TITLE PAGE

STATISTICAL ANALYSIS PLAN

Version Number: 3.0

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)

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Compound: ALXN2050

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

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VERSION HISTORY

This statistical analysis plan (SAP) for Study ALXN2050-NEPH-201 is based on Protocol Amendment 3.0, dated 21 Feb 2024.

SAP Version	Version Date	Change	Rationale
1.0	23 Nov 2022	Not applicable	Original version.
2.0	10 May 2023	Included the option to perform an early interim analysis	For Phase 3 planning purposes.
		Other minor edits	For clarity.
3.0	12 Nov 2024	Deleted data presentation for Safety Follow-up Period	Safety Follow-up Period is not a treatment period.
		Revised the derivation of the primary endpoint	Visit window is changed.
		Added ALXN2050 Total group into data presentation	To evaluate the overall ALXN2050 treatment effect.
		Changed terminologies: "background therapy" to "allowed concomitant therapy" and "rescue therapy" to "additional standard-of-care therapy"	To align with EU CTR requirements.
		Added an analysis of abnormal liver enzyme elevations	To evaluate drug-induced liver injury.
		Added a sensitivity analysis due to dosing pause	Screening, enrollment, and study intervention administration have been temporarily paused as of 06 September 2024.
		Other minor edits	For minor corrections.

APPROVAL SIGNATURES

[redacted] Biostatistics — Date dd Mmm yyyy

[redacted] Biostatistics — Date dd Mmm yyyy

[redacted] — Date dd Mmm yyyy

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	alternative pathway
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
Bb	Bb fragment of complement factor B
bid	twice daily
BLQ	below the limit of quantification
C1q	complement component C1q
C3	complement component 3
C4	complement component 4
CDF	cumulative distribution function
CI	confidence interval
CNI	calcineurin inhibitor
COVID-19	coronavirus disease 2019
CRR	complete renal response
cTTO	composite time trade-off
CV	coefficient of variation
CV%	coefficient of variation percentage
dsDNA	double-stranded DNA
EC	exclusion criteria
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EQ-5D-5L	5-level EuroQol-5 Dimensions
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FAS	Full Analysis Set
FD	factor D
GM	geometric mean
GMR	geometric mean ratio
hpf	high power field
IC	inclusion criteria
IE	intercurrent event

Abbreviation	Definition
IgAN	immunoglobulin A nephropathy
LLN	lower limit of normal
LN	lupus nephritis
MAR	missing-at-random
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MEST-C	mesangial, endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy-presence of crescents
MI	multiple imputation
MMF	mycophenolate mofetil
MNAR	missing not at random
OLE	open-label extension
ORR	overall renal response
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPS	Per-Protocol Set
PRR	partial renal response
PT	Preferred Term
QoL	quality of life
RAS	renin-angiotensin system
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis Software®
SF-36	36-item Short Form Health Survey
SLE	systemic lupus erythematosus
SLEDAI-2K SELENA Modification	Systemic Lupus Erythematosus Disease Activity Index Safety of Estrogen in Lupus Erythematosus National Assessment Modification
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TTO	time trade-off

Abbreviation	Definition
ULN	upper limit of normal
UP	urine protein
UPCR	urine protein-to-creatinine ratio
VAS	visual analog scale
WHO-DRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods for analyzing data for Protocol ALXN2050-NEPH-201, "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)." Standard data presentation instructions and table, figure, and listing specifications are contained in the Data Presentation Plan (DPP) in a separate document.

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 participants with LN or IgAN.

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 evaluation of the primary endpoint and Phase 3 planning and will have no impact on the progression of this study. The sponsor will be unblinded at this time to conduct the primary analysis. After completion of the 26-week Blinded Initial Evaluation Period, participants in the LN cohort will continue receiving their randomized allocation of study intervention, and both the participants and the investigative site personnel will remain blinded for the remaining 24-week Blinded Extended Treatment Period.

An additional analysis will be performed for each disease-specific cohort at the end of the 24-week Blinded Extended Treatment Period after all participants in the disease-specific cohorts have completed Week 50 or withdrawn from the study.

The final analysis will occur at the end of the 2-year Open-label Extension (OLE) Period after all participants have completed the Safety Follow-up Visit and will include all planned analyses that will be presented in the final clinical study report.

Screening, enrollment, and study intervention have been paused as of 06 Sep 2024. Sensitivity analyses due to dosing pause are added into the relevant sections.

1.1. Objectives, Endpoints, and Estimands

Table 1: 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])

Table 1: Objectives and Endpoints

Objectives	Endpoints
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 Weeks 26 and 50 compared to baseline (based on 24-hour urine collection[s] at each time point)
	Change from baseline in eGFR at Weeks 26 and 50
Secondary (LN Cohort Only)	
To evaluate the efficacy of ALXN2050 on measures of kidney function in participants with LN	Meeting the criteria for complete renal response **(**CRR) at Weeks 26 and 50
	Meeting the criteria for partial renal response **(**PRR) at Weeks 26 and 50
	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 through Week 50
	Experience of an extrarenal systemic lupus erythematosus (SLE) flare through Week 50
	Meeting the criteria for treatment failure through Week 50
	Meeting the criteria for suboptimal response through Week 50
	Absolute values and change from baseline in serum albumin at Weeks 26 and 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 Weeks 26 and 50
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

Table 1: Objectives and Endpoints

Objectives	Endpoints
Safety	
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 Weeks 102 and 154 (based on 24-hour urine collection[s])
	Change from baseline in eGFR at Weeks 102 and 154
To evaluate the efficacy of ALXN2050 on hematuria in participants with LN or IgAN	Absolute value and change from baseline in RBC in urine from baseline to Weeks 26 and 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-36v2 at Weeks 26 and 50
	Change from baseline in EQ-5D-5L at Weeks 26 and 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 Weeks 26 and 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 Weeks 26 and 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 Weeks 26 and 50
Exploratory (IgAN Cohort Only)	
To assess the efficacy of ALXN2050 in exploratory efficacy endpoints	Slope of eGFR computed from baseline to Weeks 26 and 50

Abbreviations: anti-C1q = anti-C1q complement component; anti-dsDNA = anti double-stranded DNA; AP = alternative pathway; Bb = Bb fragment of complement factor B; CRR = complete renal response; eGFR = estimated glomerular filtration rate; EQ-5D-5L = 5-level EuroQol-5 Dimensions; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; IgAN = immunoglobulin A nephropathy; LN = lupus nephritis; PD = pharmacodynamic; PK = pharmacokinetic(s); PRR = partial renal

Table 1: Objectives and Endpoints

Objectives	Endpoints

response; RBC = red blood cells; SF-36v2 = 36-item Short Form Health Survey version 2; SLE = systemic lupus erythematosus; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; UPCR = urine protein-to-creatinine ratio

Primary Estimand

The estimand is described by the following attributes:

- Population: Full Analysis Set (FAS)
- Endpoint: Percentage change from baseline to Week 26 in proteinuria
- Treatment: ALXN2050 180 mg bid versus placebo
- Intercurrent events: Receipt of additional standard of care therapy (LN cohort only) or treatment discontinuation
- Population-level summary: Difference in mean percentage change in proteinuria between ALXN2050 180 mg bid and placebo groups

1.2. Study Design

Study ALXN2050-NEPH-201 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.

All participants must have a diagnosis of LN with an active flare based on kidney biopsy or IgAN 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 for LN and defined as mean protein ≥ 1 g/24 hours from 2 valid 24-hour urine collections for IgAN. Participants with IgAN 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.

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 (Figure 1 and Figure 2).

All participants, Investigators, and site personnel will remain blinded to treatment assignment from Day 1 through the end of the 24-week Blinded Extended Treatment Period (ie, Week 50). During the OLE Period, participants, Investigators, and site personnel will no longer be blinded to treatment assignment. In this study, the independent Data Monitoring Committee will be responsible for review of efficacy and safety data.

Eligible participants will be assigned to a treatment arm by stratified randomization (approximately 70 participants in the LN cohort and approximately 56 participants in the IgAN cohort). For each disease cohort, participants will be randomly assigned in a 3:1:3 ratio to receive ALXN2050 180 mg bid, ALXN2050 120 mg bid, or placebo bid, respectively, during the

26-week Blinded Initial Evaluation Period. The LN cohort will continue with the same treatment allocation during the 24-week Blinded Extended Treatment Period (ALXN2050 180 mg bid, ALXN2050 120 mg bid, or placebo bid). For the IgAN cohort, participants assigned to the placebo group will also be assigned to their active study treatment for the 24-week 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 is defined as follows:

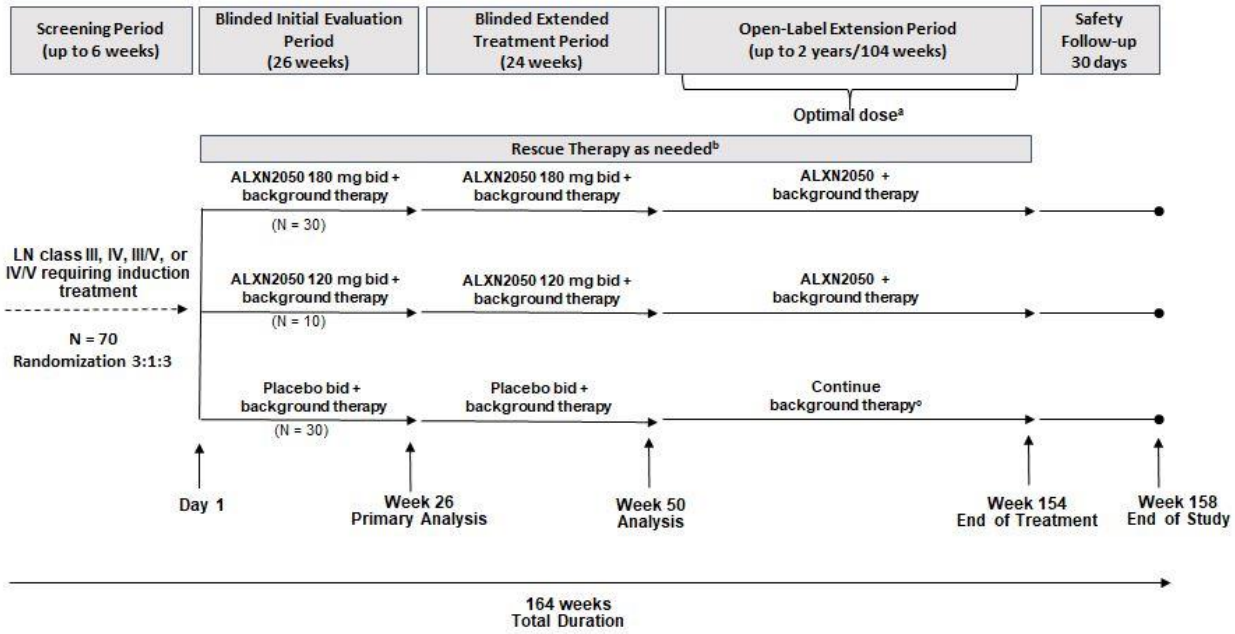
- LN cohort: corticosteroid induction treatment initiation (prior to Screening, during Screening Period)
- IgAN cohort: mean proteinuria from 2 valid 24-hour urine collections (1 to 2 g/day, > 2 g/day)

During the OLE Period, participants in both cohorts receiving ALXN2050 during the 24-week Blinded Extended Treatment Period will continue their active treatment at the same dose level. Once an optimal dose is identified based on results of the primary analysis at Week 26 for each cohort and/or Data Monitoring Committee review of the safety and efficacy data, 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 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 or suboptimal response.

In the LN cohort, participants who meet the criteria for protocol-defined renal flare or for extrarenal systemic lupus erythematosus (SLE) flare will receive additional standard of care therapy. After Week 26, participants may also receive additional standard of care therapy for protocol-defined suboptimal response. The specific choice of additional standard of care therapy(ies) is generally at the discretion of the Investigator.

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

Figure 1: Study Design Schematic (LN Cohort)



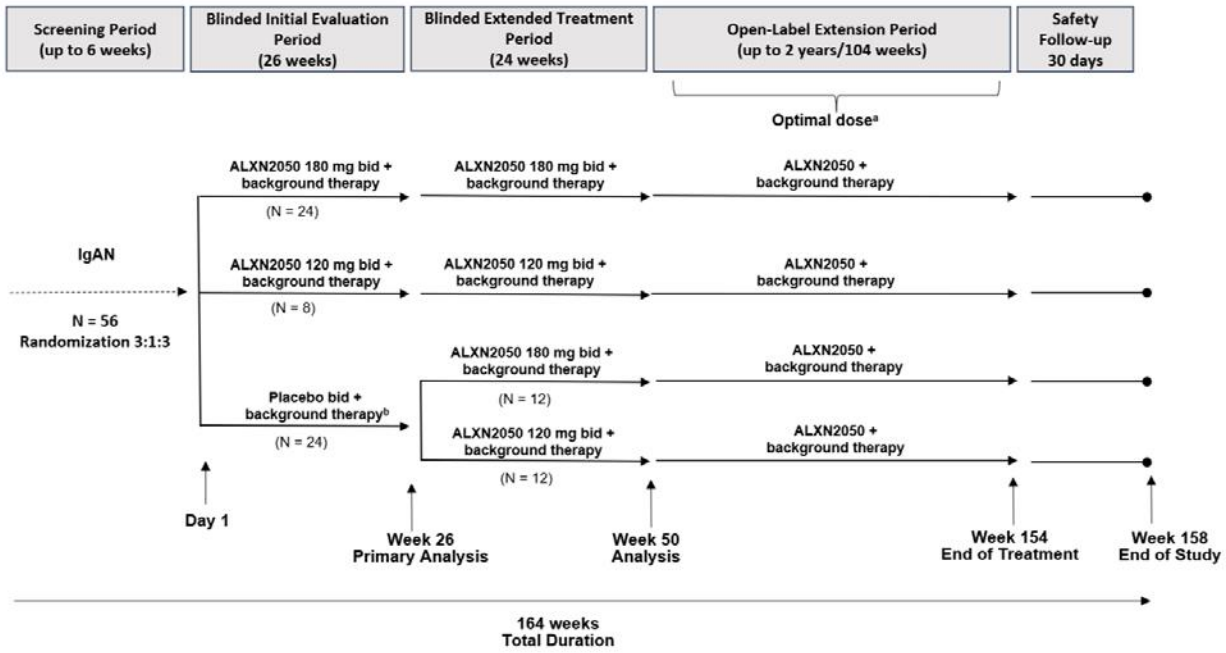
[a] The optimal dose level will be identified based on the results of the Week 26 primary analysis. Once identified, all participants on active treatment who have at least 50 weeks of treatment will receive the selected optimal dose for the remainder of the study.

[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 24-week 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 or suboptimal response.

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. Once identified, all participants 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 24-week Blinded Extended Treatment Period (ALXN2050 180 mg bid or ALXN2050 120 mg bid) in a 1:1 allocation ratio. After completion of the 26-week Blinded Initial Evaluation Period (Week 26), these participants will continue on ALXN2050 treatment during the 24-week Blinded Extended Treatment Period.

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

2. STATISTICAL HYPOTHESES

The primary hypothesis for this study is that ALXN2050 180 mg bid is superior to placebo in decreasing proteinuria. Hypothesis testing will be 1-sided and performed at the 0.05 level of significance for each disease cohort without adjusting for multiplicity.

2.1. Multiplicity Adjustment

There will be no adjustment for multiplicity.

3. ANALYSIS SETS

The participant analysis sets are defined as follows in Table 2:

Table 2: Participant Analysis Sets

Participant Analysis Set	Description
Randomized Set	The Randomized Set includes all randomized participants. Participants will be analyzed as randomized for reporting disposition, demographics, and baseline characteristics.
Full Analysis Set (FAS)	Participants who have been randomized and received at least 1 dose of study intervention will be included in the FAS. Participants in FAS will be analyzed as randomized for reporting efficacy data.
Modified Full Analysis Set (mFAS)	All FAS participants excluding participants who were impacted by coronavirus disease 2019 (COVID-19) as follows: 1. Participants who missed > 20% of total ALXN2050 dose amount assigned per protocol after the scheduled dosing time point during the 26-week Blinded Initial Evaluation Period due to COVID-19 2. Participants who withdrew early from the study during the 26-week Blinded Initial Evaluation Period due to COVID-19. 3. Participants who received concomitant treatments for COVID-19 during the 26-week Blinded Initial Evaluation Period that could potentially affect efficacy 4. Participants who were hospitalized due to a COVID-19 related adverse event during the 26-week Blinded Initial Evaluation Period Inclusion in the mFAS will be determined for each participant prior to database lock.
Per-Protocol Set (PPS)	Participants to be included in the PPS need to meet all the following criteria: • For the LN cohort, satisfy the following specific inclusion criteria (IC)/exclusion criteria (EC): o IC No. 9: Active focal or diffuse proliferative LN Class III or IV confirmed by biopsy obtained ≤ 6 months prior to Screening or during Screening Period o IC No. 10: Clinically active LN at Screening requiring/receiving immunosuppression induction treatment o IC No. 11: Proteinuria with UPCR ≥ 1 g/g based on one 24-hour urine collection o EC No. 28: Received any of the specified treatments defined in Protocol Section 5.2.2 o EC No. 29: Uncontrolled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg) on 2 or more measurements

Table 2: Participant Analysis Sets

Participant Analysis Set	Description
	○ EC No. 30: Prior history or clinically active SLE-related cerebritis, seizures, pericarditis, stroke, or stroke syndrome requiring treatment • For the IgAN cohort, satisfy the following specific inclusion criteria (IC) or exclusion criteria (EC): ○ IC No. 12: Established diagnosis of primary IgAN based on kidney biopsy ○ IC No. 13: Mean proteinuria ≥ 1 g/day on 2 complete and valid 24-hour urine collections ○ IC No. 15: Compliance with stable and optimal dose of RAS inhibitor treatment ○ IC No. 16: Controlled and stable blood pressure (defined as < 140/90 mmHg) ○ EC No. 35: Prednisone or prednisone equivalent > 20 mg/day for > 14 consecutive days or any other systemic immunosuppression within 6 months prior to Screening ○ EC No. 37: Body mass index ≥ 38 kg/m^2 during Screening • For both cohorts, satisfy the following criteria: ○ Participants who have an eGFR > 30 mL/min/1.73 m^2 during Screening ○ Participant informed consent/assent was provided prior to study procedures being carried out ○ Received correct treatment per randomization schedule ○ Remained blinded to treatment allocation during the 26-week Blinded Initial Evaluation Period ○ Received > 80% of planned dose of study intervention during the 26-week Blinded Initial Evaluation Period ○ Received appropriate allowed concomitant therapy during the 26-week Blinded Initial Evaluation Period ○ Received appropriate additional standard of care therapy, if required by protocol, during the 26-week Blinded Initial Evaluation Period (LN cohort only) ○ Did not receive any disallowed medications or therapies considered having significant impact on the primary efficacy measure during the 26-week Blinded Initial Evaluation Period (defined in Protocol Section 6.5.2) The PPS will be determined prior to database lock.
Safety Set (SS)	All participants who received at least 1 dose of study intervention will be included in the SS. Participants will be analyzed according to the study intervention they actually received for reporting exposure and safety data. The SS is the primary analysis for all safety and exposure analyses.

Table 2: Participant Analysis Sets

Participant Analysis Set	Description
Pharmacokinetic (PK) Analysis Set	All randomized participants who received at least 1 dose of study intervention and who have a baseline PK value and at least 1 evaluable postdose PK assessment will be included in PK Analysis Set.
Pharmacodynamic (PD) Analysis Set	All randomized participants who received at least 1 dose of study intervention and who have a baseline PD value and at least 1 evaluable postdose PD assessment will be included in PD Analysis Set.

4. STATISTICAL ANALYSES

4.1. General Considerations

All data collected in this study will be presented separately by disease cohort using summary tables, figures, and data listings. All analyses will be performed using Statistical Analysis Software® (SAS®) release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software.

All efficacy and safety analyses will be summarized separately for the 26-week Blinded Initial Evaluation Period, 24-week Blinded Extended Treatment Period, and 2-year OLE Period.

The analyses for participants in the LN cohort and IgAN cohort will be conducted and reported separately.

The primary comparison will be on the ALXN2050 180 mg treatment group versus the placebo treatment group. A smaller number of participants randomized to the ALXN2050 120 mg treatment group will be used for supportive data and will be summarized descriptively only with no formal statistical comparisons planned. As supplemental analyses, the comparisons will be carried out on the ALXN2050 Total treatment group (ALXN2050 180 mg and ALXN2050 120 mg) versus the placebo treatment group.

For the IgAN cohort, participants initially randomized to the placebo treatment group will receive ALXN2050 in the 24-week Blinded Extended Treatment Period. Therefore, analysis of the secondary endpoints during the 24-week Blinded Extended Treatment Period (Weeks 26 through 50) will be summarized separately for each treatment group assigned during the 26-week Blinded Initial Evaluation Period (Baseline through Week 26). During the 24-week Blinded Extended Treatment Period, baseline for the placebo treatment group will be redefined as the last measurement taken before the first dose of ALXN2050 during the 24-week Blinded Extended Treatment Period (ie, the Week 26 measurement).

The applied methods for statistical descriptive analyses and presentations will be based on the types of variables being tested.

1. Overall summary of descriptive statistics for continuous variables will include number of observations, mean, standard deviation (SD), median, minimum, and maximum, interquartile range (IQR), first quartile, and third quartile values in each treatment group. Observed difference will be summarized in a 2-sided 90% confidence interval (CI).
2. Overall summary of descriptive statistics for categorical variables will include frequency counts, percentage of participants, and 2-sided 95% CI of point estimate based on exact confidence limits using the Clopper-Pearson method.

Summaries of study and participant characteristics (eg, disposition, demographics and baseline characteristics, medical history, and protocol deviations) are described in Section 6.2.

4.1.1. Data Presentation for the 26-Week Blinded Initial Evaluation Period

Data summaries for the 26-week Blinded Initial Evaluation Period will be presented by randomized treatment group (ie, "ALXN2050 180 mg", "ALXN2050 120 mg", "ALXN2050 Total" and "Placebo") and total when applicable. All assessments for Week 26 will be performed prior to dosing. Dosing on Week 26 will be considered the start of the 24-week Blinded Extended Treatment Period.

4.1.2. Data Presentation for the 24-Week Blinded Extension Treatment Period

For the LN cohort, data summaries for the 24-week Blinded Extension Treatment Period will be presented by randomized treatment group and total when applicable.

For the IgAN cohort, summaries will be presented by treatment sequence (ie, "ALXN2050 180 mg", "ALXN2050 120 mg" and "Placebo to ALXN2050 180 mg" or "Placebo to ALXN2050 120 mg"). ALXN2050 Total, which consists of all the participants who were treated with ALXN2050 during the 24-week Blinded Extended Treatment Period, will be added when applicable. "ALXN2050 120 mg & 180 mg" which consists of participants who initially randomized to ALXN2050, will be included in efficacy tables when applicable. In addition, the baseline for the IgAN cohort will be defined as the originally randomized baseline and re-baseline will be defined as the last measurement collected prior to Week 26.

4.1.3. Data Presentation for the 2-Year OLE Period

For the LN cohort, data summaries for the OLE Period will be presented by treatment sequence if the optimal dose is identified at Week 26 (ie, "ALXN2050 180 mg to optimal dose", "ALXN2050 120 mg to optimal dose" and "Placebo to allowed concomitant therapy only"). The optimal dose presented here can be replaced with the actual identified dose based on the results of the Week 26 primary analysis.

For the IgAN cohort, summaries will also be presented by treatment sequence (ie, "ALXN2050 180 mg to optimal dose", "ALXN2050 120 mg to optimal dose" and "Placebo to ALXN2050 180 mg to optimal dose", "Placebo to ALXN2050 120 mg to optimal dose"). ALXN2050 Total, which consists of all the participants who treated with ALXN2050 during this period, will be added when applicable.

4.1.4. Handling of Dropouts or Missing Data

No imputation will be performed for missing baseline values. For missing postbaseline data not due to IEs, no imputation will be performed.

To derive duration of disease, partial date of diagnosis will be imputed as follows:

- If day is missing, it will be imputed to the "01"
- If day and month are missing, they will be imputed to "January 01"

Partial concomitant medication start dates and AE start dates will follow the same imputation rule to derive study phase.

Missing outcome data due to the COVID-19 pandemic (eg, dropout due to COVID-19) is assumed missing-at-random (MAR).

Missing outcome data due to dosing pause is assumed MAR.

Missing data for quality-of-life (QoL) instruments will be handled as specified in the instructions for each instrument in Section 6.3.

The following may occur during the study:

- Receipt of additional standard-of-care therapy (LN cohort only)
- Treatment discontinuation (LN and IgAN cohorts)
- Dosing pause

The handling of IEs is detailed in each analysis section.

4.2. Primary Endpoint Analysis

The primary efficacy endpoint analysis will be based on the FAS.

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

The primary analysis of the primary efficacy endpoint 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 cohorts have completed or withdrawn from the 26-week Blinded Initial Evaluation Period. The estimand for the primary analysis is defined in Table 3.

Table 3: Estimand for Primary Analysis

Estimand	Treatment	Population	Variable	Intercurrent Event	Population-level Summary
Primary analysis	ALXN2050 180 mg, Placebo	FAS	Percentage change in proteinuria from baseline to Week 26	• Receipt of additional standard-of-care therapy (LN cohort only) • Treatment discontinuation	Difference in mean of percentage change in proteinuria between ALXN2050 180 mg bid treatment and placebo groups

Abbreviations: bid = twice daily; FAS = Full Analysis Set; LN = lupus nephritis

4.2.1. Derivation of Endpoint(s)

The primary endpoint for the study is percentage change from baseline to Week 26 in proteinuria based on 24-hour urine collection(s) at each time point.

Proteinuria will be measured by absolute urine protein (UP) in g/day as well as by urine protein-to-creatinine ratio (UPCR) in g/g for each disease cohort as follows:

- For the LN cohort, proteinuria measured by UPCR as well as by UP is derived from a single 24-hour urine collection at Screening and the mean of 2 separate 24-hour urine collections within 3 weeks prior to or 1 week after Week 26 Visit to assess the primary endpoint. Two separate 24-hour collections should be obtained at Week 50 Visit to assess the secondary endpoint, as long as they are collected within 3 weeks prior to Week 50 Visit. Additional 24-hour urine collections are also scheduled for Weeks 102 and 154.
- For the IgAN cohort, proteinuria measured by UP as well as UPCR is derived from the mean of 2 valid 24-hour urine collections during the Screening Period and within 3 weeks prior to Week 26 Visit to assess the primary endpoint. Two separate 24-hour collections should be obtained at Week 50 Visit to assess the secondary endpoint, as long as they are collected within 3 weeks prior to or 1 week after Week 50 Visit. Additional 24-hour urine collections are also scheduled for Weeks 102 and 154.

For the primary endpoint, proteinuria will be based on UPCR for the LN cohort and UP for the IgAN cohort. For both cohorts, the natural logarithm will be used to transform proteinuria values before the analysis to reduce skewness. When 2 valid 24-hour urine collections are required and only 1 valid collection is available at the visit, then this value will be used for analysis.

4.2.2. Main Analytical Approach

An analysis of covariance (ANCOVA) will be used for the primary efficacy analysis to compare reductions in proteinuria between the ALXN2050 180 mg bid treatment and placebo groups. The ANCOVA model will include change from baseline in log-transformed proteinuria as the response variable and will adjust for baseline log proteinuria and the randomization stratification factor. The treatment effect will be evaluated using the least-squares mean difference between treatment groups. The point estimate and 2-sided 90% CI for the mean difference of log-transformed proteinuria will be back transformed (via exponentiation) to obtain the geometric mean ratio (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.

The analysis will be performed for both proteinuria measures, UPCR and UP, in both cohorts even though the primary endpoint will be measured by UPCR for the LN cohort and by UP for the IgAN cohort.

The randomization stratification factor will be based on strata verified by laboratory and allowed concomitant therapy data from electronic case report form (eCRF). Sensitivity analysis may be performed using strata as randomized in the interactive response technology.

The data after the intercurrent events will be treated as missing, and all the missing data will be imputed according to the following assumptions:

- In the LN cohort, only data up to the point of additional standard of care therapy will be included as observed for participants who receive additional standard of care therapy due to renal flare. Data on or after additional standard of care therapy for these participants is treated as missing regardless of whether the data is collected or not. The measurement performed at the time of renal flare (ie, proteinuria value from the 24-hour urine collection) will be carried forward to all subsequent visits.

- In both the LN and IgAN cohorts, data occurring on or after treatment discontinuation will be treated as missing. It is assumed that study participants follow the behavior of their randomized arm. All the missing data will be imputed through multiple imputation (MI) under MAR assumption. Participants with missing data can be modeled based on similar participants with available data if relevant observed factors are accounted for in the model. This MI procedure can be performed in 3 steps: 1) Impute missing data (eg, use PROC MI, *m* times); 2) Analyze each of the *m* complete data sets (eg, use PROC ANCOVA); and 3) Combine results across *K* multiply imputed datasets using Rubin's rule (eg, PROC MIANALYZE).

4.2.3. Sensitivity Analyses

Table 4 summarizes the sensitivity analyses that will be produced for the primary endpoint.

All sensitivity analyses will be based on an ANCOVA model using the FAS population; in addition sensitivity analysis due to dosing pause will be repeated on PPS population.

Population of no impact by dosing pause will be defined as the participants who have at least one valid 24-hour urine collection obtained within 3 weeks prior to the Week 26 Visit before dosing pause.

Table 4: Sensitivity Analyses

Sensitivity Analysis	Applied Cohorts	Handling of Intercurrent Events/ Description
Placebo-based multiple imputation + carry-forward	LN cohort only	Treatment discontinuation: • Data collected on or after treatment discontinuation will be imputed using placebo-based multiple imputation. Receipt of additional standard of care therapy (LN cohort only): • Data collected on or after receipt of additional standard of care therapy will be imputed using the value collected at the time of flare (carry forward).
Placebo-based multiple imputation	LN and IgAN cohorts	Treatment discontinuation: • Data collected on or after treatment discontinuation will be imputed using placebo-based multiple imputation. Receipt of additional standard of care therapy (LN cohort only): • Data collected on or after receipt of additional standard of care therapy will be imputed using placebo-based multiple imputation.
Tipping point analysis	LN and IgAN cohorts	Participants who receive additional standard of care therapy (LN cohort only), discontinue treatment, withdraw early, or die are assumed to have outcomes that are worse than otherwise similar participants who remain in the study or did not receive additional standard of care therapy or discontinue treatment.

Table 4: Sensitivity Analyses

Sensitivity Analysis	Applied Cohorts	Handling of Intercurrent Events/ Description
Per-randomized stratification analysis	LN and IgAN cohorts	Treatment discontinuation: • Data collected on or after treatment discontinuation will be imputed using multiple imputation. Receipt of additional standard of care therapy (LN cohort only): • Data collected on or after receipt of additional standard of care therapy will be imputed using the value collected at the time of flare (carry-forward).
Sensitivity analysis due to dosing pause-excluding data points impacted by dosing pause	LN and IgAN cohorts	Dosing pause will be regarded as an intercurrent event, in which the analysis is similar to that of treatment discontinuation.
Sensitivity analysis due to dosing pause-excluding participants impacted by dosing pause	LN and IgAN cohorts	The participants in the population of no impact by dosing pause will be included.

Abbreviations: IgAN = immunoglobulin A nephropathy; LN = lupus nephritis

Further details of these sensitivity analyses are below.

- Placebo-based multiple imputation + carry-forward: The primary endpoint will be analyzed in the same manner as the primary analysis, except that data collected on or after treatment discontinuation will be assumed missing and imputed using placebo-based multiple imputation where it will be assumed that outcomes occurring after treatment discontinuation will follow the trajectory of outcomes similar to the one in the placebo treatment group, taking into account observed values prior to treatment discontinuation (Ratitch, 2014).
- Placebo-based multiple imputation: The primary endpoint will be analyzed in the same manner as the primary analysis, except data collected on or after treatment discontinuation or receipt of additional standard of care therapy (LN cohort only) will be assumed missing and imputed using placebo-based multiple imputation.
- Tipping point analysis: An additional sensitivity analysis will be performed based on the delta-adjusted stress testing method (tipping point analysis). This approach assumes that participants who discontinue from ALXN2050 treatment or who receive additional standard-of-care therapy (for the LN cohort only) experience worsening, defined by a prespecified adjustment (delta) in the primary efficacy endpoint compared with the observed efficacy score of participants who continue the study to the next visit. For each value of delta, the treatment effect will be determined, and the value of delta for which the nominal 2-sided p-value crosses 0.10 will be considered

as the "tipping point" in the sense that the conclusion drawn from the primary analysis is reversed when participants who drop out or who receive additional standard-of-care therapy are assumed to experience this fixed adjustment after the discontinuation visit or receipt of additional standard-of-care therapy. After such a tipping point is determined, clinical judgment will be applied as to the plausibility of the assumptions underlying this tipping point. This methodology is expected to inform what it would take to overturn study conclusions based on varying assumptions about missing data (Ratitch, 2013; Ratitch, 2014).

- Per-randomized stratification analysis: The primary endpoint will be analyzed in the same manner as the primary analysis, except using per-randomized stratification factor from IXRS instead of verified stratification factor.
- Additional sensitivity analysis due to dosing pause:
  - The primary endpoint will be analyzed in the same manner as the primary analysis, except that the dosing pause will be regarded as an intercurrent event, in which the analysis is similar to that of treatment discontinuation.
  - Subgroup analysis: Only include participants in the population of no impact by dosing pause.

4.2.4. Supplementary Analyses

Table 5 summarizes the supplementary analyses that will be produced for the primary endpoint.

The purpose of these supplementary analyses is to provide additional insights for the primary efficacy results in selected groups of the study population.

Table 5: Supplementary Analyses

Supplemental Analysis	Applied Cohorts	Population	Handling of IEs
Randomized Set analysis	LN and IgAN cohorts	Randomized Set	• Analysis and handling of IEs will be the same as in the primary analysis • Only performed if the FAS excludes more than 10% of the Randomized Set
mFAS analysis	LN and IgAN cohorts	mFAS	• Analysis and handling of IEs will be the same as in the primary analysis • Only performed if the mFAS excludes more than 10% of the FAS
PPS analysis	LN and IgAN cohorts	PPS	• Analysis and handling of IEs will be the same as in the primary analysis
Treatment policy analysis	LN and IgAN cohorts	FAS	• The primary endpoint will be analyzed in the same manner as in the primary analysis except that all observed data will be used, regardless of receipt of additional standard of care therapy (LN cohort only) or treatment discontinuation

Abbreviations: FAS = Full Analysis Set; IE = intercurrent event(s); IgAN = Immunoglobulin A Neuropathy; mFAS = Modified Full Analysis Set; PPS = Per-Protocol Set

In addition, the same ANCOVA model as described in Section 4.2.2 will be used for the primary efficacy analysis to compare reductions in proteinuria between the ALXN2050 Total and placebo groups.

4.3. Secondary Endpoint Analysis

The secondary efficacy analyses will be based on the FAS. These analyses will be descriptive in nature and no adjustment for multiplicity will be performed.

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

The estimands for the key secondary analyses are defined in Table 6.

Table 6: Estimands for Key Secondary Analyses

Estimand	Population	Variable	Intercurrent Event	Population-level Summary
Key secondary analysis (continuous)	FAS	• Percentage change in proteinuria from baseline to Week 50 (both cohorts) • Change from baseline in eGFR at Weeks 26 and 50 (both cohorts)	• Receipt of additional standard-of-care therapy for a protocol-defined renal flare or suboptimal response (LN cohort only) • Treatment discontinuation	• Mean difference of percentage change in proteinuria from baseline in each treatment group • Mean change in eGFR from baseline in each treatment group
Key secondary analysis (binary)	FAS	• Achieving > 30% and > 50% reduction in proteinuria at Weeks 26 and 50 compared to baseline (both cohorts) • Meeting the criteria for CRR at Weeks 26 and 50 (LN cohort only) • Meeting the criteria for PRR at Weeks 26 and 50 (LN cohort only) • Meeting the criteria for partial remission at Weeks 26 and 50 (IgAN cohort only)	• Receipt of additional standard-of-care therapy for a protocol-defined renal flare or suboptimal response (LN cohort only) • Treatment discontinuation	• Response rate in each treatment group

Abbreviations: CRR = complete renal response; eGFR = estimated glomerular filtration rate; FAS = Full Analysis Set; LN = lupus nephritis; PRR = partial renal response

4.3.1. Secondary Endpoints

4.3.1.1. Percentage Change in Proteinuria from Baseline to Week 50 (Both Cohorts)

The percentage change from baseline in proteinuria at Week 50 will be analyzed using a mixed-effect model for repeated-measures (MMRM) using all available data up to Week 50 (either complete or partial). The data after the intercurrent events will be treated as missing. The model will include change from baseline in log-transformed proteinuria as the response variable and fixed, categorical effects of treatment sequence group, randomization stratification factor, visit, and treatment sequence 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 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. The point estimate and 2-sided 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 treatment effect will be evaluated for the ALXN2050 120 mg & 180 mg bid and placebo treatment group in the same model mentioned above.

For the IgAN cohort, participants initially randomized to the placebo treatment group will switch to receive either ALXN2050 180 mg bid or ALXN2050 120 mg bid at Week 26. Percentage change from baseline in proteinuria at Week 50 will be summarized for each treatment sequence group from the MMRM analysis and no formal treatment comparison will be made. In addition, percentage change from re-baseline (ie, Week 26) in proteinuria at Week 50 will also be summarized for each treatment sequence group descriptively.

In addition to the proteinuria analyses based on 24-hour urine collections, the percentage change from baseline in spot UPCR at each scheduled visit up to Week 50 will also be analyzed using an MMRM model in a similar manner. The plot to present the trajectory of proteinuria over time based on spot UPCR will be visualized by treatment/treatment sequence group.

In addition to the MMRM analysis, observed values, change from baseline, and percent change from baseline in proteinuria will be summarized descriptively by treatment group at baseline and each post-Baseline time point separately by study phase.

The trajectory of proteinuria over time will be visually presented by plotting the mean proteinuria based on 24-hour urine collections at each time point by treatment/treatment sequence group.

4.3.1.2. Reduction in Proteinuria at Weeks 26 and 50 Compared to Baseline (Both Cohorts)

The percentage of participants achieving > 30% and > 50% reduction in proteinuria based on 24-hour urine collection at Weeks 26 and 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.

Participants for receipt of additional standard of care therapy (LN cohort only) or treatment discontinuation will be treated as failure to meet the reduction cutoff and considered nonresponders.

A bar chart will also be provided displaying the percentage of participants achieving > 30% and > 50% reduction in proteinuria at Weeks 26 and 50 by treatment group.

4.3.1.3. Change from Baseline in eGFR at Weeks 26 and 50 (Both Cohorts)

Kidney function evaluated by eGFR will be calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. For participants requiring dialysis for acute kidney injury, a value of 10 mL/min/1.73 m^2 will be imputed for while participants are on dialysis (ie, from the first day of dialysis through 5 days after the end of dialysis).

For participants in the LN cohort, baseline eGFR will be defined as the lowest measurement available prior to the first dose of study intervention. For participants in the IgAN cohort, baseline eGFR will be defined as the mean of the Screening and Day 1 measurements.

The longitudinal changes in eGFR will be analyzed using the same MMRM method specified in Section 4.3.1.1, but the log-transformation of eGFR is not required. The eGFR will be summarized at baseline and at Weeks 26 and 50 by treatment group using descriptive statistics for the observed value as well as the change from baseline. No formal treatment comparison will be made. The point estimate and 2-sided 95% CI for the change from baseline of eGFR will be presented.

For the IgAN cohort, a similar summary will be made and the change from re-baseline (ie, Week 26) in eGFR at Week 50 will also be presented for each treatment sequence group from the MMRM analysis.

The data after the intercurrent events will be treated as missing.

In addition to the MMRM analysis, observed values, change from baseline, and percent change from baseline in eGFR will be summarized descriptively by treatment group at baseline and each post-Baseline time point separately by study phase.

The trajectory of eGFR over time will be visually presented by plotting the mean eGFR at each time point by treatment group.

4.3.1.4. Complete Renal Response (LN Cohort Only)

Complete renal response (CRR) will be assessed at Weeks 26 and 50. To achieve CRR, participants in the LN cohort must meet all 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 50)
- eGFR > 60 mL/min/1.73 m^2 or no eGFR reduction ≥ 20% from the baseline value based on the mean of 2 values. The first eGFR value must be obtained within 2 weeks prior to the study visit (Week 26 or 50) and the second eGFR value will be obtained on the study visit (Week 26 or 50)
- No treatment failure (as defined in Section 4.3.1.10)

The percentage of participants meeting the criteria for CRR as well as individual components of CRR will be summarized at Weeks 26 and 50 by treatment group by calculating the point estimate and 2-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method.

Study participants with treatment discontinuation will be treated as failure to meet CRR criteria and considered nonresponders.

A bar chart will also be provided displaying the proportion of participants meeting the criteria for CRR as well as individual components of CRR at Weeks 26 and 50 by treatment group.

4.3.1.5. Partial Renal Response (LN Cohort Only)

Partial renal response (PRR) will be assessed at Weeks 26 and 50. To achieve PRR, participants who did not achieve CRR in the LN cohort must meet all of the following criteria:

- 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 50)
- eGFR > 60 mL/min/1.73 m^2 or no eGFR reduction ≥ 20% from the baseline value based on the mean of 2 values. The first eGFR value must be obtained within 2 weeks prior to the study visit (Week 26 or 50) and the second eGFR value will be obtained on the study visit (Week 26 or 50)
- No treatment failure (as defined in Section 4.3.1.10)

The percentage of participants meeting the criteria for PRR as well as individual components of PRR will be summarized at Weeks 26 and 50 by treatment group by calculating the point estimate and 2-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method.

Study participants with treatment discontinuation will be treated as failure to meet PRR criteria and considered nonresponders.

A bar chart will also be provided displaying the proportion of participants meeting the criteria for PRR as well as individual components of PRR at Weeks 26 and 50 by treatment group.

4.3.1.6. Time to the First Occurrence of UPCR ≤ 0.5 g/g (LN Cohort Only)

Time to the first occurrence of UPCR ≤ 0.5 g/g will be summarized by spot urine sample.

Participants will be censored at the earliest of their treatment discontinuation time, receipt of additional standard of care therapy (LN cohort only), study withdrawal or death, or at Week 50 when the event of UPCR ≤ 0.5 g/g has not yet occurred.

Kaplan-Meier will be used to estimate the survival curve. The corresponding Kaplan-Meier curve for each treatment group will be created by plotting the cumulative proportion surviving against the survival times.

The curves for the ALXN2050 180 mg and placebo treatment groups will be statistically compared with a log-rank test of the null hypothesis that there is no difference between the population survival curve over time. A corresponding summary table will present the cumulative distribution function (CDF) estimate, the number of participants at risk, the number of participants responding (ie, occurrence of UPCR ≤ 0.5 g/g), and the number of participants censored at each post-Baseline time point by treatment group. The table will also present first quartile, median, and third quartile, along with corresponding 2-sided 95% CI of time to response.

4.3.1.7. Corticosteroid Taper (LN Cohort Only)

A corticosteroid taper will commence at Week 2 (Day 15). From Weeks 12 to 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 Weeks 46 to 50, the dose of corticosteroids must not be changed.

The percentage of participants receiving ≤ 7.5 mg/day will be summarized at Weeks 12, 26, and 50 by treatment group by calculating the point estimate and 2-sided 95% CI based on exact confidence limits using the Clopper-Pearson method.

4.3.1.8. Renal Flare (LN Cohort Only)

Renal flare is determined in the opinion of the Investigator in addition to the criteria outlined below and will be recorded on the Renal Flare eCRF:

- For participants who achieve CRR, a renal flare is the reproducible recurrence of proteinuria ≥ 1 g/g
- For all other participants, a renal flare is either of the following:
  - Reproducible increase of serum creatinine > 25% higher than baseline or above the upper limit of normal, plus any one of the following:
    - Reproducible proteinuria ≥ 75% higher than baseline
    - Worsening active urinary sediment compared to baseline as defined by an increase of ≥ 5 red blood cells (RBC)/high power field (hpf) or new RBC casts (based on local laboratory results from at least 2 samples)
    - Kidney biopsy demonstrating LN Class III or IV activity that 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 a morning spot urine collection be confirmed by a central laboratory UPCR based on 24-hour urine collected within 2 weeks.

Reproducibility of serum creatinine requires 2 blood tests within a 2-week period.

The percentage of participants meeting the criteria for renal flare through 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.

4.3.1.9. Extrarenal SLE Flare (LN Cohort Only)

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

The trajectory of SLEDAI-2K SELENA Modification score over time will be visually presented by plotting the mean values at each time point by treatment group.

The percentage of participants meeting the criteria for extrarenal SLE flare and severe extrarenal SLE flare through 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.

4.3.1.10. Treatment Failure (LN Cohort Only)

Treatment Failure is defined as the receipt of additional standard of care therapy at any time up during the study for protocol-defined renal flare, severe extrarenal SLE flare, or suboptimal response as recorded on the Additional Standard of Care Therapy eCRF.

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. If a calcineurin inhibitor (CNI) is used for additional standard of care therapy, study intervention will need to be discontinued 3 days prior to CNI administration.

The percentage of participants meeting the criteria for treatment failure through 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.

4.3.1.11. Suboptimal Response (LN Cohort Only)

For the LN cohort, a suboptimal response is determined in the opinion of the Investigator in addition to the following criteria after the Week 26 Visit:

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

Reproducibility of proteinuria requires that UPCR from a morning spot urine collection be confirmed by a central laboratory UPCR based on 24-hour urine collected within 2 weeks.

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.

The percentage of participants meeting the criteria for suboptimal response will be summarized through Week 50 by treatment group by calculating the point estimate and 2-sided 95% CI based on exact confidence limits using the Clopper-Pearson method.

4.3.1.12. Serum Albumin (LN Cohort Only)

Serum albumin will be summarized at baseline and at Weeks 26 and 50 by treatment group using descriptive statistics as defined in Section 4.1 for the observed value as well as the change from baseline.

The trajectory of serum albumin over time will be visually presented by plotting the mean values at each time point by treatment group.

4.3.1.13. Partial Remission (IgAN Cohort Only)

For the IgAN cohort, 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 50).

The percentage of participants meeting the criteria for partial remission will be summarized at Weeks 26 and 50 by treatment group by calculating the point estimate and 2-sided 95% CI based on exact confidence limits using the Clopper-Pearson method.

Participants who discontinue treatment prior to the endpoint will be treated as failure to meet partial remission criteria and considered nonresponders.

A bar chart will also be provided displaying the proportion of participants meeting the criteria for partial remission at Weeks 26 and 50 by treatment group.

4.3.2. Sensitivity Analysis for Key Secondary Endpoints Due to Dosing Pause

4.3.2.1. Percentage Change in Proteinuria from Baseline to Week 50 (Both Cohorts)

Two sensitivity analyses will be used to assess the impact of dosing pause.

The endpoint will be analyzed in the same manner as described in Section 4.3.1.1, except that dosing pause would be regarded as intercurrent event, in which the analysis is similar to that of treatment discontinuation.

The endpoint will also be analyzed in the same manner as described in Section 4.3.1.1, except that only the participants in the population of no impact by dosing pause are included.

4.3.2.2. Reduction in Proteinuria at Weeks 26 and 50 Compared to Baseline (Both Cohorts)

The endpoint will also be analyzed in the same manner as described in Section 4.3.1.2, except that only participants in the population of no impact by dosing pause are included.

4.3.2.3. Change from Baseline in eGFR at Weeks 26 and 50 (Both Cohorts)

Two sensitivity analysis will be used to assess the impact of dosing pause.

The endpoint will be analyzed in the same manner as described in Section 4.3.1.3, except that dosing pause would be regarded as intercurrent event, in which the analysis is similar to that of treatment discontinuation.

The endpoint will also be analyzed in the same manner as described in Section 4.3.1.3, except that only the participants in the population of no impact by dosing pause are included.

4.3.2.4. Complete Renal Response (LN Cohort Only)

The endpoint will also be analyzed in the same manner as described in Section 4.3.1.4, except that only the participants in the population of no impact by dosing pause are included.

4.3.2.5. Partial Renal Response (LN Cohort Only)

The endpoint will also be analyzed in the same manner as described in Section 4.3.1.5, except that only the participants in the population of no impact by dosing pause are included.

4.3.2.6. Partial Remission (IgAN Cohort Only)

The endpoint will also be analyzed in the same manner as described in Section 4.3.1.13, except that only the participants in the population of no impact by dosing pause are included.

4.4. Exploratory Endpoint Analysis

The exploratory analyses will be based on the FAS. These analyses will be descriptive in nature and no adjustment for multiplicity will be performed. In addition, there will be no imputation for missing data or data collected on or after the receipt of additional standard-of-care therapy (LN cohort only) or treatment discontinuation unless otherwise specified.

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

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

4.4.1. Percentage Change in Proteinuria from Baseline to Weeks 102 and 154 (Both Cohorts)

The analysis will be performed at Weeks 102 and 154 using the same approach as defined in Section 4.3.1.1. Results will be presented for each treatment sequence group.

4.4.2. Change from Baseline in eGFR at Weeks 102 and 154 (Both Cohorts)

The analysis will be performed at Weeks 102 and 154 using the same approach as defined in Section 4.3.1.3. Results will be presented for each treatment sequence group.

4.4.3. Effect on Hematuria (Both Cohorts)

For both cohorts, the effect on hematuria will be measured by the following:

- RBC in urine from baseline to Weeks 26 and 50
- Participants achieving < 10 RBC/hpf

RBC in urine will be summarized at each time point by treatment group using frequency statistics for categorical variables. The percentage of participants with < 10 RBC will be summarized at each scheduled visit by calculating the point estimate and 2-sided 95% CI based on exact confidence limits using the Clopper-Pearson method.

4.4.4. SF-36 (Both Cohorts)

The 36-item Short Form Health Survey (SF-36) version 2 is a set of generic, coherent, and easily administered QoL measures. It has 36 items grouped in 8 dimensions. For both cohorts, the SF-36 total score, Physical Component Summary (PCS), Mental Component Summary (MCS), and domain scores as defined in Table 7 will be summarized by treatment group at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline.

The longitudinal changes in SF-36 will be analyzed using MMRM method specified in Section 4.3.1.1 except the log-transformation of SF-36 is not performed. Change from baseline in SF-36 at Weeks 26 and 50 will be summarized for each treatment group from the MMRM analysis and no formal treatment comparison will be made. The point estimate and 2-sided 95% CI for the change from baseline of SF-36 will be presented. Data collected on or after receipt of additional standard of care therapy (LN cohort only) or treatment discontinuation will be assumed missing and handled in the MMRM model as MAR.

Refer to Section 6.3 for a more detailed description of the SF-36 calculation and scoring methods.

Table 7: SF-36 Domain Scores

Scale	Number of Items	Definition of Scale
Physical Functioning (PF)	10	Limitations in physical activity because of health problems
Social Functioning (SF)	2	Limitations in social activities because of physical or emotional problems
Role Limitations Due to Physical Health (RP)	4	Limitations in usual role activities because of physical health problem
Bodily Pain (BP)	2	Prescence of pain and limitations due to pain
General Health (GH)	5	Self-evaluation of personal health
Mental Health (MH)	5	Psychological distress and well-being
Role Limitations Due to Emotional Problems (RE)	3	Limitations in usual role activities because of emotional problems
Vitality (VT)	4	Energy and fatigue

Abbreviation: SF-36 = 36-item Short Form Health Survey

4.4.5. EQ-5D-5L (Both Cohorts)

The 5-level EuroQol-5 Dimensions (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.

Refer to Section 6.3 for a more detailed description of the EQ-5D-5L calculation and scoring methods.

For both cohorts, the EQ-5D-5L index score and visual analog scale (VAS) score will be summarized by treatment group at baseline and each post-Baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline.

Change from baseline in EQ-5D-5L scores at Weeks 26 and 50 will also be analyzed using the same MMRM method, and no formal treatment comparison will be made. The point estimate and 2-sided 95% CI for the change from baseline of EQ-5D-5L scores will be presented. Data collected on or after receipt of additional standard of care therapy or treatment discontinuation will be assumed missing and handled in the MMRM model as MAR.

4.4.6. Exploratory Biomarkers (Both Cohorts)

Exploratory blood and urine biomarker analyses will be documented in a separate biomarker SAP.

4.4.7. Time to First CRR or PRR (LN Cohort Only)

For LN cohorts, time to the first occurrence of CRR or PRR will be summarized by spot urine sample.

Participants will be censored at the earliest of their treatment discontinuation time, receipt of additional standard of care therapy, study withdrawal or death, or at Week 50 when the event of CRR or PRR has not yet occurred.

The analysis will be performed using 2 approaches:

- Time to the first CRR (using spot UPCR)
- Time to the first CRR or PRR (using spot UPCR) – time to the first event (either CRR or PRR, whichever occurred first)

Kaplan-Meier will be used for estimating the survival curve. The corresponding Kaplan-Meier curve for each treatment group will be created by plotting the cumulative proportion surviving against the survival times.

The curves for the ALXN2050 180 mg and placebo treatment groups will be statistically compared with a log-rank test of the null hypothesis that there is no difference between the population survival curve over time. A corresponding summary table will present the CDF estimate, the number of participants at risk, the number of participants responding (ie, occurrence of first CRR or PRR), and the number of participants censored at each post-Baseline time point by treatment group. The table will also present first quartile, median, and third quartile, along with corresponding 2-sided 95% CI of time to response.

4.4.8. Overall Renal Response (LN Cohort Only)

For the LN cohort, Overall Renal Response (ORR) is defined as the composite of CRR and PRR.

The percentage of participants meeting the criteria for ORR will be summarized at Weeks 26 and 50 by treatment group by calculating the point estimate and 2-sided 95% CI based on exact confidence limits using the Clopper-Pearson method.

Participants with additional standard of care therapy (LN cohort only) or treatment discontinuation will be treated as failure to meet ORR criteria and considered nonresponders.

4.4.9. Time to the First Occurrence of UPCR > 50% Decrease from Baseline (LN Cohort Only)

For the LN cohort, time to the first occurrence of UPCR > 50% decrease from baseline will be summarized by spot urine sample.

Participants will be censored at the earliest of their treatment discontinuation time, receipt of additional standard of care therapy, study withdrawal or death, or at Week 50 when the event of UPCR > 50% decrease has not yet occurred.

Kaplan-Meier will be used to estimate the survival curve. The corresponding Kaplan-Meier curve for each treatment group will be created by plotting the cumulative proportion surviving against the survival times.

The curves for the ALXN2050 180 mg and placebo treatment groups will be statistically compared with a log-rank test of the null hypothesis that there is no difference between the population survival curve over time. A corresponding summary table will present the CDF estimate, the number of participants at risk, the number of participants responding (ie, occurrence of UPCR decrease > 50%), and the number of participants censored at each post-Baseline time point by treatment group. The table will also present first quartile, median, and third quartile, along with corresponding 2-sided 95% CI of time to response.

4.4.10. FACIT-Fatigue Total Score (LN Cohort Only)

For the LN cohort, the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue total score will be summarized by treatment group at baseline and at Weeks 26 and 50 for the change from baseline using descriptive statistics for continuous variables.

The longitudinal changes in FACIT-Fatigue total score will be analyzed using MMRM method specified in Section 4.3.1.1, except the log-transformation of score is not performed.

Change from baseline at Weeks 26 and 50 will be summarized for each treatment group from the MMRM analysis, and no formal treatment comparison will be made. The point estimate and

2-sided 95% CI for the change from baseline of FACIT-Fatigue total score will be presented. Data collected on or after receipt of additional standard of care therapy or treatment discontinuation will be assumed missing and handled in the MMRM model as MAR.

Refer to Section **Error! Reference source not found.** for a more detailed description of the FACIT-Fatigue calculation and scoring methods.

4.4.11. Histology (LN Cohort Only)

For participants in the LN cohort who complete an optional post-treatment biopsy at Week 50, changes in histology will be summarized using the central pathology biopsy results. Activity index and chronicity index scores will be summarized at baseline and at Week 50 by treatment group using descriptive statistics for the observed value as well as the change from baseline. In addition, shift tables will display the change in LN class, C3 staining, and C1q staining from pretreatment renal biopsy to post-treatment renal biopsy.

4.4.12. Anti-dsDNA and Anti-C1q Antibodies (LN Cohort Only)

For the LN cohort, anti-dsDNA and anti-C1q antibodies will be summarized at baseline and at Weeks 26 and 50 by treatment group using descriptive statistics for the observed value as well as the change from baseline.

In addition, the proportion of participants with anti-dsDNA antibodies below the lower limit of normal (LLN) and with anti-C1q antibodies below the LLN will be summarized descriptively at each study visit by treatment group by calculating the point estimate and 2-sided 95% CI, based on exact confidence limits using the Clopper-Pearson method.

4.4.13. Slope of eGFR (IgAN Cohort Only)

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

4.4.14. Clinical Complement Tests (Both Cohorts)

For both cohorts, C3, C4, FD, and CH50 will be summarized at each visit by treatment group using descriptive statistics for the observed value as well as the change from baseline.

4.5. Safety Analyses

The safety and tolerability of ALXN2050 will be assessed based on adverse events (AEs), clinical laboratory findings, vital sign findings, electrocardiogram (ECG) abnormalities, and physical examination. All safety analyses will be performed on the SS based on the actual treatment received.

AEs will be coded in Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 or higher and presented by MedDRA system organ class (SOC) and preferred term (PT).

All safety data will be provided in participant listings by treatment group. No formal hypothesis testing is planned. Safety data will be presented separately for the 26-week Blinded Initial Evaluation Period, 24-week Blinded Extended Treatment Period, and 2-year OLE Period.

4.5.1. Extent of Exposure

The cumulative and total drug exposure, compliance, and treatment duration will be summarized descriptively by treatment group for each disease cohort separately. The SS will be used for the analysis.

Treatment duration will be calculated (in weeks) as the difference between the date of last dose and the date of first dose plus 1, then divided by 7. The duration will be summarized with descriptive statistics.

Treatment compliance will be calculated as a percentage based on number of tablets received out of the number of tablets expected, where the number of tablets received= the number of tablets dispensed - the number of tablets returned; Number of tablets expected= 6 tablets/day × duration in number of days.

In addition to descriptive summary, the number and proportion of participants who had treatment compliance percentage in range by increments of 10% (eg, ≥ 90% to ≤ 100%; ≥ 80% to < 90%; ≥ 70% to < 80%) will also be summarized by treatment group for each disease cohort separately.

The expected and received total dose amounts will be calculated as follows:

Expected total dose amount = assigned dose × daily frequency (bid) × duration in number of days

Received total dose amount = 60 mg × number of tablets received

4.5.2. Adverse Events

The following definitions will be used for AEs:

- **Pretreatment AE:** Any AE that starts after providing informed consent, but before the first dose of study intervention (ALXN2050 or placebo)
- **Treatment-emergent adverse event (TEAE):** Any AE that starts between the start of the first dose of study intervention and up to 30 days after the last dose of study intervention
- **Treatment-emergent serious adverse event (TESAE):** A TEAE that is serious
- **Post-treatment AEs:** Any AE that starts 30 days or later after the last dose of study intervention

All AEs will be coded using MedDRA version 26.1 or higher and will be summarized by SOC and PT overall, by severity, and by relationship to treatment.

Participants having multiple AEs within a category (eg, overall, SOC, PT) will be counted once in that category. For severity/relationship tables, the participant's highest grade/most related event within a category will be counted.

TEAEs and serious adverse events (SAEs) will be summarized descriptively by treatment group. Percentages will be based on the number of treated participants in the SS within a treatment group. Tables will be sorted by descending frequency of SOC and by descending frequency of PT within an SOC.

Pretreatment and post-treatment AEs will be provided in by-participant listings and will not be included in summary tables.

In addition, AEs that occur after the receipt of additional standard of care therapy will be provided in a separate listing.

4.5.2.1. Overall Summary of AEs

The following event subcategories will be summarized by treatment group for each disease cohort separately. The number of events (n) and number and percentage of participants with events (n, %) will be shown.

- TEAEs
- TEAEs leading to withdrawal from the study
- TEAEs leading to study treatment discontinuation
- Related TEAEs
- TEAEs by toxicity grade

The summary will be prepared separately for all AEs and SAEs. Additionally, the number and percentage of participants who died on study will be presented.

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.

4.5.2.2. AEs and SAEs by SOC and PT

The number of TEAEs and TESAEs and the number and percentage of participants with events will be presented by SOC and PT. Participants are counted once in each SOC and PT. Percentages will be based on the total number of treated participants in the treatment group. SOCs will be listed in descending order of frequency of occurrence.

Additional summary tables stratifying AEs and SAEs by age, gender, and race will also be provided.

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

The number of TEAEs, TESAEs, and the number and percentage of participants with events will be presented by SOC and PT as described above by relationship (related, not related). If a participant has more than 1 occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. SAEs will be summarized similarly.

4.5.2.4. AEs by SOC, PT, and Severity

The number of TEAEs and the number and percentage of participants with events will be presented by SOC and PT as described above by toxicity grade (Grade 1, Grade 2, Grade 3,

Grade 4, and Grade 5). If a participant has more than 1 occurrence of an AE, the most severe occurrence will be used in the summary table.

4.5.2.5. Deaths and Other Significant AEs

Individual listings will be presented for AEs leading to study treatment discontinuation, AEs leading to withdrawal from the study, meningococcal infections, seizures, and fatal AEs.

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Parameters

Laboratory assessments are defined in Protocol Section 10.2.

Observed values and changes from baseline in clinical chemistry, hematology, coagulation, and urinalysis will be summarized descriptively by treatment group at baseline and at each scheduled post-Baseline 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. For analysis purposes, laboratory results based upon standardized units will be used.

Box plots will be presented for the following central laboratory parameters by visit: ALT, AST, and creatinine.

In addition, abnormal liver enzyme elevations will be addressed by a table that presents the counts and percentages of participants who met any of the following criteria by treatment group at baseline, at each scheduled post-Baseline time point, and during treatment separately for each disease cohort:

- 3×, 5×, 10×, and 20× ULN elevations of AST, ALT.
- 1.5× ULN elevation of ALP.
- Elevation of bilirubin (> 2× ULN).
- Elevation of ALT (> 3× ULN) accompanied by elevated bilirubin (> 2× ULN).
- Elevation of ALT (> 3×ULN) accompanied by elevated bilirubin (> 2× ULN), without elevated ALP, that is, ALP< 2× ULN.

A listing of ALT, AST, total bilirubin, and ALP at all visits will be generated for all participants who met any of the above criteria. Data from local laboratory will not be included in the analysis, except liver enzyme elevations when unit and ULN are available. All central and local laboratory data will be presented in listings, and a specific listing of abnormal results will be provided.

4.5.3.2. Vital Signs

Vital signs will include systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]), and pulse oximetry (%).

Observed values as well as changes from baseline vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be summarized descriptively at each time point by treatment group separately for each disease cohort.

A listing of vital signs will be presented for each disease cohort by treatment group, participant, vital sign, and visit.

4.5.3.3. Electrocardiograms

By-participant data listings of ECG parameters will be provided separately for each disease cohort. ECGs will be evaluated and summarized as normal, abnormal not clinically significant, or abnormal clinically significant.

A shift of overall interpretation 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 post-Baseline time point. QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

4.5.3.4. Physical Examinations

The types and the list of physical examinations are specified in Protocol Section 8.3.1. Adverse changes from baseline in physical examination findings will be classified as AEs and analyzed accordingly. Abnormal physical examination results will be summarized by visit for each treatment group for the SS.

4.6. Other Analyses

4.6.1. Other Variables and/or Parameters

This study will also include PK analysis, PD analysis, COVID-19-related analysis, and subgroup analysis as described in the following sections.

4.6.2. PK/PD Analysis (Both Cohorts)

The SS will be used for PK concentration listings and individual figures, and the PK Analysis Set will be used for PK parameter listings, summary tables, and mean figures.

4.6.2.1. Plasma PK Concentrations

Individual plasma concentrations of ALXN2050 will be presented in data listings and summarized separately using descriptive statistics (N, n [nonmissing values within the population], arithmetic mean, SD, CV%, median, minimum, and maximum) by treatment group, day, and scheduled time point. Individual plasma concentrations of ALXN2050 will be plotted for each participant by actual time (in days) for both treatment periods on both linear and semilogarithmic scales. Mean plasma concentrations of ALXN2050 versus nominal time (in days) will be plotted for both treatment periods on both linear and semilogarithmic scales and with active treatment groups overlayed on the same plot.

Plasma concentrations of ALXN2050 will be reported to 3 significant figures in summary statistics except for CV%, which will be reported to 1 decimal place, and N and n, which will be reported as an integer.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of descriptive statistics. When all concentrations are BLQ for a time point, the mean will be presented as BLQ, and the SD and CV will be reported as not applicable, otherwise the calculated mean will be presented.

4.6.2.2. Plasma PK Parameters

Plasma PK parameters of ALXN2050 will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) by treatment group and day.

4.6.2.3. PD Analysis

The SS will be used for PD listings and individual figures, and the PD Analysis Set will be used for PD summary tables and mean figures.

The predose sample will be classified as the baseline value. Individual absolute values and change from baseline in serum alternative pathway (AP) activity and plasma Bb fragment of complement factor B (Bb) concentrations will be presented in data listings and summarized separately using descriptive statistics (N, n [nonmissing values within the population], arithmetic mean, SD, CV%, median, minimum, and maximum) by treatment group, treatment period, day, and scheduled time point.

Individual absolute values and change from baseline in serum AP activity and plasma Bb concentrations will be plotted for each participant by actual time (in days). Mean change from baseline in serum AP activity and plasma Bb concentrations will be plotted by nominal time (in days) continuous for both periods and with all treatment groups overlayed on the same plot.

Missing concentrations will be excluded from all calculations and PD analyses.

Serum AP activity and plasma Bb concentration will be reported to 3 significant figures in summary statistics except for CV%, which will be reported to 1 decimal place and N and n, which will be reported as an integer.

4.6.2.4. Population PK and PK/PD Analysis

Details of population PK modeling as well as PK/PD modeling will be presented in a separate analysis plan. Results from the population PK/PD analyses will be presented in a separate report.

4.6.3. COVID-19-Related Analysis

The following COVID-19 related data will be collected in this study:

- Modified and missed study visits (and COVID-19-related reasons)
- Discontinuations impacted by COVID-19
- COVID-19 exposure
- AEs related to COVID-19
- Protocol deviations related to COVID-19 (visit performed remotely, visit not done, visit procedures not done, laboratory draws missed due to COVID-19, site staff not available to see study participants)

A listing of all participants affected by these COVID-19-related study disruptions will be provided by participant identifier and investigative site, including a description of the COVID-19 related study disruption.

The number of participants with missed study visits and the reasons for missed study visits (COVID-19-related or other) will be summarized by treatment groups and overall. In addition, the number of participants with modified study visits and the reasons for modified study visits (COVID-19-related or other) will be summarized by treatment group and overall. Similarly, the number of participants with modified study visits and the ascertainment method for the modified visit will be summarized by treatment group and overall. A by-participant listing of visit status and assessment ascertainment for participants with modified visits will also be produced.

To assess the impact of change in endpoint ascertainment, descriptive statistics of the primary and key secondary endpoints by method of assessment (in-clinic versus alternative method) will be provided using the FAS.

The number of participants with known exposure to COVID-19 will be summarized for pretreatment known exposure and treatment-emergent known exposure by treatment group and overall. A by-participant listing of participants with COVID-19 known exposure or diagnosis will also be produced.

An overall summary table of TEAEs related to COVID-19 will be presented. In addition, the number of TEAEs related to COVID-19 and the number and percentage of participants with TEAEs related to COVID-19 will be presented by SOC and PT.

Protocol deviations related to COVID-19 will be summarized with the overall protocol deviations as specified in Section 6.2.6.

4.6.4. Subgroup Analyses

Summaries of the primary efficacy endpoint will be presented by the following subgroups for both cohorts:

- Age at Screening (18 to 65 years, > 65 years)
- Sex (female, male)
- Baseline eGFR (≤60, > 60-90, > 90 mL/min/1.73 m^2)
- Baseline C3/C4 (at least 1 C3/C4 low, no low C3/C4) Assessment method (in-clinic or alternative method)
- Concomitant therapy with SGLT-2 inhibitors (Yes, No), optional for LN cohort

For the LN cohort, summaries of the primary efficacy endpoint will be presented by the following additional subgroups:

- Duration of disease (≤ 1 year, > 1 year)
- Race/ethnicity (African American, non-African American)
- Baseline proteinuria (≤ 3.5 g/g, > 3.5 g/g)
- Corticosteroid induction timing (prior to Screening, during Screening Period)

- LN class based on central pathology (III or III/V, IV or IV/V)
- TMA on renal biopsy based on central pathology (yes, no)
- Disease status (naïve, relapse)
- Baseline renal biopsy activity index based on central pathology (≤ median, > median)
- Baseline renal biopsy chronicity index based on central pathology (≤ median, > median)

For the IgAN cohort, summaries of the primary efficacy endpoint will be presented by the following additional subgroups:

- Duration of disease (≤ 1 year, 1-5 years, > 5 years)
- Race (Asian or Other Pacific Islander, non-Asian or Other Pacific Islander)
- Baseline proteinuria (1-2 g/day, > 2 g/day)
- Baseline MEST-C score based on central pathology (M0, M1, E0, E1, S0, S1, T0, T1, T2, C0, C1, C2)
- Baseline C3 staining based on central pathology (presence, absence)
- Assessment method (in-clinic or alternative method)

For the IgAN cohort, summaries of the primary efficacy endpoint by subgroups of baseline MEST-C score and baseline C3 staining will be presented separately for participants with biopsies within 1 year of randomization and for participants with biopsies greater than 1 year before randomization if feasible based on sample size.

Given that the number of participants in some subgroups may be limited, subgroup categories may be combined as appropriate. Otherwise, the subgroup analysis may not be performed if deemed infeasible based on sample size.

Forest plots will be produced showing the results of the primary efficacy endpoint (percentage change in proteinuria from baseline to Week 26) with means and corresponding CIs for each subgroup described above.

4.7. Interim Analyses

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 Blinded Initial 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 the LN cohort, will be conducted by a separate unblinded team and will be for Phase 3 planning purposes only, including any applicable regulatory interactions, with no impact on the progression of the study.

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.

An additional analysis will be performed for each disease-specific cohort at the end of the 24-week Blinded Extended Treatment Period after all participants in the disease-specific cohort have completed the Week 50 Visit or withdrawn from the study early. This additional analysis will include all planned efficacy, PK/PD, and safety analyses.

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 and will include all planned analyses that will be presented in the final clinical study report.

4.8. Changes to Protocol-planned Analyses

Based on actual data received from laboratory, the RBC in urine is categorical data. Hence, the endpoint of hematuria will be analyzed as categorical variable instead of continuous variable.

5. 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 Mar 2018, an NKF-sponsored workshop on surrogate endpoints for clinical studies in early stages of chronic kidney disease was held. A 20% to 30% reduction in the geometric mean of albuminuria or 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 participant data from relevant studies in IgAN was previously used to estimate variability and expected changes in proteinuria for participants on placebo with background standard of care treatment (Fellström, 2017). Based on this data, the geometric mean (GM) of the ratio 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 180 mg bid to placebo at Week 26), the GM of the ratio of 26-week to baseline 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 SD of log change is assumed to be 0.60 (Fellström, 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 participants with LN who were treated with mycophenolate mofetil (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 GM of the ratio 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 180 mg bid to placebo at Week 26), the GM of ratio of 26-week to baseline 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 (Fellström, 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.

6. SUPPORTING DOCUMENTATION

6.1. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

6.1.1. Disease Duration

Disease duration will be presented as the number of years between date of first dose and date of diagnosis as reported on the Medical History eCRF. Missing dates will be handled as described in Section 4.1.4.

6.1.2. Definition of Baseline Values

For the 26-week Blinded Initial Evaluation Period, baseline is defined as the last available assessment value prior to the first dose of study intervention. For the 24-week Blinded Extended Treatment Period, a re-baseline is defined as the last available assessment prior to the first dose of study intervention administered in the extension period.

6.1.3. Change from Baseline

Change from baseline will be calculated as the baseline value subtracted from the value at a particular time point. If one of the values is missing and there are no prespecified missing value imputation rules (see Section 4.1.4), then a change from baseline will not be calculated.

6.1.4. Percent Change from Baseline

Percent change from baseline will be calculated as (change from baseline / baseline value) × 100%. If one of the values is missing and there are no prespecified missing value imputation rules (see Section 4.1.4) or if the baseline value is zero, then a percentage change from baseline will not be calculated.

6.1.5. Analysis Visits

Summaries over post-Baseline time points or analyses at specific post-Baseline time points will be performed based on the list of visits described in the schedule of assessment of the protocol. For all assessments, the number of days from baseline will be calculated using the following formula: (date of assessment) – (date of first study treatment) + 1. Relative days prior to Day 1 are calculated as (date of assessment – date of Day 1 Visit). This number of days will be used to assign analysis visit.

The analysis visit assignment for a specific assessment will be based on visit windows around each scheduled visit for that specific assessment. The windows for each scheduled visit will go from the midpoint (in days) between the current visit and the previous scheduled visit to the midpoint between the current visit and the subsequent scheduled visit. If the interval separating 2 scheduled visits is an even number of days, that middle day will be included in the later visit window and excluded from the prior visit window. For example, for an assessment with a scheduled visit Day 127, and a prior scheduled visit Day of 113 and subsequent scheduled visit Day of 141, the window will start at 120 days from baseline and will go to 133 days from baseline.

6.1.6. Analysis Value

The values being considered for analysis at a specific post-Baseline time point will be based on the analysis visit assigned to that value. If there is more than 1 nonmissing value for a specific assessment with the same analysis visit, the value used for analysis will be the one for which the calculated number of days from baseline is closest to the scheduled visit day. If 2 values have the same analysis visit and are the same distance away from the scheduled visit day, the earlier of the 2 values will be used for analysis.

6.1.7. Adverse Events

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

Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first dose of study intervention and up to 30 days after the last dose of study intervention. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose or 30 days after the last dose, then the determination of treatment-emergent status will be based on the following:

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

All other AEs are considered pretreatment adverse events (PTAEs) if the start date is prior to the first dose of study intervention or post-treatment adverse events if the start date is 30 days or later after the last dose of study intervention.

6.1.8. Complete Renal Response (LN Cohort Only)

To achieve CRR, 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 50)
- eGFR > 60 mL/min/1.73 m^2 or no eGFR reduction $\geq 20\%$ 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 50) and the second eGFR value will be obtained on the study visit (Week 26 or 50)
- No treatment failure

Only central laboratory results from both scheduled and unscheduled visits will be used to assess CRR.

In the presence of missing central laboratory values, the following rules will be applied:

- If only 1 nonmissing collection is available at the visit, then this value will be used for analysis.
- If both collections are missing at the visit, then CRR will be treated as missing.

Treatment failure is defined as the receipt of additional standard of care therapy at any time up during the study for protocol-defined renal flare, severe extrarenal SLE flare, or suboptimal response. Therefore, no treatment failure will be determined as the absence of additional standard of care therapy received at any time (Week 26 or 50) as recorded on the Additional Standard of Care Therapy eCRF.

6.1.9. Concomitant Medications/Therapies

The analysis of concomitant medications and therapies is described in detail in Section 6.2.4.

Concomitant medications or therapies are defined as any nonstudy medications or therapies that were taken or given while the participant also received study intervention. A medication or therapy will be considered concomitant if the start date is on or after the date of the first dose of study intervention (Day 1), or if the start date is before the first dose of study intervention and the end (stop) date is after the first dose of study intervention. If the start date of a medication/therapy is partially or completely missing and the end (stop) date of the medication/therapy does not indicate that it ended prior to first dose of study intervention, then the determination of the concomitant status will be based on the following:

- If the start year is after the year of the first dose of study intervention, then the medication/therapy is concomitant; else,
- If the start year is the same as the year of the first dose of study intervention and
  - The start month is missing, then the medication/therapy is concomitant; else,
  - If the start month is present and is the same or after the month of the first dose of study intervention, then the medication/therapy is concomitant; else,
- If the start date is completely missing, then the medication/therapy is concomitant

All other medications/therapies are considered prior medications/therapies.

6.1.10. 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 50).

Only central laboratory results from both scheduled and unscheduled visits will be used to assess partial remission.

In the presence of missing central laboratory values, the following rules will be applied:

- If only 1 nonmissing 24-hour urine collection is available at the visit, then this value will be used for analysis.
- If both collections are missing at the visit, then partial remission will be treated as missing.

6.1.11. Partial Renal Response (LN Cohort Only)

To achieve PRR, participants who did not achieve CRR in the LN cohort must meet all 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 50)
- eGFR > 60 mL/min/1.73 m^2 or no eGFR reduction ≥ 20% from the baseline value based on the mean of 2 values. The first eGFR value must be obtained within 2 weeks prior to the study visit (Week 26 or 50) and the second eGFR value will be obtained on the study visit (Week 26 or 50)
- No treatment failure

Only central laboratory results from both scheduled and unscheduled visits will be used to assess PRR.

In the presence of missing central laboratory values, the following rules will be applied:

- If only 1 nonmissing collection is available at the visit, then this value will be used for analysis.
- If both collections are missing at the visit, then PRR will be treated as missing.

Treatment failure is defined as the receipt of additional standard of care therapy at any time up during the study for protocol-defined renal flare, severe extrarenal SLE flare, or suboptimal response. Therefore, no treatment failure will be determined as the absence of additional standard of care therapy received at any time (Week 26 or 50) as recorded on the Additional Standard-of-Care Therapy eCRF.

6.1.12. Serum Creatinine and Estimated Glomerular Filtration Rate

Serum creatinine measurements are not reliable with concurrent dialysis. Therefore, all serum creatinine values obtained while a participant is on dialysis will be excluded from all analyses. eGFR will be imputed with a value of 10 (mL/min/1.73 m^2) while a participant is on dialysis. A participant will be considered on dialysis from the first day of dialysis through 5 days after the end of dialysis. This rule will only be applied to post-Baseline assessments of serum creatinine and eGFR.

6.2. Study and Participant Characteristics

6.2.1. Study Participants

A summary of enrolled participants, including the number and percentage of participants by region, country, and site, will be presented by treatment group and overall.

In addition, a summary of participants who did not satisfy the inclusion/exclusion criteria will be presented by treatment group and overall.

A summary of participant disposition will include the number and percentage of participants who completed the study or discontinued from the study (along with the primary reason for discontinuation) will be presented. Discontinuation status will be presented overall as well as separately for discontinuations impacted by COVID-19. Number of participants who experienced dosing pause will also be presented. Participant disposition will be presented separately for overall, 26-week Blinded Initial Evaluation Period, 24-week Blinded Extended Treatment Period, and 2-year OLE Period.

The number and percentage of participants in each defined analysis set will also be presented. A summary of enrolled participants by region will be presented by treatment group and overall.

Participants who are randomized but did not satisfy the inclusion/exclusion criteria will be presented by treatment group and overall for each criterion not satisfied.

By-participant data listings for disposition and analysis populations will be provided as well as a listing of participants who did not satisfy the inclusion/exclusion criteria.

6.2.2. Demographics and Baseline Characteristics

All demographic and baseline disease characteristics will be summarized using the FAS. Summary statistics will be presented by treatment group and overall for each disease cohort.

By-participant listings of these data will also be provided.

6.2.2.1. Demographics

The following demographic variables will be summarized:

- Sex
- Race
- Ethnicity
- Age at Screening (years): descriptive statistics (n, mean, median, SD, minimum, maximum) and by frequency of participants in each age category: 18 to 65 years, > 65 years
- Baseline weight (kg): descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories: < 60 kg, 60 to < 100 kg, ≥ 100 kg
- Baseline height (cm)

- Baseline body mass index (kg/m^2)
- Geographical region (North America, Latin America, Europe, and Asia Pacific)

6.2.2.2. Baseline Disease Characteristics

The following baseline disease characteristic will be summarized:

- Duration of disease (years): descriptive statistics (n, mean, median, SD, minimum, maximum)
- Baseline eGFR ($mL/min/1.73m^2$): descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories: <= 60, > 60-90, > 90
- Baseline C3: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants with low C3
- Baseline C4: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants with low C4
- Baseline serum albumin: descriptive statistics (n, mean, median, SD, minimum, maximum)
- Baseline SF-36 score: descriptive statistics (n, mean, median, SD, minimum, maximum)
- Baseline EQ-5D-5L: descriptive statistics (n, mean, median, SD, minimum, maximum)

For the LN cohort, the following additional disease characteristics will be summarized:

- Time from eligibility biopsy to randomization (< 1 month, 1-3 months, 3-6 months, > 6 months)
- LN class based on central pathology (III or III/V, IV or IV/V)
- LN class based on local pathology (III or III/V, IV or IV/V)
- Glomerular C3 staining based on central pathology (0+, 1+, 2+, 3+)
- Glomerular C1q staining based on central pathology (0+, 1+, 2+, 3+)
- Tubulointerstitial C3 staining based on central pathology (0+, 1+, 2+, 3+)
- Tubulointerstitial C1q staining based on central pathology (0+, 1+, 2+, 3+)
- Vascular C3 staining based on central pathology (0+, 1+, 2+, 3+)
- Vascular C1q staining based on central pathology (0+, 1+, 2+, 3+)
- Renal biopsy activity index based on central pathology: descriptive statistics (n, mean, median, SD, minimum, maximum)
- Renal biopsy chronicity index based on central pathology: descriptive statistics (n, mean, median, SD, minimum, maximum)
- TMA on renal biopsy based on central pathology (yes, no)

- Baseline 24-hour UPCR: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories: ≤ 3.5 g/g, > 3.5 g/g
- Baseline spot UPCR: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories: ≤ 3.5 g/g, > 3.5 g/g
- Baseline disease status (naïve, relapse)
- Corticosteroid induction timing (prior to Screening, during Screening Period)
- Baseline SLEDAI-2K SELENA Modification score: descriptive statistics (n, mean, median, SD, minimum, maximum)
- Baseline FACIT-Fatigue score: descriptive statistics (n, mean, median, SD, minimum, maximum)
- Baseline anti-dsDNA autoantibodies: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants with antibody levels < LLN
- Baseline anti-C1q autoantibodies: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants with antibody levels < LLN
- Concomitant therapy with SGLT-2 inhibitors (Yes, No)

For the IgAN cohort, the following additional disease characteristics will be summarized:

- Baseline 24-hour urine protein (g/day): descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories: (1-2 g/day, > 2 g/day)
- Baseline 24-hour UPCR (g/g): descriptive statistics (n, mean, median, SD, minimum, maximum)
- Time from eligibility biopsy to randomization (< 1 month, 1-3 months, 3-6 months, 6-12 months, 12-24 months, > 24 months)
- MEST-C score based on central pathology (M0, M1, E0, E1, S0, S1, T0, T1, T2, C0, C1, C2)
- C3 staining based on central pathology (0+, 1+, 2+, 3+)
- C1q staining based on central pathology (0+, 1+, 2+, 3+)
- Concomitant therapy with SGLT-2 inhibitors (Yes, No)

The agreement between local and central pathology diagnosis will be assessed for each disease cohort by inter-rater reliability analysis using the kappa statistic reported with Cohen's K-coefficient and its 95% CIs. In addition, if central pathology results are limited, then local pathology results may be summarized as well in the disease characteristic summary.

6.2.3. Medical History

Medical history will be summarized using MedDRA, version 26.1 or later, SOC and PT by treatment group and overall for each disease cohort separately for the SS.

By-participant listings of medical/surgical history and abnormal physical examinations will also be produced.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and procedures will be summarized using the SS.

Prior medications and/or vaccines (including vitamins, herbal preparations, and those discussed in the eligibility criteria in Protocol Section 5) and procedures (eg, surgery, biopsy, physical therapy) are those received or underwent ≤ 30 days prior to Screening or during the Screening Period, as well as any meningococcal vaccine administered within the last 3 years.

Concomitant medications (including any medication, vitamin, herbal preparation, or supplement) and procedures defined in Protocol 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.

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DRUG) version in use by Alexion at the time of the analysis, while nonpharmacologic therapies and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) will be coded using MedDRA version 26.1 or later.

Prior medication and concomitant medication, summaries will be presented by WHO-DRUG anatomical therapeutic chemical (ATC) Level 3 and by WHO-DRUG generic name using number and percentage of participants by treatment group. Procedures will be summarized similarly but presented by MedDRA Class and PT. In addition, protocol-required vaccinations will be summarized similarly.

By-participant listings of prior and concomitant medications, procedures, and protocol-required vaccinations will also be produced.

6.2.5. Allowed Concomitant and Additional Standard of Care Therapy

Background and additional standard of care therapy medications will be summarized using the SS.

Allowed concomitant therapy for participants in the LN cohort consist of standard of care treatment for induction and maintenance treatment of LN including corticosteroids and MMF or MMF equivalent. In the LN cohort, participants will receive additional standard of care therapy in the event of a protocol-defined renal flare, severe extrarenal SLE flare, or suboptimal response. Additional standard of care therapy is defined as intensification of current standard of care or introduction of new immunosuppressive therapies. Additional standard of care therapy will be presented by WHO-DRUG ATC Level 3 and by WHO-DRUG generic name by type of flare using number and percentage of participants by treatment group.

Allowed concomitant therapy for participants in the IgAN cohort consist of standard of care treatment including maximally tolerated dose of RAS-blocking agents such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs).

Allowed concomitant therapy use within 3 months prior to Screening and up to the first dose of study intervention will be presented by WHO-DRUG ATC Level 3 and by WHO-DRUG generic name using number and percentage of participants by treatment group. In addition, allowed concomitant therapy use at baseline will be summarized by treatment group. Changes in allowed concomitant therapy use during the study as well as the reason for change will be summarized by treatment group.

By-participant listings of allowed concomitant therapy and additional standard of care therapy will also be produced.

6.2.6. Protocol Deviations

The number and percentage of participants with specific protocol deviations will be summarized for all enrolled participants by important and nonimportant deviations. Protocol deviations will be presented overall as well as separately for those related to COVID-19.

Summary statistics will be presented by treatment group and overall.

6.3. Instrument Scoring Details

6.3.1. SF-36

The SF-36 version 2 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, Social Functioning, Role Limitations Due to Physical Health, Bodily Pain, General Health, Mental Health, Role Limitations Due to Emotional Problems, and Vitality. Eight health domain scores and 2 component scores (PCS and MCS) will be calculated.

The SF-36 version 2 Health Survey with the standard (4-week) recall period will be used in this study. The OPTUM PRO CoRE 1.5 Smart Measurement System will be used to derive the 8 domain scores and 2 component scores. The algorithms used by the software are described below (as excerpted from the User's Guide).

6.3.1.1. Data Cleaning and Item Recoding

First, the data are checked for out-of-range values. Out-of-range values are any values that are outside the range of acceptable item response values for the SF-36 version 2 Health Survey. Out-of-range values will be converted to missing values. Next, 10 items (BP01, BP02, GH01, GH03, GH05, VT01, VT02, SF01, MH03, MH05) are reverse-scored. Reverse scoring of these items is required so that a higher item response value indicates better health for all SF-36 version 2 Health Survey items and summary measures.

6.3.1.2. Item Recalibration

For most of the SF-36 version 2 Health Survey items, research to date offers good support for the assumption of a linear relationship between the item scores and the underlying health concept defined by their scales. However, empirical work has shown that 2 items, GH01 and BP01, require recalibration to satisfy this important scaling assumption. The Bodily Pain scale requires additional scoring rules because the items offer both different numbers and different content of

response choices and administration of item BP02 depended upon the response to an item like item BP01 in past studies.

6.3.1.3. Computation of Raw Scale Scores

After recoding and recalibrating the required item values, a raw score is computed for each scale. This score is the simple algebraic sum of the final values for all items in that scale.

6.3.1.4. Transformation of Raw Scale Scores to 0 to 100 Scale

The next step involves transforming each raw scale score to a 0 to 100 scale. This transformation converts the lowest and highest possible scores to zero and 100, respectively. Scores between these values represent the percentage of the total possible score achieved.

6.3.1.5. Transformation of 0 to 100 Scores to T-Score-Based Scores

The first step in T-score based scoring consists of standardizing each SF-36 version 2 Health Survey scale using a z-score transformation. A z-score indicates how far a score deviates from the mean in standard deviation units. The z-score for each scale is computed by subtracting the mean 0 to 100 score observed in the 2009 general US population from each SF-36 version 2 Health Survey scale score (0 to 100) scale and dividing the difference by the corresponding scale standard deviation observed in the 2009 general US population. The means and standard deviations utilized are dependent upon the recall period option chosen by the user, based on the SF-36 version 2 Health Survey form used to collect the data being scored.

The next step of the T-score based scoring is to linearly transform each SF-36 version 2 Health Survey z-score to have a mean score of 50 and a standard deviation of 10. This is done by multiplying each SF-36 version 2 Health Survey z-score by 10 and adding the resulting product to 50. These are referred to as “norm-based” scores. The norm-based scores will be used for the 8 domain scores.

6.3.1.6. Scoring the SF-36 Version 2 Healthy Survey Component Summary Measures

The first step in scoring the component summary measures consists of standardizing each SF-36 version 2 Health Survey scale using a z-score transformation. The z-score for each scale is computed by subtracting the mean 0 to 100 score observed in the 2009 general US population from each SF-36 version 2 Health Survey scale score (0 to 100) scale and dividing the difference by the corresponding scale standard deviation observed in the 2009 general US population. The means and standard deviations utilized are dependent upon the recall period option chosen by the user based on the SF-36v2 Health Survey form used to collect the data being scored.

After a z-score has been computed for each SF-36 version 2 Health Survey scale, the second step involves computation of aggregate scores for the physical and mental summaries using weights (factor score coefficients) derived from the 1990 general US population. These are the same weights as those used to score PCS and MCS from the SF-36 version 2 Health Survey. An aggregate physical score is computed by multiplying the z-score of each SF-36 version 2 Health Survey scale by its associated physical factor score coefficient and summing the 8 products. If any of the scale scores are missing, then the aggregate physical score is not computed. An aggregate mental score is computed by multiplying the z-score of each SF-36 version 2 Health

Survey scale by its associated mental factor score coefficient and summing the 8 products. If any of the scale scores are missing, then the aggregate mental score is not computed.

The third step involves transforming the aggregate physical and mental summary scores to the T-score based (50, 10) scoring. This is done by multiplying each aggregate summary score obtained from the second step by 10 and adding the resulting product to 50.

6.3.1.7. Handling of Missing Items

The maximum data recovery option will be used for missing data estimation. This results in the application of algorithms that compute a scale score for those respondents who have answered at least 1 item that represents that construct. For the Physical Functioning scale, item parameters obtained through item response theory methods are used to estimate a missing value on an item based upon a respondent's responses to answered items. For the 7 remaining scales, a person-specific estimate based on the mean response to the answered items on the scale is used to estimate a missing value. Additionally, a PCS and MCS score is calculated for those respondents who have calculated scores on at least 7 of the 8 SF-36 version 2 Health Survey scales. However, PCS is not estimated if the Physical Functioning scale is missing, and MCS is not estimated if the MH scale is missing.

6.3.2. Five-Level EuroQol-5 Dimension (EQ-5D-5L)

The EQ-5D-5L version will be used in this study. EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (ie, state 11111). The collection of index values (weights) for all possible EQ-5D health states is called a value set. EQ-5D-5L index scores for this study will be obtained using the composite time trade-off (cTTO) method based on the Tobit model (Pickard, 2019). The calculation is illustrated in Table 8.

Table 8: EQ-5D-5L cTTO Calculation

US cTTO		**Example: The Value for Health State 21354**
Full health (11111)		Full Health=1
Mobility level 2	-0.096	-0.096
Mobility level 3	-0.122	
Mobility level 4	-0.237	
Mobility level 5	-0.322	
Self-Care level 2	-0.089	0
Self-Care level 3	-0.107	
Self-Care level 4	-0.220	
Self-Care level 5	-0.261	

Table 8: EQ-5D-5L cTTO Calculation

US cTTO		**Example: The Value for Health State 21354**
Usual Activity level 2	-0.068	
Usual Activity level 3	-0.101	-0.101
Usual Activity level 4	-0.255	
Usual Activity level 5	-0.255	
Pain/Discomfort level 2	-0.060	
Pain/Discomfort level 3	-0.098	
Pain/Discomfort level 4	-0.318	
Pain/Discomfort level 5	-0.414	-0.414
Anxiety/Depression level 2	-0.057	
Anxiety/Depression level 3	-0.123	
Anxiety/Depression level 4	-0.299	-0.299
Anxiety/Depression level 5	-0.321	
Health State Index Score		=1-0.096-0-0.101-0.414-0.299=0.090

Abbreviations: cTTO = composite time trade-off; EQ-5D-5L = 5-level EuroQol-5 Dimension

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

The VAS records the respondent's self-rated health on a vertical, visual analog scale where the endpoints are labeled, "The best health you can imagine" for 100 and "The worst health you can imagine" for 0. Missing values will be coded as "999." If there is a discrepancy between where the respondent has placed the X and the number written in the box, number in the box will be used for VAS.

6.3.3. FACIT-Fatigue

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

- All negatively stated items (ie, all items except An5 and An7 from the eCRF) are to be reversed by subtracting the response from 4.
- After reversing the proper items, all items are summed to obtain a score.

- The Fatigue subscale score is then calculated by multiplying the sum of the item scores by 13, then dividing by the number of items answered.

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered. The score has a range of 0 to 52, with higher scores indicating better QoL.

6.4. Additional Details on Statistical Methods

6.4.1. SAS Code for ANCOVA Analysis

The primary analysis of the primary endpoint utilizes ANCOVA analysis for evaluating the percentage change from baseline to Week 26 in proteinuria. Sample code is provided below:

Step 1: Impute data on or after receipt of additional standard of care therapy (LN cohort only) using the value collected at the time of flare

Step 2: Impute data on or after treatment discontinuation using multiple imputation as described in Section 6.4.3.

Step 3: Analyze imputed datasets using ANCOVA analysis, including comparisons between the 180mg vs placebo and alxn2050 vs placebo:

```
proc mixed data = xxxx;
        by shift _imputation_ ;
        class  trt01pn  (ref = "3") stratavn;
        model chg =  trt01pn  base stratavn/ solution;
         lsmestimate trt01pn '120 mg' 1 0 0/cl alpha=0.05;
         lsmestimate trt01pn '180 mg' 0 1 0/cl alpha=0.05;
         lsmestimate trt01pn 'placebo' 0 0 1/cl alpha=0.05;
         lsmestimate trt01pn '120 mg and 180 mg' 0.25 0.75 0/cl alpha=0.05;
         estimate '180 mg vs placebo'  trt01pn 0 1 -1/cl alpha=0.1;
         estimate '120 mg and 180 mg vs placebo-dif weight'  trt01pn  0.25 0.75 -1/cl
    alpha=0.1;
      ods output Estimates=est_;
      ods output LSMEstimates=estlsm_;
    run;
```

where trt01pn is the randomized treatment group, base is the proteinuria value at baseline, strat is the randomization stratification variable, and chg is the change from baseline in log(proteinuria).

Step 4: Inferences from each complete data set will be combined to obtain an overall test statistic for each treatment effect.

```
proc mianalyze data=xxxx;
    by label;
    modeleffects estimate;
    stderr;
run;
```

6.4.2. SAS Code for MMRM Analysis

The secondary endpoint of percentage change from baseline to Week 50 in proteinuria utilizes MMRM analysis. Other secondary endpoints assessing longitudinal changes will also utilize MMRM analysis. Sample code is provided below:

Step 1: Impute data on or after receipt of additional standard of care therapy (LN cohort only) using the value collected at the time of flare or suboptimal response, if applicable

Step 2: Analyze imputed dataset using MMRM analysis-adjust the least square mean estimate based on number of scheduled visit for each of the endpoint/relevant analysis.

```
proc mixed data=xxxx method=reml;
      class usubjid  trtseqan avisitn stratavn;
      model CHG= trtseqan avisitn trtseqan*avisitn base stratavn /ddfm=kr2 solution;
       repeated avisitn/type=un subject=usubjid;
        lsmeans trtseqan*avisitn / cl  alpha=0.05;
        lsmestimate trtseqan*avisitn "120 mg and 180 mg at day 183"  0.25 0
                                                  0.75 0
                                                    0 0
                                                    0 0  /cl alpha=0.05;
       lsmestimate trtseqan*avisitn "120 mg and 180 mg at day 351"  0 0.25
                                                  0 0.75
                                                    0 0
                                                    0 0 /cl alpha=0.05;
        ods output  LSMEstimates=lsmall  LSMeans=lsm;
     run;
```

where subjid is the participant identifier variable, trt01pn is the randomized treatment group, avisitn is the visit variable, base is the proteinuria value at baseline, strat is the randomization stratification variable, and chg is the change from baseline in log(proteinuria).

6.4.3. SAS Code for Multiple Imputation

For the primary analysis of the primary endpoint, responses after treatment discontinuation will be imputed using a multiple imputation approach assuming the data are MAR and using a regression model. Sample code is provided below:

Step 1: Imputation using a monotone regression model at Week X

```
proc mi data=ADEFF out=outmi seed=123 nimpute=1000;
    class trt01pn strat;
    var trt01pn base strat Week26;
    monotone reg(/details);
run;
```

where trt01pn is the randomized treatment group, base is the proteinuria value at baseline, strat is the randomization stratification variable, and Week26 is the change from baseline in log(proteinuria) at Week 26.

6.4.4. SAS Code for Placebo-Based Imputation

A sensitivity analysis for the primary endpoint will be performed using placebo-based imputation for responses after treatment discontinuation. In this analysis, data occurring after treatment discontinuation will be set to missing and multiple imputation will then be performed using a regression method obtained only from placebo-treated participants with terms for baseline value and the randomization stratification variable.

The following is a partial SAS code for the placebo-based pattern imputation at Week 26:

```
proc mi data=ADEFF out=outmi seed=123 nimpute=1000;
    class trt01pn strat;
    var base strat Week26;
    monotone reg(/details);
    mnar model (Week26/modelobs=(trt01pn='Placebo'));
run;
```

where trt01pn is the randomized treatment group, base is the proteinuria value at baseline, strat is the randomization stratification variable, and Week26 is the change from baseline in log(proteinuria) at Week 26.

The 1000 imputed data sets are then analyzed using ANCOVA (refer to Section 6.4.1 for SAS code) and PROC MIANALYZE procedure will be used to generate valid statistical inferences about these parameters.

6.4.5. SAS Code for Tipping Point Analysis

A sensitivity analysis for the primary endpoint will be performed using the tipping point approach where a search is conducted for a tipping point that reverses the study conclusion from being favorable to ALXN2050 to being unfavorable. For the tipping point sensitivity analysis, the missing data mechanism for the missing change from baseline in log proteinuria values at Week 26 will be considered to be missing not at random (MNAR). Imputations are performed for missing change observations for ALXN2050 treated participants assuming not the full treatment effect, but the treatment effect adjusted by a shift parameter delta. After obtaining complete data sets for multiple shift parameters, the complete data sets will be used in the MMRM analysis, and inferences from each complete dataset will be combined using SAS PROC MIANALYZE to obtain an overall test statistic for each shift value. Multiple shift parameters will be tested until the inference concludes that statistical significance disappears.

The following is a partial SAS code for the multiple imputation analysis for a specified shift parameter at Week 26:

```
proc mi data=ADEFF out=outmi seed=123 nimpute=1000;
    class trt01pn strat;
    monotone method=reg ;
    var trt01pn strat base Week26;
    mnar adjust (Week 26 /shift=delta adjustobs=(trt01pn='ALXN2050'));
```

where trt01pn is the randomized treatment group, base is the proteinuria value at baseline, Week26 is the change from baseline in log(proteinuria), and strat is the randomization stratification.

The 1000 imputed data sets are then analyzed using ANCOVA (refer to Section 6.4.1 for SAS code) and PROC MIANALYZE procedure will be used to generate valid statistical inferences about these parameters.

7. REFERENCES

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

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

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

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

Pickard AS, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. Value Health. 2019;22(8):931-941.

Ratitch B, O'Kelly M et al. Clinical Trials with Missing Data: A Guide for Practitioners. Chichester: John Wiley & Sons, 2014.

Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharm Stat. 2013;12(6):337-47.

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