests/assays including diagnostic tests related to ALXN2050, LN, and IgAN.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to ALXN2050 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 ALXN2050 continues but no longer than 25 years after all data have been collected for the study or other period/time point per local requirements.

10.7. Systemic Lupus Erythematosus Diagnosis Classification

The 2019 EULAR/ACR 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.

10.8. 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 National Institutes of Health (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)

10.9. IgAN Diagnosis Classification Criteria

A participant must have a biopsy proven diagnosis of IgAN based on an appropriate standardized classification method (eg, 2016 Oxford Classification [(Trimarchi, 2017)]; Haas classification (Haas, 1997); Lee's glomerular grading system (Lee, 2005). A description of the 2016 Oxford Classification criteria is provided below.

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)

10.10. Participant-reported Outcome Instruments

All instruments will be self-reported and administered at visits specified in the SoAs. Information about these instruments and questionnaires, with the correct version and the validated language versions, if needed, will be provided to the sites prior to the start of the study.

10.10.1. EQ-5D-5L (For Both Cohorts)

The EQ-5D-5L is a self-reported standardized instrument to measure health-related QoL and has been used in a wide range of health conditions. The EQ-5D-5L is defined by 5 dimensions: mobility, usual activities, self-care, pain/discomfort, and anxiety/depression. A 0 to 1 health state index score (or utility score), where 0 indicates a health state equivalent to death and 1 indicates perfect health, will be calculated from individual health profiles using a US TTO value set. Negative values indicate health states considered worse than death. Each of the EQ-5D-5L dimensions may be summarized and analyzed as a categorical variable, providing data on the health profile of the study patients. The visual analog scale (VAS) and EQ-5D-5L index score may be summarized and analyzed as continuous variables.

10.10.2. SF-36 (For Both Cohorts)

The Short Form (36) Health Survey (SF-36) is a set of generic, coherent, and easily administered QoL measures. It has 36 items grouped in 8 dimensions: It measures each of the following 8 health domains: Physical Functioning, Physical, Bodily Pain, Vitality, General Health, Emotion, Mental Health, and Social Functioning.

10.10.3. FACIT-FATIGUE (For LN Cohort Only)

The FACIT-Fatigue scale is a collection of QoL questions pertaining to the management of fatigue symptoms due to a chronic illness. The FACIT-Fatigue scale (Version 4) is a short, 13-item, self-reported, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a five-point Likert-type scale (0 = not at all fatigued; 1 = a little bit fatigued, 2 = somewhat fatigued, 3 = quite a bit fatigued, and 4 = very much fatigued). All items contribute to the sum score with equal weight. This instrument will be used in the LN cohort.

10.11. COVID-19 Risk Assessment

Lupus nephritis 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 LN and IgAN 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. The site Investigator will therefore balance the risk/benefit considerations in 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 14.

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

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform 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, 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

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

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		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: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

10.12. 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 ALXN2050 administration, based on ALXN2050's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ALXN2050.The same precautions should be taken as described in Section 6.5.5.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. If possible, consider vaccination when the underlying complement-mediated disease is clinically controlled. 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 subsequent complement blockade is relatively high, shortly after administration.

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

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

Table 15: Potential Risks and Mitigation Measures due to COVID19 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 the data is missing (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

10.13. 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 study 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.

ALXN2050-NEPH-201 is a Phase 2 study in participants 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.

10.14. Management of Seizures

Seizure is considered a potential risk that is to be closely monitored in participants. Seizures are defined as a transient occurrence of clinical signs and/or symptoms that are due to abnormal excessive or synchronous neuronal activity in the brain.

Convulsions and/or electroencephalogram (EEG) abnormalities have been observed during dog and mouse repeat-dose toxicology studies. The dog is the most sensitive nonclinical species studied, and the NOAEL based on the dog 13-week toxicology study is 62.5 mg/kg/day.

Should a suspected seizure occur during the study, the following procedures should be performed:

- Participants and/or family members should be instructed to call an ambulance or report to a medical facility if the participant experiences a seizure. In general, most seizures are self-limiting and do not require acute pharmacologic intervention.
- For seizures that are not self-limiting, the participant should be treated medically according to local protocols for ongoing seizure.
- Participants and family members should be instructed to call the Investigator to inform them of the seizure.
- Treatment with study intervention should be suspended until a complete work up is performed.
- The following assessments are recommended for all participants with suspected seizure:
  - Blood samples should be taken to evaluate electrolytes (including calcium and magnesium), glucose, complete blood count, renal function tests, liver function tests, creatinine kinase, toxicology screen, ethanol level, and serum lactate. Any other tests or investigations determined to be pertinent should also be performed (eg, brain imaging, blood, and urine cultures).
  - Blood samples should be taken to evaluate PK levels.
  - An EEG should be performed.
- If the etiology of the seizure is assessed as related to the study intervention, the study intervention will be discontinued, and the participant will be also discontinued from the study.
- If an alternative cause for the seizure is determined, dosing with study intervention may resume as deemed appropriate by the Investigator in consultation with the Medical Monitor.

Any event of seizure or suspected seizure must be reported to Alexion within 24 hours of the Investigator's awareness as a treatment-emergent serious adverse event (TESAE). The following clinical information in addition to the above recommended assessments should also be collected:

- Seizure start date and time

- Description of the seizure
  - The type of seizure (eg, generalized tonic-clonic seizure, partial seizure)
  - A detailed description of what the participant was doing before, during, and after each seizure. If possible, describe all aspects from start to end.
  - What was the earliest sign of seizure onset?
  - Duration of seizure(s)
  - Was the participant unconscious, unaware, or confused?
  - Was there evidence of bowel or bladder dysfunction?
  - Post-ictal period duration and signs
  - Neurologic examination findings
  - EEG results
  - Evidence of injury from the seizure (eg, tongue bites, bruises, or other injuries)
  - How did the participant recover after the seizure?
- Document identifiable seizure triggers
  - Was there any recognizable trigger that may have provoked the seizures for the participant? Please include any recent medication changes, illness, or sleep deprivation.
  - Was there any history of alcohol or drug use, or recent discontinuation of alcohol use?
- Past medical and surgical history review
  - Is there relevant medical history?
  - Document concomitant medications

10.15. Selected Medications Known to Lower the Seizure Threshold and/or Cause Seizure

The following medications are PROHIBITED while on the study:

- Meperidine/pethidine
- Tramadol
- Typical (first generation) antipsychotics
- Clozapine
- Olanzapine
- Lithium
- Tricyclic antidepressants
- Bupropion
- Aminophylline/theophylline

10.16. List of Inhibitors, Inducers and Substrates of CYP3A

Table 16: List of Prohibited Inducers, Inhibitors and Substrates of CYP3A

Classification	Medication	Table Number[a]
Strong CYP3A inhibitors	boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, and nelfinavir	3-2
Moderate CYP3A inhibitors	aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil	3-2
Strong inducers of CYP3A	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort	3-3
Moderate inducers of CYP3A	bosentan, efavirenz, etravirine, phenobarbital, and primidone	3-3
Sensitive substrates of CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	3-1

[a] Table number from FDA Table of Clinical CYP Inhibitors and Inducers
Abbreviation: CYP3A = cytochrome P450, family 3, subfamily A
Note: This list is complete as of 25 Jan 2021. Please visit the link below for the most up-to-date information.
Source: (FDA, 2022)

10.17. Protocol Amendment History

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

DOCUMENT HISTORY	
Document/Type of Amendment (Global or Country-specific)/Date	**Summary of Key Changes in the Amendment**
Amendment 2.0 (Global)/31 May 2023	Revised to address the requirements for conducting a clinical study under the EU CTR.
Amendment 1.2/China/31 Aug 2022	Removed exploratory biomarkers and references to sending tissue sample slides to the Central Pathology Laboratory outside China as shipping of biological samples out of China is restricted.
Amendment 1.1/United Kingdom/10 Jun 2023	Revised to incorporate comments from the Medicines and Healthcare products Regulatory which were made in Amendment 0.1.
Amendment 1 (Global)/17 May 2022	Revised to incorporate in the global protocol, where appropriate, the changes made at the request of regulatory authorities, IRBs, IECs, and Investigators. The eligibility criteria were clarified or modified, and a secondary endpoint to assess Suboptimal Response was added for the LN cohort. Of note, the maximum dose of MMF a participant in the LN Cohort can receive was increased, and additional corticosteroid taper following Week 26 was allowed. Also of note, additional COVID-19 related mitigation and monitoring guidance were included.
Amendment 0.2/Germany/05 May 2022	Revised to address comments from the German EC
Amendment 0.1/United Kingdom/ 24 Nov 2021	Revised to address comments from the Medicines and Healthcare products Regulatory Agency
Original protocol/03 Jun 2021	Not applicable

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