TITLE PAGE

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Multicenter Study to Evaluate the Efficacy and Safety of ALXN2050 in Adult Participants with Generalized Myasthenia Gravis

Alexion Protocol Number: ALXN2050-MG-201

AstraZeneca Protocol Number: D7840C00001

Compound: ALXN2050

Study Phase: 2

Brief Title: Phase 2 Study of ALXN2050 in Generalized Myasthenia Gravis

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address:

Alexion Pharmaceuticals
121 Seaport Boulevard
Boston, MA 02210
USA

Regulatory Agency Identifier Number(s)

IND:154567

EudraCT: 2021-001229-26

EU CT: 2022-502905-14

Release Date: 15 Nov 2023

Sponsor Signatory:

[redacted] **Date**

Alexion Pharmaceuticals, Inc.

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

Medical Monitor Name and Contact Information can be found in the study contact list.

INVESTIGATOR'S AGREEMENT

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

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2.0	09 Mar 2023
Amendment 1.0	22 Jul 2021
Original Protocol	28 Apr 2021

Amendment 3 (Global 15 Nov 2023)

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

OVERALL RATIONALE FOR THE AMENDMENT

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

Section # and Name	**Description of Change**	**Brief Rationale**
TITLE PAGE and Section 1.1 Synopsis	Updated regulatory agency identifier name. Changed Short Title to **Brief Title.**	To provide information required under EU CTR
Section 4.4 End of Study Definition	The EOS is defined as the date of the last visit of the last participant for any protocol-related activity in the study.	To align with EU CTR requirements.
Section 6.1 Study Intervention(s) Administered Section 8.3.5.2 Medication Error Section 8.3.5.3 Drug Abuse Section 8.3.5.4 Drug Misuse Section 8.4 Treatment of Overdose Section 10.4 Medication Error, Drug Abuse, and Drug Misuse	Added AxMP = auxiliary medicinal product and removed NIMP.	To align with EU CTR requirements.
Section 8.3.4 Regulatory Reporting Requirements for SAEs Section 10.3.5 Unexpected Events	Described reporting requirements and updated definition of unexpected events, respectively.	To align with EU CTR requirements.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.5.1 Timelines	Simplified text to reflect that Alexion or designee will be informed of an event of medication error, drug abuse, or misuse immediately.	To align with EU CTR requirements.
Section 8.4 Treatment of Overdose	Added details on process to capture and report an event of overdose.	To align with EU CTR requirements.
Section 10.4 Medication Error, Drug Abuse, and Drug Misuse	Described reporting requirements for medication error, drug abuse, and drug misuse.	To align with EU CTR requirements.
Section 10.1.1 Regulatory and Ethical Considerations	Added details on serious breach (including personal data breach) prevention, identification, notification, and impact mitigation	To align with EU CTR requirements.
Section 10.1.5 Data Protection	Updated text to reflect that unique identifier was assigned by a third party contracted by Alexion. Described data protection measures to ensure patient identity remains secure	To align with EU CTR requirements.
Section 10.1.7 Quality Data Assurance	Specified document retention period at investigative site to be at least 25 years after study completion.	To align with EU CTR requirements.

Abbreviations: AxMP = auxiliary medicinal product; CTR = Clinical Trials Regulation; EU = European Union; NIMP = non-investigational medicinal product

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LIST OF ABBREVIATIONS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
AChEI	acetylcholinesterase inhibitor
AChR	acetylcholine receptor
ADL	activities of daily living
AE	adverse event
Anti-HBc	positive hepatitis B core antibody
Anti-HBs	anti-HBc with negative surface antibody
AP	alternative pathway
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AxMP	auxiliary medicinal product
Ba	Ba fragment of complement factor B
Bb	Bb fragment of complement factor B
bid	twice daily
C	complement component
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum (peak) plasma concentration of the drug
COVID-19	coronavirus disease 2019
CP	classical pathway
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
C_{trough}	predose concentration
CYP3A	cytochrome P450, family 3, subfamily A
ECG	electrocardiogram
eCRF	electronic case report form

Table 1: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
EDC	electronic data capture
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EOS	end of study
ETP	Extended Treatment Period
EU	European Union
FAS	Full Analysis Set
FB	factor B
FcRn	human neonatal Fc receptor
FD	factor D
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDS	Global Drug Safety
gMG	generalized myasthenia gravis
HbsAg	hepatitis B positive hepatitis surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL-6	interleukin 6
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
IST	immunosuppressive therapy
IV	intravenous(ly)
IVIg	intravenous immunoglobulin G

Table 1: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
LLN	lower limit of normal
LP	lectin pathway
LRP4	low density lipoprotein receptor-related protein 4
MAC	membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post-Intervention Status
MM	minimal manifestation
MMP	matrix metalloproteinase
MMRM	mixed-effects model with repeated measures
MRI	magnetic resonance imaging
MuSK	muscle-specific tyrosine kinase
Neuro QoL™ Fatigue	Quality of Life in Neurological Disorders Fatigue questionnaire
NMJ	neuromuscular junction
NOAEL	no-observed-adverse-effect-level
OLE	Open-label Extension
oMG	ocular myasthenia gravis
PD	pharmacodynamic(s)
PE	plasma exchange
PEP	Primary Evaluation Period
PK	pharmacokinetic(s)
PP	plasmapheresis
PPS	Per Protocol Set
QMG	Quantitative Myasthenia Gravis
QRS	combination of the Q wave, R wave, and S wave
QT	interval between the start of the Q wave and the end of the T wave
QTc	corrected QT interval
QTcF	corrected QT interval using Fridericia's formula

Table 1: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SCIg	subcutaneous immunoglobulin
SoA	Schedule of Activities
SOC	System Organ Class
SS	Safety Set
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Multicenter Study to Evaluate the Efficacy and Safety of ALXN2050 in Adult Participants with Generalized Myasthenia Gravis

Brief Title: Phase 2 Study of ALXN2050 in Generalized Myasthenia Gravis

Regulatory Agency Identifier:

IND:154567

EudraCT: 2021-001229-26

EU CT: 2022-502905-14

Rationale: ALXN2050 is a potent, reversible, small molecule inhibitor of complement factor D (FD), which is a key component of the alternative pathway (AP). The complement system is involved in the pathophysiology of generalized myasthenia gravis (gMG), and its inhibition has been proven to generate clinical benefit. ALXN2050 is an oral molecule that has the potential to provide a unique option to patients with gMG who suffer from debilitating and often incapacitating symptoms.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on improvement in the MG-ADL total score	Proportion of participants with an MG-ADL total score reduction of ≥ 2 points in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy
Secondary	
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on improvement in the QMG total score	• Change from baseline in QMG total score at Week 8 • Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the QMG total score at Week 8 • Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the QMG total score in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on improvement in quality of life measures	• Change from baseline in Neuro-QoL™ Fatigue score at Week 8

Objectives	Endpoints
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on additional endpoints involving the MG-ADL total score	• Change from baseline in MG-ADL total score at Week 8 • Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the MG-ADL total score in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy • Proportion of participants with at least a 2-, 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the MG-ADL total score at Week 8
PK/PD	
To characterize the PK/PD of ALXN2050 and to establish the PK/PD relationship in participants with gMG	• Observed C_{max} and C_{trough} values over time • Absolute values and change from baseline in plasma Bb concentration and serum AP activity over time
Biomarker	
To assess the effect of FD inhibition on complement biomarkers	Plasma FD concentration, serum C3 concentration, and serum CP activity over time
Safety	
To characterize the overall safety of ALXN2050 compared with placebo in participants with gMG	• Incidence of TEAEs and TESAEs over time • Changes from baseline in laboratory assessments

Objectives	Endpoints
Tertiary/Exploratory	
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on other efficacy endpoints	• Proportion of participants with an MG-ADL total score reduction of ≥ 2 points and a QMG total score reduction of ≥ 3 points in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy • Proportion of participants with at least a 2-point improvement in the MG-ADL total score for 4 consecutive weeks (measured from Day 1 to Week 8 for Groups 1, 2, and 3 and from Week 8 to Week 16 for Groups 3a and 3b) and who did not receive any rescue therapy • Change from baseline in MG-ADL total score at Week 8 for Groups 1, 2, and 3; and from Week 8 to Week 16 for Groups 3a and 3b • Change from baseline in MG-ADL total score at Week 26 for Groups 1 and 2[a]; and from Week 8 to Week 34 for Groups 3a and 3b[a] • Incidence of Clinical Deterioration of gMG over time • MGFA-PIS at Week 8 and Week 26[a] • Proportion of participants with a classification of Minimal Manifestations at Week 8 and Week 26[a] (as measured by the MGFA-PIS) • Proportion of participants who receive rescue therapy over time
To assess the effect of FD inhibition on AChR antibody titers in participants with gMG	Change of anti-AChR antibody titers over time
To characterize nongenetic biomarkers in adult participants with gMG	• Detection of gMG-associated autoantibodies, which may include baseline and/or later timepoints (eg, MuSK, LRP4) • In vitro evaluation of autoantibody activity (eg, AChR blocking, complement deposition) • Absolute values and change from baseline in levels of complement proteins and complement pathway regulators (eg, C5b-9, Properdin) • Change from baseline in biomarkers of inflammation and NMJ damage (eg, MMP-10, IL-6)

[a] The comparator will be discussed in detail in the Statistical Analysis Plan.

Abbreviations: AChR = acetylcholine receptor; AP = alternative pathway; Bb = Bb fragment of complement factor B; C3 = complement component 3; C5b-9 = terminal complement complex; C_{max} = maximum (peak) plasma concentration of the drug; CP = classical pathway; C_{trough} = predose concentration; FD = factor D; gMG = generalized myasthenia gravis; IL = interleukin; LRP4 = low density lipoprotein receptor-related protein 4; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MMP-10 = matrix metalloproteinase 10; MuSK = muscle-specific tyrosine kinase; Neuro-QoL™ Fatigue = Quality of Life in Neurological Disorders Fatigue questionnaire; NMJ = neuromuscular junction; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative

Myasthenia Gravis; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

Overall Design

This is a Phase 2, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the efficacy and safety of ALXN2050 in adult participants (≥ 18 years of age) diagnosed with gMG with a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification between Class II to IV at the Screening Visit and a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥ 5 (with at least 50% of the score attributed to non-ocular elements) at the Screening Visit and at randomization (Day 1).

Approximately 70 eligible participants will be stratified by MG-ADL total score at baseline (5 to 6 [capped to approximately 10% of total enrollment] versus ≥ 7) and randomized on Day 1 in a 2:1:2 ratio to 1 of 3 treatment groups: ALXN2050 180 mg twice daily (bid) (Group 1), ALXN2050 120 mg bid (Group 2), or placebo (Group 3). Participants randomized to Group 1 and Group 2 will receive ALXN2050 during the Primary Evaluation Period (PEP; 8 weeks) and the Extended Treatment Period (ETP; 26 weeks). Participants in Group 3 will receive placebo treatment during the PEP and at the end of the PEP, will be rerandomized in a 1:1 ratio to receive either ALXN2050 180 mg bid (Group 3a) or ALXN2050 120 mg bid (Group 3b). During the Open-label Extension (OLE) Period (up to approximately 1.5 years), all participants will receive ALXN2050 and will be switched to the optimal dose of ALXN2050 if that dose has been identified during the study, as long as the participant has completed the first 34 weeks of treatment.

Disclosure Statement: This is a parallel-group treatment study with 3 groups that are participant and Investigator blinded during the PEP.

Number of Participants: Approximately 70 participants will be initially randomized to 1 of 3 treatment groups.

Intervention Groups and Duration:

The study consists of a Screening Period of up to 4 weeks, a PEP of 8 weeks, an ETP of 26 weeks, and an OLE Period of up to approximately 1.5 years. An End of Study (EOS) Visit will occur 30 days after the last dose of study intervention for all participants.

The overall study duration for an individual participant will be approximately 125 weeks (from the Screening Visit through the EOS Visit).

Data Monitoring Committee: No

Ethical Considerations and Benefit-Risk Assessment

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

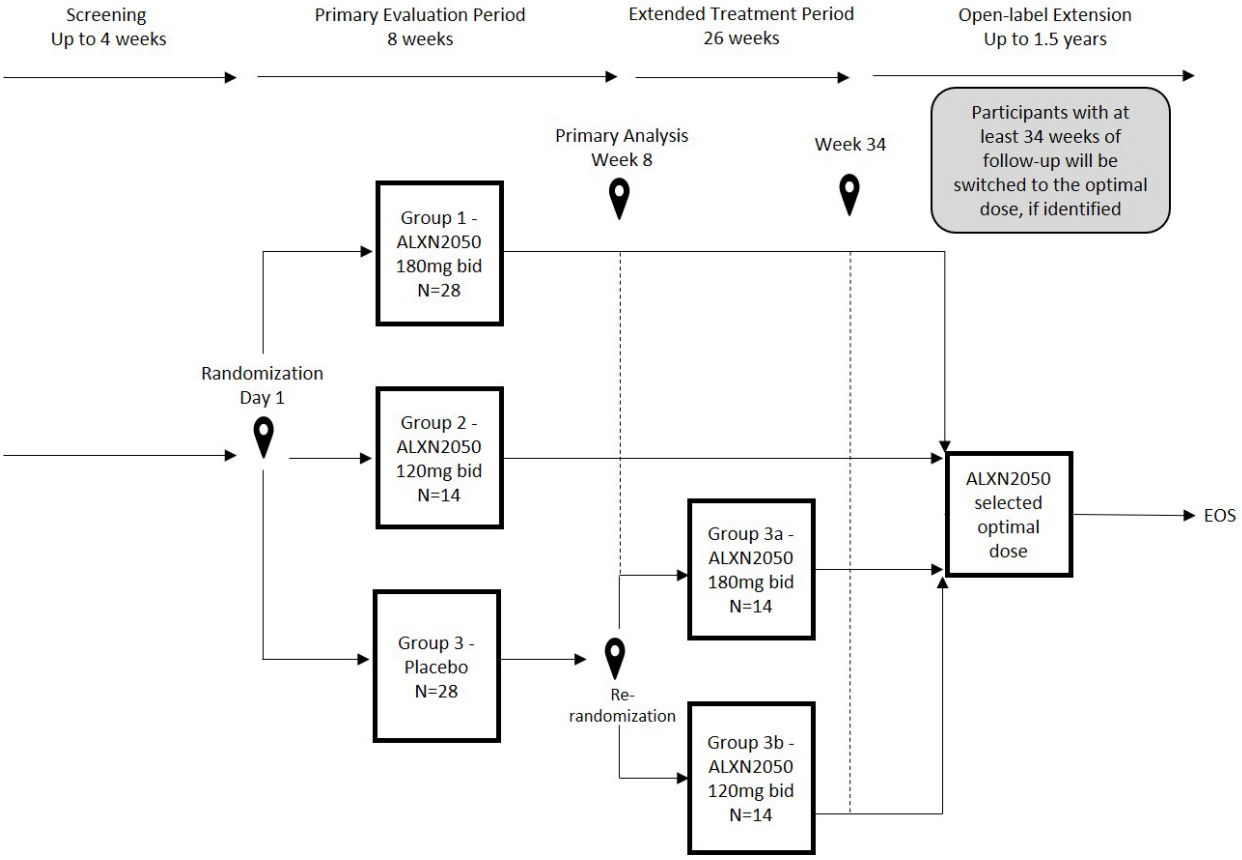
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

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

1.2. Schema

The study design is depicted in Figure 1.

Figure 1: ALXN2050-MG-201 Study Design Schematic



Note: Participants randomized to placebo will only receive placebo for 8 weeks during the study.
Abbreviations: bid = twice daily; EOS = end of study; N = number of participants

1.3. Schedule of Activities (SoA)

Schedules of activities are provided as follows:

- Screening and Primary Evaluation Periods (Table 2)
- Extended Treatment Period (Table 3)
- Open-label Extension Period (Table 4)

Table 2: Schedule of Activities (Screening and Primary Evaluation Periods)

Period	**Screening Period**	**Primary Evaluation Period**											
Study Day (D)	**Up to 27 days prior to D1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**ED[a]**	**CD[b]**	**EOS[a]**
Study Week (W)	**NA**	**NA**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**NA**	**NA**	**NA**
Study Window (days)	**NA**	**NA**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**NA**	**NA**	**±2**
Eligibility													
Informed consent	X												
Inclusion/exclusion	X	X[c]											
Medical history[d]	X												
MG history[e]	X												
MGFA classification[f]	X												
Height	X												
Weight	X												
Demographics	X												
Study Administrative													
Vaccination or confirmation of vaccination against *Neisseria meningitidis*[g]	X												
Screening Laboratory Tests													
HIV-1, HIV-2, Hepatitis B and C	X												
Serum pregnancy[h]	X										X		X
Urine pregnancy[h]		X				X				X		X	
Follicle-stimulating hormone[i]	X												
Randomization													
Randomized to study intervention[j]		X								X[k]			
Study Intervention													

Table 2: Schedule of Activities (Screening and Primary Evaluation Periods)

Period	**Screening Period**	**Primary Evaluation Period**											
Study Day (D)	**Up to 27 days prior to D1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**ED[a]**	**CD[b]**	**EOS[a]**
Study Week (W)	**NA**	**NA**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**NA**	**NA**	**NA**
Study Window (days)	**NA**	**NA**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**NA**	**NA**	**±2**
Dispensation of study intervention[l]		X	X	X	X	X	X	X	X	X			
Administration of ALXN2050 or Placebo[m]		X	X	X	X	X	X	X	X	X[n]			
Complete participant eDiary (optional)		Immediately following administration of study intervention											
Efficacy Assessments													
QMG[f, o]		X	X	X	X	X	X	X	X	X	X	X	
MG-ADL[f, p]	X	X	X	X	X	X	X	X	X	X	X	X	
MGFA-PIS[f]						X				X	X		
Neuro-QoL™ Fatigue		X				X				X	X	X	
Safety Assessments													
C-SSRS Baseline[q]		X											
C-SSRS Since Last Visit[q]			X	X	X	X	X	X	X	X	X	X	
Electrocardiogram	X	X								X	X		
Complete physical examination, including neurological component	X										X	X	
Abbreviated physical examination[r, s]		X	X	X	X	X	X	X	X	X			
Vital sign measurements[t]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess for CD[b]		X	X	X	X	X	X	X	X	X	X		
Review Participant Safety Card[u]		X	X	X	X	X	X	X	X	X	X	X	
Safety Laboratory Tests[v]													

Table 2: Schedule of Activities (Screening and Primary Evaluation Periods)

Period	**Screening Period**	**Primary Evaluation Period**											
Study Day (D)	**Up to 27 days prior to D1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**ED[a]**	**CD[b]**	**EOS[a]**
Study Week (W)	**NA**	**NA**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**NA**	**NA**	**NA**
Study Window (days)	**NA**	**NA**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**NA**	**NA**	**±2**
Clinical chemistry	X	X				X				X	X	X	
Hematology	X	X				X				X	X	X	
Coagulation panel	X	X				X				X	X	X	
Urinalysis	X	X				X				X	X	X	
PK/PD Tests[w]													
PK		X[x]				X[y]				X[x]		X[y]	
PD: AP activity and Bb[z]		X				X				X		X	
Biomarker Tests													
Anti-AChR antibody	X	X[aa]				X				X	X	X	
Factor D, C3, CP activity, nongenetic exploratory biomarkers (eg, MuSK, LRP4)[ab]		X				X				X	X	X	
Other													
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Nonpharmacologic treatments and therapies	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] If a participant is discontinued from the study during the PEP, an ED Visit will be performed, and then an EOS Visit will be performed 30 (±2) days after the last dose of study intervention.

[b] Evaluation of CD must be performed as soon as possible, within 48 h of notification to the Investigator of symptom onset. If CD occurs between scheduled visits, only the assessments for the CD Visit are needed. If CD occurs on a scheduled visit, all scheduled assessments should be performed for that visit as well as for the evaluation of CD. Additional evaluation visits may be scheduled at the discretion of the Investigator.

Table 2: Schedule of Activities (Screening and Primary Evaluation Periods)

[c] Confirm on Day 1.

[d] Includes substance usage, and past and current medical conditions, including surgical history.

[e] MG history parameters that will be obtained are listed in Section 8.11.4.

[f] MG assessments should be performed at approximately the same time of day by a properly trained Clinical Evaluator (preferably the same evaluator) throughout the study. The MG-ADL should always be performed first, followed by the QMG.

Note: A Clinical Evaluator may be a neurologist, neurologist in training, or delegated member of the investigational site staff who has been certified in administering the assessments.

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

[h] Pregnancy tests must be performed on all participants of childbearing potential at the specified time points. Serum pregnancy test will be performed at the Screening, ED, and EOS visits; urine pregnancy tests will be performed locally at all other specified time points. Additional pregnancy tests (urine or serum) may also be performed at any in-clinic visit at the Investigator's discretion.

[i] Follicle-stimulating hormone may be obtained at the Screening Visit to confirm postmenopausal status in female participants who are considered postmenopausal ONLY. This test is not needed for men and will not be conducted in women of childbearing potential.

[j] All participants who continue to meet all inclusion criteria and none of the exclusion criteria and have been cleared for randomization by the Investigator will be centrally randomized via an interactive response technology.

[k] Participants randomized to placebo will be further randomized to 1 of the 2 active treatment groups (ie, ALXN2050 120 or 180 mg bid).

[l] Ensure kit and lot number are recorded on the drug accountability log.

[m] Dosing is by mouth bid throughout the PEP.

[n] Participants will receive newly dispensed study intervention at Week 8 and the first dose will be administered during this visit. The participant will then continue at home dosing per protocol.

[o] The QMG assessment should be performed by a properly trained Clinical Evaluator (preferably the same evaluator) throughout the study. If a participant is taking a cholinesterase inhibitor, the dose must be withheld for at least 8 h prior to the assessment and, whenever possible, the time from the last dose to the QMG assessment should be kept similar between visits.

[p] The MG-ADL is required to be performed first, followed by the QMG. The MG-ADL assessment should be performed by a properly trained Clinical Evaluator (preferably the same evaluator) throughout the study. The recall period for MG-ADL is the preceding 7 days or since the last visit if the visit interval is less than 7 days.

[q] C-SSRS will be assessed for both lifetime and past 12 months at Baseline, and Since Last Visit for subsequent visits.

[r] The abbreviated physical examination will be performed, if necessary, on the basis of the participant's health status and the clinical judgment of the Investigator.

[s] A symptom based neurologic examination should be performed if the participant has any complaints or clinical findings attributable to the central nervous system and if positive for findings, a full neurologic examination will need to be performed at that assessment time point and at future time points as needed (determined by the Investigator).

[t] Vital sign measurements will include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). On dosing days, vital signs will be taken before study intervention administration and after the participant has been resting for at least 5 minutes.

Table 2: Schedule of Activities (Screening and Primary Evaluation Periods)

[u] Participants will be given a safety card prior to the first dose of study intervention. At each visit throughout the study, investigational site staff will ensure that the participant has the safety card and will review the guidelines with the participant.

[v] Safety laboratory samples will be analyzed by the central laboratory. A list of parameters that will be obtained during the study are provided in Table 11.

[w] Baseline and trough blood samples for serum PK will be collected predose (within 30 minutes prior to the administration of study intervention). Peak blood samples for serum PK/PD are to be taken 2 ± 0.5 h and 4 ± 0.5 h postdose. All collection times will be recorded in the participant's electronic case report form.

[x] Trough (within 30 minutes predose) and peak (2 ± 0.5 h and 4 ± 0.5 h postdose).

[y] Trough (within 30 minutes predose).

[z] AP activity within 30 minutes predose and 2 ± 0.5 h and 4 ± 0.5 h postdose at Day 1 and Week 8, and within 30 minutes predose at Week 4 and CD. Bb sampling within 30 minutes predose and 2 ± 0.5 h postdose at Day 1, and within 30 minutes predose at all other in clinic visits.

[aa] Collect predose on Day 1.

[ab] Collect predose.

Abbreviations: AChR = acetylcholine receptor; AP = alternative pathway; Bb = Bb fragment of complement factor B; bid = twice daily; C3 = complement component 3; CD = Clinical Deterioration; CP = classical pathway; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; ED = early discontinuation; eDiary = electronic diary; EOS = end of study; h = hour(s); HIV = human immunodeficiency virus; LRP4 = low density lipoprotein receptor-related protein 4; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MuSK = muscle-specific tyrosine kinase; NA = not applicable; Neuro-QoL™ Fatigue = Quality of Life in Neurological Disorders Fatigue questionnaire; PD = pharmacodynamic; PEP = Primary Evaluation Period; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis score for disease severity; W = Week

Table 3: Schedule of Activities (Extended Treatment Period)

Period	**Extended Treatment Period[a]**												
Study Year	**Year 1**												
Study Day (D)	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D183**	**D239**	**ED[b]**	**CD[c]**	**EOS[b]**
Study Week (W)	**W9**	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W26**	**W34**	**NA**	**NA**	**NA**
Visit Type	**Phone call**	**Phone call**	**Phone call**	**In-clinic**	**Phone call**	**Phone call**	**Phone call**	**In-clinic**	**In-clinic**	**In-clinic**	**In-clinic**	**In-clinic**	**In-clinic**
Study Window (days)	**NA**	**NA**	**NA**	**±3**	**NA**	**NA**	**NA**	**±3**	**±3**	**±3**	**NA**	**NA**	**±2**
Administration of Study Intervention													
Dispensation of study intervention[d]				X				X	X	X			
Administration of ALXN2050[e]	X	X	X	X	X	X	X	X	X	X[f]			
Complete participant eDiary (optional)	Immediately following administration of study intervention												
Efficacy Assessments													
QMG[g, h]				X				X	X	X	X	X	
MG-ADL[g, i]	X	X	X	X	X	X	X	X	X	X	X	X	
MGFA-PIS[g]				X				X	X	X	X		
Neuro-QoL™ Fatigue				X				X	X	X	X	X	
Safety Assessments													
C-SSRS Since Last Visit[j]				X				X	X	X	X	X	
Electrocardiogram									X	X	X		
Complete physical examination, including neurological component											X	X	
Abbreviated physical examination[k, l]				X				X	X	X			
Vital sign measurements[m]				X				X	X	X	X	X	
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess for CD[c]	X	X	X	X	X	X	X	X	X	X	X		
Review Participant Safety card[n]	X	X	X	X	X	X	X	X	X	X	X	X	

Table 3: Schedule of Activities (Extended Treatment Period)

Period	**Extended Treatment Period[a]**												
Study Year	**Year 1**												
Study Day (D)	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D183**	**D239**	**ED[b]**	**CD[c]**	**EOS[b]**
Study Week (W)	**W9**	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W26**	**W34**	**NA**	**NA**	**NA**
Visit Type	**Phone call**	**Phone call**	**Phone call**	**In-clinic**	**Phone call**	**Phone call**	**Phone call**	**In-clinic**	**In-clinic**	**In-clinic**	**In-clinic**	**In-clinic**	**In-clinic**
Study Window (days)	**NA**	**NA**	**NA**	**±3**	**NA**	**NA**	**NA**	**±3**	**±3**	**±3**	**NA**	**NA**	**±2**
Safety Laboratory Tests[o]													
Serum pregnancy[p]											X		X
Urine pregnancy[p]				X				X	X	X		X	
Clinical chemistry				X				X	X	X	X	X	
Hematology				X				X	X	X	X	X	
Coagulation panel				X				X	X	X	X	X	
Urinalysis				X				X	X	X	X	X	
PK/PD Tests[q]													
PK				X[r]				X[s]	X[r]	X[r]		X[r]	
PD: AP activity and Bb[t]				X				X	X	X		X	
Biomarker Tests													
Anti-AChR antibody				X				X	X	X	X	X	
Factor D, C3, CP activity, nongenetic exploratory biomarkers (eg, MuSK, LRP4)[u]				X				X	X	X	X	X	
Other				X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Nonpharmacologic treatments and therapies	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] The ETP begins at the Day 57 (Week 8) Visit after all assessments of the visit are performed, but before the administration of ALXN2050 in the clinic and postdose PK/PD sampling.

Table 3: Schedule of Activities (Extended Treatment Period)

[b] If a participant is discontinued from the study during the ETP, an ED Visit will be performed, and then an EOS Visit will be performed 30 (±2) days after the last dose of study intervention.

[c] Evaluation of CD must be performed as soon as possible, within 48 h of notification to the Investigator of symptom onset. If CD occurs between scheduled visits, only the assessments for the CD Visit are needed. If CD occurs on a scheduled visit, all scheduled assessments should be performed for that visit as well as for the evaluation of CD. Additional evaluation visits may be scheduled at the discretion of the Investigator.

[d] Ensure kit and lot number are recorded on the drug accountability log.

[e] Dosing is by mouth bid throughout the ETP.

[f] Participants will receive newly dispensed study intervention at Week 34 and the first dose will be administered during this visit. The participant will then continue at home dosing per protocol.

[g] MG assessments should be performed at approximately the same time of day by a properly trained Clinical Evaluator (preferably the same evaluator). The MG-ADL should always be performed first, followed by the QMG.

Note: A Clinical Evaluator may be a neurologist, neurologist in training, or delegated member of the investigational site staff who has been certified in administering the assessments.

[h] The QMG assessment should be performed by a properly trained Clinical Evaluator (preferably the same evaluator) throughout the study. If a participant is taking a cholinesterase inhibitor, the dose must be withheld for at least 8 h prior to the assessment and, whenever possible, the time from the last dose to the QMG assessment should be kept similar between visits.

[i] The MG-ADL is required to be performed first, followed by the QMG. The MG-ADL assessment should be performed by a properly trained Clinical Evaluator (preferably the same evaluator) throughout the study. The recall period for MG-ADL is the preceding 7 days or since the last visit if the visit interval is less than 7 days. The MG-ADL will be assessed by phone at Weeks 9, 10, 11, 13, 14, and 15.

[j] C-SSRS will be assessed Since Last Visit.

[k] To be performed, if necessary, on the basis of the participant's health status and the clinical judgment of the Investigator.

[l] A symptom based neurologic examination should be performed if the participant has any complaints or clinical findings attributable to the central nervous system and if positive for findings, a full neurologic examination will need to be performed at that assessment time point and at future time points as needed (determined by the Investigator).

[m] Vital sign measurements will include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). On dosing days, vital signs will be taken before study intervention administration and after the participant has been resting for at least 5 minutes.

[n] Participants will be given a safety card prior to the first dose of study intervention. At each visit throughout the study, investigational site staff will ensure that the participant has the safety card and will review the guidelines with the participant.

[o] Safety laboratory samples will be analyzed by the central laboratory. A list of parameters that will be obtained during the study are provided in Table 11.

[p] Pregnancy tests must be performed on all participants of childbearing potential at the specified time points. A serum pregnancy test will be performed at the ED and EOS visits; urine pregnancy tests will be performed locally at all other specified time points. Additional pregnancy tests (urine or serum) may also be performed at any in-clinic visit at the Investigator's discretion.

[q] Trough blood samples for serum PK will be collected predose (within 30 minutes prior to the administration of study intervention). Peak blood samples for serum PK/PD are to be taken 2 ± 0.5 h and 4 ± 0.5 h postdose. All collection times will be recorded in the participant's electronic case report form.

[r] Trough (within 30 minutes predose).

[s] Trough (within 30 minutes predose) and peak (2 ± 0.5 h and 4 ± 0.5 h postdose).

Table 3: Schedule of Activities (Extended Treatment Period)

[t] AP activity within 30 minutes predose at Weeks 12, 26, 34, and CD, and within 30 minutes predose and 2 ± 0.5 h and 4± 0.5 h postdose at Week 16. Bb sampling within 30 minutes predose at all visits.

[u] Collect predose.

Abbreviations: AChR = acetylcholine receptor; AP = alternative pathway; Bb = Bb fragment of complement factor B; bid = twice daily; C3 = complement component 3; CD = Clinical Deterioration; CP = classical pathway; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; ED = early discontinuation; eDiary = electronic diary; EOS = end of study; ETP = Extended Treatment Period; h = hour(s); LRP4 = low density lipoprotein receptor-related protein 4; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MuSK = muscle-specific tyrosine kinase; NA = not applicable; Neuro-QoL™ Fatigue = Neurological Quality of Life Fatigue questionnaire; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis score for disease severity; W = Week

Table 4: Schedule of Activities (Open-label Extension Period)

Period	**Open-label Extension Period**[a]								
Study Year	**Year 1 (cont'd)**	**Year 2+**					**ED**[b]	**CD**[c]	**EOS**[b]
Study Day (D)	**D365**	**D456**	**D547**	**D638**	**D729**	**D820**	**NA**	**NA**	**NA**
Study Week (W)	**W52**	**W65**	**W78**	**W91**	**W104**	**W117**	**NA**	**NA**	**NA**
Study Window (days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**	**NA**	**±2**
Administration of Study Intervention									
Dispensation of study intervention[d]	X	X	X	X	X				
Administration of ALXN2050[e]	X	X	X	X	X	X			
Complete participant eDiary (optional)	Immediately following administration of study intervention								
Efficacy Assessments									
QMG[f,g]	X	X	X	X	X	X	X	X	
MG-ADL[f,h]	X	X	X	X	X	X	X	X	
MGFA-PIS[f]	X		X		X	X	X	X	
Neuro-QoL™ Fatigue	X	X	X	X	X	X	X	X	
Safety Assessments									
C-SSRS Since Last Visit[i]	X	X	X	X	X	X	X	X	
Electrocardiogram						X	X		
Complete physical examination, including neurological component						X	X	X	
Abbreviated physical examination[j,k]	X	X	X	X	X				
Vital sign measurements[l]	X	X	X	X	X	X	X	X	
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X
Assess for CD[c]	X	X	X	X	X	X	X		
Review Participant Safety Card[m]	X	X	X	X	X	X	X	X	
Safety Laboratory Tests[n]									
Serum pregnancy[o]							X		X

Table 4: Schedule of Activities (Open-label Extension Period)

Period	**Open-label Extension Period**[a]								
Study Year	**Year 1 (cont'd)**	**Year 2+**					**ED**[b]	**CD**[c]	**EOS**[b]
Study Day (D)	**D365**	**D456**	**D547**	**D638**	**D729**	**D820**	**NA**	**NA**	**NA**
Study Week (W)	**W52**	**W65**	**W78**	**W91**	**W104**	**W117**	**NA**	**NA**	**NA**
Study Window (days)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**	**NA**	**±2**
Urine pregnancy[o]	X	X	X	X	X	X		X	
Clinical chemistry	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	
Coagulation panel	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	
PK/PD Tests[p]									
PK[q]								X	
PD: AP activity and Bb[r]								X	
Biomarker Tests									
Anti-AChR antibody	X					X	X	X	
Factor D, C3, CP activity, nongenetic exploratory biomarkers (eg, MuSK, LRP4)[r]								X	
Other									
Concomitant medication	X	X	X	X	X	X	X	X	X
Nonpharmacologic treatments and therapies	X	X	X	X	X	X	X	X	X

[a] The OLE Period begins at the Day 239 (Week 34) visit after all assessments of the visit are performed, but before the administration of ALXN2050 in the clinic and postdose PK/PD sampling. The next in-clinic visit will be at Week 52.

[b] If a participant is discontinued from the study during the OLE Period, an ED Visit will be performed, and then an EOS Visit will be performed 30 (±2) days after the last dose of study intervention.

[c] Evaluation of CD must be performed as soon as possible, within 48 h of notification to the Investigator of symptom onset. If CD occurs between scheduled visits, only the assessments for the CD Visit are needed. If CD occurs on a scheduled visit, all scheduled assessments should be performed for that visit as well as for the evaluation of CD. Additional evaluation visits may be scheduled at the discretion of the Investigator.

[d] Ensure kit and lot number are recorded on the drug accountability log.

Table 4: Schedule of Activities (Open-label Extension Period)

[e] Dosing is by mouth bid throughout the OLE Period.

[f] MG assessments should be performed at approximately the same time of day by a properly trained Clinical Evaluator (preferably the same evaluator). The MG-ADL should always be performed first, followed by the QMG.

[g] The QMG assessment should be performed by a properly trained Clinical Evaluator (preferably the same evaluator) throughout the study. If a participant is taking a cholinesterase inhibitor, the dose must be withheld for at least 8 h prior to the assessment and, whenever possible, the time from the last dose to the QMG assessment should be kept similar between visits.

[h] The MG-ADL is required to be performed first, followed by the QMG. The MG-ADL assessment should be performed by a properly trained Clinical Evaluator (preferably the same evaluator) throughout the study. The recall period for MG-ADL is the preceding 7 days or since the last visit if the visit interval is less than 7 days.

[i] C SSRS will be assessed Since Last Visit.

[j] The abbreviated physical examination will be performed, if necessary, on the basis of the participant's health status and the clinical judgment of the Investigator.

[k] A symptom based neurologic examination should be performed if the participant has any complaints or clinical findings attributable to the central nervous system and if positive for findings, a full neurologic examination will need to be performed at that assessment time point and at future time points as needed (determined by the Investigator).

[l] Vital sign measurements will include systolic and diastolic blood pressure (millimeters of mercury [mmHg]), heart rate (beats/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). On dosing days, vital signs will be taken before study intervention administration and after the participant has been resting for at least 5 minutes.

[m] Participants will be given a safety card prior to the first dose of study intervention. At each visit throughout the study, investigational site staff will ensure that the participant has the safety card and will review the guidelines with the participant.

[n] Laboratory samples will be analyzed by the central laboratory. A list of parameters that will be obtained during the study is provided in Table 11.
Note: A Clinical Evaluator may be a neurologist, neurologist in training, or delegated member of the investigational site staff who has been certified in administering the assessments.

[o] Pregnancy tests must be performed on all participants of childbearing potential at the specified time points. Serum pregnancy test will be performed at the ED and EOS visits; urine pregnancy tests will be performed locally at all other specified time points. Additional pregnancy tests (urine or serum) may also be performed at any visit at the Investigator's discretion.

[p] Trough blood samples for serum PK will be collected predose (within 30 minutes prior to the administration of study intervention). All collection times will be recorded in the participant's electronic case report form.

[q] Trough (within 30 minutes predose).

[r] Collect predose (within 30 minutes).

Abbreviations: AChR = acetylcholine receptor; AP = alternative pathway; Bb = Bb fragment of complement factor B; bid = twice daily; C3 = complement component 3; CD = Clinical Deterioration; CP = classical pathway; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; ED = early discontinuation; eDiary = electronic diary; EOS = end of study; h = hour(s); LRP4 = low density lipoprotein receptor-related protein 4; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MuSK = muscle-specific tyrosine kinase; NA = not applicable; Neuro-QoL™ Fatigue = Neurological Quality of Life Fatigue questionnaire; OLE = Open-label Extension; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis score for disease severity; W = Week

2. INTRODUCTION

2.1. Study Rationale

ALXN2050 is a potent, reversible, small molecule inhibitor of complement FD, which is a key component of the AP. The complement system is involved in the pathophysiology of anti-acetylcholine receptor (AChR) antibody-positive gMG, and its inhibition has been proven to generate clinical benefit (Howard, 2017). ALXN2050 is an oral molecule that has the potential to provide a unique option to patients with gMG who suffer from debilitating and often incapacitating symptoms.

2.2. Background

2.2.1. Myasthenia Gravis

Myasthenia gravis is a rare, debilitating, chronic, complement-mediated autoimmune disease characterized by the failure of neuromuscular signal transmission. Voluntary muscle contraction requires the release of acetylcholine from nerve endings at the neuromuscular junction (NMJ). The majority of patients with myasthenia gravis (MG) produce autoantibodies that target the AChR. However, a minority of patients instead produce autoantibodies against other targets, such as muscle-specific tyrosine kinase (MuSK), which is involved in AChR clustering at the surface of muscle fibers (Conti-Fine, 2006; Gilhus, 2015; Nesargikar, 2012).

MG is clinically characterized by weakness and rapid fatigability of skeletal muscles that is exacerbated during periods of activity and improves after periods of rest (Barnett, 2014; Sieb, 2014). Based on criteria established by the MGFA, clinical severity of the disease is classified from Class I for ocular symptoms and signs only to Class V for severe generalized weakness that requires intubation for mechanical ventilation or the prevention of aspiration (Jaretzki, 2000). Approximately 80% of patients initially present with signs and symptoms consistent with ocular weakness: drooping eyelids (ptosis) and impaired eye movements causing double vision (diplopia). Of these, close to 85% will develop gMG (Grob, 2008). Generalized MG may affect the ability to speak or swallow, involve weakness of neck and limb muscles, lead to breathing difficulty, and result in increased general fatigue (Hoffmann, 2016). Muscle weakness and fatigue cause disability, impede activities of daily living (ADL), and impact the quality of patients' lives.

MG has a prevalence of 107 to 278 per million persons and affects men and women in an approximately equal ratio (Cetin, 2012; Cortes-Vicente, 2020; Fang, 2015; Heldal, 2009; Murai, 2011; Park, 2016). In younger people, MG is more prevalent in women than in men, and this trend is reversed in older people (Asmail, 2019; Grob, 2008; Keesey, 2004; Park, 2016). Of the 15% to 20% of patients who will experience a myasthenic crisis during the course of their disease, most (75% of patients) will experience an event within 2 years of diagnosis, requiring hospitalization and ventilatory support (Grob, 2008). Based on data reported from 2006 through 2016, mortality among patients with MG is approximately 1.5% (Westerberg, 2020).

The international consensus guidance for management of gMG includes cholinesterase inhibitors for the strengthening of neuromuscular transmission and immunosuppression for the reduction of

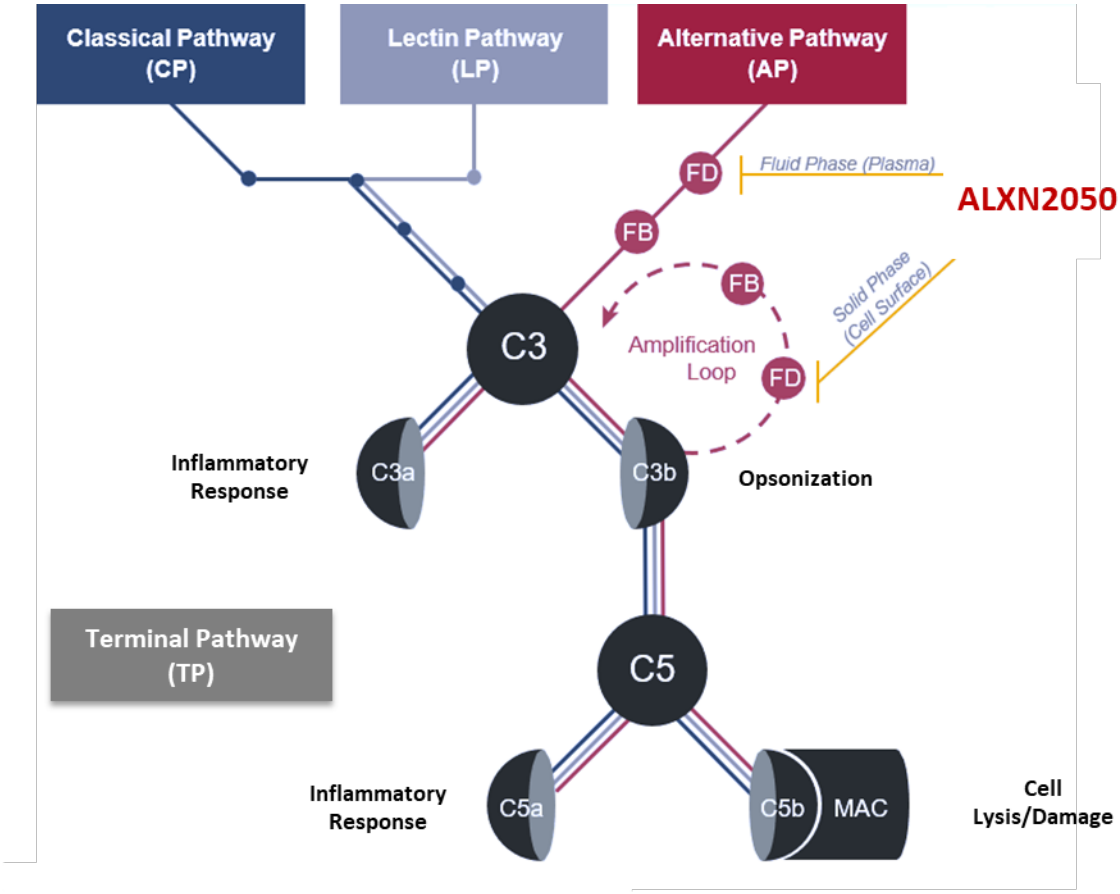
autoantibodies (Gilhus, 2019; Narayanaswami, 2021); however, in many cases only temporary relief of symptoms is provided, and overall disease activity persists (Guptill, 2016). Targeted blockade of terminal complement activity is another therapeutic option for patients with gMG that has been established to address the unmet need of patients who do not respond, or insufficiently respond, to prior treatments (Howard, 2017).

2.2.2. ALXN2050

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

FD is a serine protease that catalyzes the cleavage of complement factor B (FB) into Ba and Bb, which allows for the formation of the AP complement component (C)3 convertase (C3bBb). Factor D was chosen as a therapeutic target because, of the complement proteins, it has the lowest abundance in serum, and it catalyzes the essential step of AP activation and amplification, which leads to opsonization by C3 fragments and eventual activation of the terminal complement cascade. Although ALXN2050 does not inhibit components specific to the classical pathway (CP) or lectin pathway (LP), nor does it directly inhibit components of the terminal complement pathway, it will inhibit the AP-mediated amplification of complement activity initiated via the CP and LP (Harboe, 2004).

Figure 2: Complement Pathways



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

2.2.3. Rationale for Evaluating ALXN2050 in Participants with Generalized Myasthenia Gravis

Preclinical and clinical data suggest that activated terminal complement plays a role in the destruction of NMJ endplate morphology and impairment of neuromuscular transmission (Zhou, 2007). Anti-AChR antibodies bind to the postsynaptic cleft activating complement, which ultimately leads to the formation of the membrane attack complex (MAC). The MAC damages the NMJ, thus impairing neuromuscular transmission (affecting approximately 85% of patients with MG) (Mantegazza, 1988; Somnier, 1993; Vincent, 1985).

Complement activation by AChR autoantibodies is an important pathophysiological mechanism in gMG. The clinical importance of complement activation in gMG was demonstrated by the therapeutic benefits that have been achieved with the C5 inhibitor eculizumab (SOLIRIS®) and ravulizumab (ULTOMIRIS®). Eculizumab increased muscle strength measured by the Quantitative Myasthenia Gravis (QMG) score in Phase 2 and Phase 3 studies involving participants with gMG who previously did not respond to immunosuppressive therapy (IST) (Howard, 2013; Howard, 2017). Eculizumab also reduced the general fatigue associated with gMG (Andersen, 2019). Treatment with ravulizumab resulted in improvements in MG-ADL and QMG scores within 1 week that were maintained through the treatment period (Vu, 2022). Additional information may be found in the eculizumab and ravulizumab product labels.

Eculizumab and ravulizumab exert their effects by directly inhibiting the cleavage of C5 into C5a and C5b. This prevents the activation of the terminal complement pathway, which results in protection of the NMJ from complement-mediated damage, even in the presence of anti-AChR antibodies. This preservation of NMJ activity translates clinically into improved muscle strength and function.

While the role of the AP, and specifically FD, has not been studied in as much detail as the CP and terminal pathway in gMG, in vitro and preclinical evidence support a contribution of the AP to the pathophysiology of gMG. In a preclinical autoimmune MG rat model, direct inhibition of FB, another key protein in the AP, was shown experimentally to prevent the passive induction of MG (Subias, 2014). Given that FD catalyzes the rate limiting cleavage of AP protein FB into Ba and Bb, pharmacologic inhibition of FD will ultimately result in a reduction of FB activity and may therefore produce similar effects to direct FB inhibition.

Additionally, the AP-based amplification loop plays an important role in augmenting the function of the CP, including the formation of the terminal complement components that are responsible for the NMJ damage observed in patients with gMG. This importance has been quantified by in vitro data which shows that decreasing the AP amplification loop via FD inhibition results in a greater than 80% reduction of the terminal MAC (Harboe, 2004).

Factor D is the least abundant complement protein, yet it is a rate limiting component of the AP, thus making it an ideal pharmaceutical target. ALXN2050 is a potent inhibitor of FD with demonstrated dose-dependent inhibition of complement AP activity after administration to healthy volunteers in single-ascending and multiple-ascending dose studies. Plasma Bb concentrations also showed significant dose-dependent reductions.

As an orally administered small molecule, ALXN2050 would provide an important first-in-class treatment option for patients with gMG. Available approved therapies, and many of those currently in development, rely on intravenous (IV) or subcutaneous administration. This may

result in a treatment burden for patients with gMG and their families, especially if the disease manifestation is severe enough to impair mobility, vision, or dexterity. An approved, effective, oral molecule would provide these patients with a more convenient and accessible option for gMG therapy, which may lead to better compliance and clinical outcomes.

Additional nonclinical and clinical data may be found in the ALXN2050 IB.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Potential risks associated with participation in this study and risk mitigation measures are presented in Table 5.

Table 5: Potential Risks and Mitigation Strategies

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
Meningococcal infection	Participants receiving Factor D complement inhibitor therapy may have an increased risk of infections, particularly *Neisseria meningitidis*.	All participants must be vaccinated against meningococcal disease within 3 years prior to, or at the time of, initiating the study intervention. Participants who initiate study intervention less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination. Participants must carry the Participant Safety Card dispensed at the Day 1 Visit at all times to promote rapid recognition of any potential signs or symptoms of infection.
Seizure	Convulsions and/or electroencephalogram abnormalities have been observed during nonclinical repeat dose toxicology studies. Refer to Section 4.3 for information on the safety margin.	Participants with history of seizures are excluded. Procedures specified in Section 10.7 are to be followed if a suspected seizure occurs.

Table 5: Potential Risks and Mitigation Strategies

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
Pregnancy exposure or lactation	No studies of ALXN2050 have been conducted in pregnant women. There are no data available on excretion of ALXN2050 in breast milk.	Pregnancy testing will be conducted as specified in the Schedule of Activities (SoA; Section 1.3). A negative serum pregnancy test (Screening Visit) and a negative urine pregnancy test (Day 1) are required prior to randomization. If a pregnancy is reported during the study, safety follow-up will be performed (Section 10.5.3). Pregnant or nursing women are excluded from participating in this clinical study. Participants and their spouses/partners must use a highly effective method of contraception during the study and for a period of 30 days following the final dose of study intervention.

2.3.1.1. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this protocol amendment. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.9.

2.3.2. Benefit Assessment

Potential benefits include:

- Targeted therapy with a new treatment for gMG
- More frequent routine assessments/procedures (eg, physical examinations and vital signs assessments) at prespecified in-clinic study visits

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with ALXN2050 are justified by the anticipated benefits that may be afforded to participants with gMG.

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on improvement in the MG-ADL total score	Proportion of participants with an MG-ADL total score reduction of ≥ 2 points in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy
Secondary	
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on improvement in the QMG total score	• Change from baseline in QMG total score at Week 8 • Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the QMG total score at Week 8 • Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the QMG total score in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on improvement in quality of life measures	• Change from baseline in Neuro-QoL™ Fatigue score at Week 8
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on additional endpoints involving the MG-ADL total score	• Change from baseline in MG-ADL total score at Week 8 • Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the MG-ADL total score in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy • Proportion of participants with at least a 2-, 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the MG-ADL total score at Week 8
PK/PD	
To characterize the PK/PD of ALXN2050 and to establish the PK/PD relationship in participants with gMG	• Observed C_{max} and C_{trough} values over time • Absolute values and change from baseline in plasma Bb concentration and serum AP activity over time
Biomarker	
To assess the effect of FD inhibition on complement biomarkers	Plasma FD concentration, serum C3 concentration, and serum CP activity over time

Objectives	Endpoints
Safety	
To characterize the overall safety of ALXN2050 compared with placebo in participants with gMG	• Incidence of TEAEs and TESAEs over time • Changes from baseline in laboratory assessments
Tertiary/Exploratory	
To assess the efficacy of ALXN2050 compared with placebo in the treatment of gMG based on other efficacy endpoints	• Proportion of participants with an MG-ADL total score reduction of ≥ 2 points and a QMG total score reduction of ≥ 3 points in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy • Proportion of participants with at least a 2-point improvement in the MG-ADL total score for 4 consecutive weeks (measured from Day 1 to Week 8 for Groups 1, 2, and 3 and from Week 8 to Week 16 for Groups 3a and 3b) and who did not receive any rescue therapy • Change from baseline in MG-ADL total score at Week 8 for Groups 1, 2, and 3; and from Week 8 to Week 16 for Groups 3a and 3b • Change from baseline in MG-ADL total score at Week 26 for Groups 1 and 2[a]; and from Week 8 to Week 34 for Groups 3a and 3b[a] • Incidence of Clinical Deterioration of gMG over time[s] • MGFA-PIS at Week 8 and Week 26[a] • Proportion of participants with a classification of Minimal Manifestations at Week 8 and Week 26[a] (as measured by the MGFA-PIS) • Proportion of participants who receive rescue therapy over time
To assess the effect of FD inhibition on AChR antibody titers in participants with gMG	Change of anti-AChR antibody titers over time

Objectives	Endpoints
To characterize nongenetic biomarkers in adult participants with gMG	• Detection of gMG-associated autoantibodies, which may include baseline and/or later timepoints (eg, MuSK, LRP4) • In vitro evaluation of autoantibody activity (eg, AChR blocking, complement deposition) • Absolute values and change from baseline in levels of complement proteins and complement pathway regulators (eg, C5b-9, Properdin) • Change from baseline in biomarkers of inflammation and NMJ damage (eg, MMP-10, IL-6)

[a] The comparator will be discussed in detail in the Statistical Analysis Plan.
[b] Clinical Deterioration is defined in Section 8.2.5.

Abbreviations: AChR = acetylcholine receptor; AP = alternative pathway; Bb = Bb fragment of complement factor B; C3 = complement component 3; C5b-9 = terminal complement complex; C_{max} = maximum (peak) plasma concentration of the drug; CP = classical pathway; C_{trough} = predose concentration; FD = factor D; gMG = generalized myasthenia gravis; IL = interleukin; LRP4 = low density lipoprotein receptor-related protein 4; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MMP-10 = matrix metalloproteinase 10; MuSK = muscle-specific tyrosine kinase; Neuro-QoL™ Fatigue = Quality of Life in Neurological Disorders Fatigue questionnaire; NMJ = neuromuscular junction; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the efficacy and safety of ALXN2050 in adult participants with gMG. Approximately 70 eligible participants will be stratified by MG-ADL total score at baseline (5 to 6 [capped to approximately 10% of total enrollment] versus ≥ 7) and randomized on Day 1 in a 2:1:2 ratio to 1 of 3 treatment groups: ALXN2050 180 mg bid (Group 1), ALXN2050 120 mg bid (Group 2), or placebo (Group 3).

Participants will receive the study intervention bid from Day 1 through Week 117. Participants may continue to receive a stable regimen of acetylcholinesterase inhibitors (AChEIs), supportive IST (with some exceptions as described in Section 6.5.2), and/or corticosteroid therapy that was being administered prior to the Screening Visit, but no new AChEIs/ISTs/steroids and no change in AChEI/IST/steroid dosages are permitted during the Screening Period, the PEP, or the ETP, except for safety reasons as identified by the Investigator. During the OLE Period (ie, after 34 weeks of treatment), changes in supportive AChEIs/ISTs/steroids can be made at the discretion of the Investigator.

Rescue therapy (eg, plasmapheresis [PP]/plasma exchange [PE], intravenous immunoglobulin [IVIg], or high-dose corticosteroid) is allowed at any time for participants who experience a protocol-defined Clinical Deterioration of MG (defined in Section 8.2.5). The treatment approach for a specific participant should be determined by the Investigator.

Multiple outcome measures will be administered to evaluate the efficacy and safety objectives. In the clinic, assessments should be performed or administered by a properly trained Clinical Evaluator (eg, neurologist, neurologist in-training, or delegated member of the investigational site staff).

Table 6: Responsibility for the Clinical Evaluation of gMG

Study Assessment	Responsible Study Staff
MGFA Classification	Neurologist[a]
MG-ADL	Clinical Evaluator[b]
QMG	Clinical Evaluator[b]
MGFA-PIS	Neurologist[a]
Diagnosis of Clinical Deterioration	Neurologist[a]
C-SSRS	Clinical Evaluator
Neuro-QOL™ Fatigue	Participant self-assessment

[a] Can be an appropriately qualified senior neurology resident in training.
[b] Neurologist or appropriately qualified other study team member as delegated by the Investigator, eg, senior neurology resident in training, physician assistant, or nurse practitioner. Vital capacity, which is part of the QMG assessment, may also be measured by a qualified physical therapist.
Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; gMG – generalized myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; Neuro-QoL™ Fatigue = Neurological Quality of Life Fatigue questionnaire; QMG = Quantitative Myasthenia Gravis score for disease severity

There will be 4 periods in this study (Figure 1):

- Screening Period of up to 4 weeks – During this timeframe, participants will present to the clinic at least once wherein screening procedures and assessments as indicated in the Schedule of Activities (SoA; Section 1.3 [Table 2]) will be performed to determine eligibility. The participant may be asked to return to the clinic for additional follow-up (eg, blood redraw), although it is not anticipated that this will be a frequent occurrence.
- Primary Evaluation Period of 8 weeks (Day 1 to Week 8) – Treatment during this timeframe will be blinded for participants, Investigators, site personnel, and Alexion clinical study staff. The participant will present to the clinic every week for the first 8 weeks for fulfillment of procedures and assessments as specified in the SoA (Table 2). For the first visit on Day 1, and after confirmation of eligibility, the participant will be randomized to 1 of 3 treatment groups. The participant will be provided with sufficient study intervention to last until their next study visit. In the clinic, the participant will be administered a dose of study intervention (3 tablets). The participant will be instructed to take the second dose of study intervention (3 tablets) at home. The participant will also be dispensed the safety card that discusses some of the risks associated with treatment, and steps to take in the event of an emergency. The participant must be instructed to carry the safety card at all times. The last visit for the PEP will be the Week 8 Visit.
- Extended Treatment Period of 26 weeks (Week 8 to Week 34) – The ETP begins at the Day 57 (Week 8) Visit after all assessments of the visit are performed, but before the administration of ALXN2050 in the clinic and postdose PK/PD sampling. During this timeframe, participants in the ALXN2050 180 mg bid and ALXN2050 120 mg bid groups will continue taking the dose to which they are randomized. Participants in the placebo group will be stratified by MG-ADL total score at baseline (pre-placebo) and re-randomized in a 1:1 ratio to either ALXN2050 180 mg bid (Group 3a) or ALXN2050 120 mg bid (Group 3b). All participants will receive active study intervention; however, the actual dosage of ALXN2050 will be blinded to participants, Investigators, and site personnel. Visits at Weeks 9, 10, 11, 13, 14, and 15 will be conducted via telephone contact (Table 3). Participants will present for in-clinic visits at Weeks 12, 16, 26, and 34. The first dose of study intervention during in-clinic visit days will be administered by the site personnel. The participant will take the second dose of study intervention at home. The last visit for the ETP will be the Week 34 Visit.
- Open-label Extension Period of up to approximately 1.5 years (Week 34 to Week 117) – The OLE Period begins at the Day 239 (Week 34) Visit after all assessments of the visit are performed, but before the administration of ALXN2050 in the clinic and postdose pharmacokinetics/pharmacodynamics (PK/PD) sampling. During this timeframe, all participants will receive active study intervention. If an optimal dose of ALXN2050 has been identified, all participants will be switched to this optimal dose, as long they have completed the first 34 weeks of treatment. However, the actual dose of ALXN2050 will continue to be blinded to participants, Investigators, and site personnel during this study period until they are switched to the

optimal dose, if one is identified during the study. Participants will return to the clinic approximately every 3 months as indicated in the SoA (Table 4). The first dose of study intervention during in-clinic visit days will be administered by the site personnel. The participant will take the second dose of study intervention at home. The last visit for the OLE Period is the EOS Visit.

An EOS Visit will occur 30 (±2) days after the last dose of study intervention for all participants. The overall study duration for an individual participant will be approximately 125 weeks (from the Screening Visit through the EOS Visit).

4.2. Scientific Rationale for Study Design

Justification of specific study design elements is discussed in Table 7.

Table 7: Scientific Rationale for the Design of Study ALXN2050-MG-201

Design Element	Rationale
Target population	○ There are few available approved treatments for gMG. ALXN2050 has the potential to address an unmet need by providing a convenient, oral treatment option for patients with gMG, irrespective of disease severity.
Randomized, double-blind, placebo-controlled Primary Evaluation Period (PEP)	○ A randomized, double-blind placebo-controlled study or study period (eg, PEP) facilitates the unbiased evaluation of the efficacy and safety/tolerability of an intervention and can thereby establish a cause-and-effect relationship between the administration of an intervention and improved clinical outcomes (Vamvakas, 1997).
Selection of 2 dose levels (ALXN2050 180 mg bid and ALXN2050 120 mg bid)	○ Multiple dosage regimens of up to 200 mg bid have been evaluated in a healthy volunteer study and were noted to be well tolerated with sustained PD activity. A primary goal of Study ALXN2050-MG-201 is to identify the dosage regimen that will provide the best benefit-risk balance in participants with gMG.
Primary endpoint (MG-ADL)	○ MG-ADL is a validated instrument that is used to assess MG disease severity over time. A 2-point improvement in the total score (ie, decrease in 2 points at any time point compared to baseline) indicates clinically significant improvement.

Table 7: Scientific Rationale for the Design of Study ALXN2050-MG-201

Design Element	Rationale
Secondary endpoints	○ QMG is a scoring system considered to be an objective evaluation of MG signs and is based on quantitative testing of sentinel muscle groups. ○ Neuro-QoL™ Fatigue questionnaire assesses the extent of participant fatigue over time. Fatigue is a common complaint amongst patients with MG which adversely impacts quality of life.
PK/PD and exposure-response analysis	○ The PD biomarkers selected for evaluation during this study are appropriate based on the mechanism of action of ALXN2050, in which factor D inhibition results in attenuation of the alternative pathway of the complement system. Factor B binds to C3b (C3bB complex) and is cleaved by complement Factor D into Ba and Bb fragments. Bb remains bound to C3b and becomes C3 convertase (C3bBb), which amplifies the alternative complement pathway. ○ The exposure-response analysis will be performed to evaluate the PK/PD relationship and to determine the appropriate Phase 3 dose.
Safety endpoints	○ Safety endpoints are included in order to actively assess risk and ensure the safety of participants in the study.
Duration of study	○ Given the expected rapid onset of action of ALXN2050, as well as observations of the timing of clinical improvement in prior MG studies (both with complement inhibitors and medications utilizing other mechanisms of action), the 8-week PEP is an adequate timeframe for collection of efficacy data which will enable determination of a treatment effect of ALXN2050 compared with placebo to demonstrate proof-of-concept. ○ Additionally, the PEP was planned for 8 weeks as a consideration to participants receiving placebo who may benefit from direct treatment with active study intervention at an earlier time point.

Table 7: Scientific Rationale for the Design of Study ALXN2050-MG-201

Design Element	Rationale
	○ The ETP and OLE Period will facilitate collection of longitudinal efficacy and additional safety data of ALXN2050 for all participants.

Abbreviations: Ba = Ba fragment of complement factor B; Bb = Bb fragment of complement factor B; bid = twice daily; C = complement component; ETP = Extended Treatment Period; gMG = generalized myasthenia gravis; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; Neuro-QoL™ Fatigue = Neurological Quality of Life Fatigue questionnaire; OLE = Open-label Extension; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis score for disease severity

4.3. Justification for Dose

Clinical PK and PD data have been generated for ALXN2050 in single ascending and multiple ascending dose studies in healthy volunteers (Studies ACH228-001 and ACH228-002, respectively). In these Phase 1 healthy volunteer studies, ALXN2050 PK exposures increased dose-proportionally following single doses and in a greater than dose-proportional manner following multiple doses at steady state over the dose range of 40 mg bid to 200 mg bid. Corresponding PD activity as determined by AP inhibition in the AP Wieslab assay increased with increasing exposure.

In the multiple-dose Study ACH228-002, the dosage regimens of both 120 mg bid and 200 mg bid were safe and effective, showing an approximately 10-fold safety margin or greater in both maximum plasma concentration (C_{max}) and the area under the concentration-time curve from time zero to 24 hours (AUC_{0-24}) over the exposures achieved at the no-observed-adverse-effect-level (NOAEL) from nonclinical chronic toxicology studies (see IB). In addition, both dosage regimens provided complete (> 90%) and sustained inhibition of AP activity throughout the 12-hour dosing interval. Therefore, 120 mg bid is selected as the minimum therapeutic dosage.

However, large variabilities were observed in the PK and PD data and in the established PK/PD relationship. Intersubject variability in PK and the PK/PD relationship indicated that a dosage higher than 120 mg bid, such as 180 mg bid, may be required to ensure more participants reach and maintain an ALXN2050 concentration above the threshold for 90% AP inhibition.

The relationship between exposure and response (AP activity inhibition) has not been established specifically in participants in gMG. Therefore, one of the objectives of this study is to develop the exposure-response relationship in this target population and evaluate the dose that can consistently achieve > 90% AP inhibition at trough steady-state concentrations. Inclusion of the 120 mg bid group is needed to fully characterize this exposure-response relationship among participants with gMG to inform Phase 3 dose selection. Study ALXN2050-MG-201 is designed to explore the utility of both the 120 mg bid and the 180 mg bid dosage regimens to fully characterize the PK, PD, biomarker, efficacy, and safety data in participants with gMG.

4.4. End of Study Definition

A participant is considered to have completed the study if:

- The participant has completed all periods of the study including the last visit of the OLE Period, or
- In the event the study is stopped early, the participant has completed all applicable periods of the study, including the EOS Visit, or
- The participant completes the study early (and completes the EOS Visit) because the study intervention is registered or approved (in accordance with country-specific regulations).

The EOS is defined as the date of the last visit of the last participant for any protocol-related activity in the study (SoA; Section 1.3).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participant must be at least 18 years of age at the time of signing the informed consent form (ICF).

Type of Participant and Disease Characteristics

2. Diagnosed with MG at least 3 months (90 days) prior to the date of the Screening Visit.

Confirmation of MG must be made via the following:

a. Positive serologic test for anti-AChR antibodies at the Screening Visit, **and**
b. Abnormal neuromuscular transmission demonstrated by single fiber electromyography or repetitive nerve stimulation, **or**
c. Positive response to an AChEI test (eg, edrophonium chloride test), **or**
d. Improvement of signs or symptoms related to MG during treatment with an oral AChEI, as determined by the treating physician

3. Myasthenia Gravis Foundation of America Clinical Classification Class II to IV at the Screening Visit.
4. MG-ADL total score must be ≥ 5 (with at least 50% of the score attributed to non-ocular elements) at the Screening Visit and at randomization (Day 1).

   Note: Enrollment of participants with MG-ADL total score < 7 will be limited to approximately 10% of the total enrollment.
5. Participants receiving treatment with any of the following must have been receiving treatment and on a stable dose for the time periods specified below prior to the date of the Screening Visit, with no changes to the regimen expected during screening, the PEP, and/or the ETP:

Medication Name/Drug Class Name	Dosage Regimen Required Prior to the Screening Visit
AZA	≥ 6 months (180 days) on the medication, with a stable dose for ≥ 2 months (60 days)
Other immunosuppressive therapies, such as MMF, MTX, or cyclophosphamide	≥ 3 months (90 days) on the medication, with a stable dose for ≥ 1 month (30 days)
Corticosteroids (oral), maximum dose 20 mg/day prednisone or equivalent	stable dose for ≥ 4 weeks (28 days)
Acetylcholinesterase inhibitors[a]	stable dose for ≥ 2 weeks (14 days)

Note: If a participant has recently discontinued any of the above medications, a period of time equal to the stable dose requirement listed above for that medication (eg, ≥ 2 months for AZA or ≥ 4 weeks for corticosteroids) must have passed prior to the first day of the Screening Period.

[a] As needed or intermittent acetylcholinesterase inhibitor use is not permitted at any point during the study.

Abbreviations: AZA = azathioprine; MMF = mycophenolate mofetil; MTX = methotrexate

Sex

6. Male or female participant.
7. Female participants of childbearing potential and male participants must follow protocol-specified contraception guidance (Section 10.5.2).

Informed Consent

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

Other Inclusions

9. Vaccinated against meningococcal infection (*Neisseria meningitidis*) within 3 years prior to, or at the time of, randomization (Day 1).

   Participants who initiate study intervention less than 2 weeks after receiving a meningococcal vaccine must receive appropriate prophylactic antibiotics until at least 2 weeks after the vaccination against *N meningitidis*.

5.2. Exclusion Criteria

A participant will be excluded from the study if any exclusion criteria are satisfied.

Medical Conditions

1. Any medical condition (eg, cardiac, pulmonary, renal, oncologic, or psychiatric) that, in the opinion of the Investigator or the Medical Monitor, might interfere with participation in the study, pose any added risk to the participant, or confound the assessment of the participant.
2. History of thymectomy, thymomectomy, or any other thymic surgery within 12 months prior to the Screening Visit.
3. Any untreated thymic malignancy, carcinoma, or thymoma.

   Participants with a history of treated thymic malignancy or carcinoma are eligible for enrollment if they meet the following conditions:

   a. Treatment completed > 5 years prior to the Screening Visit
   b. No known recurrence within the 5 years prior to the Screening Visit
   c. No radiological indication of recurrence in a computed tomography (CT) or magnetic resonance imaging (MRI) scan, including administration of IV contrast, performed within 6 months of randomization (Day 1)

   Participants with a history of treated benign thymoma are eligible if they meet the following conditions:

   d. Histopathological or equivalent records indicating the diagnosis of benign thymoma

e. Treatment completed > 12 months prior to the Screening Visit
f. No known recurrence within the 12 months prior to the Screening Visit
g. No radiological indication of recurrence in a CT or MRI scan, including administration of IV contrast, performed within 6 months of randomization (Day 1)
h. If adequate records confirming the diagnosis of benign thymoma are not available, the participant must satisfy the eligibility criteria for thymic malignancy or carcinoma stated above.

Thymomas classified as ≤ Stage II according to the Masaoka Staging System are considered benign; thymomas classified as ≥ Stage III are considered malignant (Detterbeck, 2014; Masaoka, 2010).

4. Clinical features that, in the opinion of the Investigator, are consistent with Clinical Deterioration of MG at the time of the Screening Visit or at any time during the Screening Period prior to randomization (Day 1).
5. History of seizure.
6. History of *N meningitidis* infection.
7. Evidence of human immunodeficiency virus (HIV antibody positive) infection at the Screening Visit.
8. History of hypersensitivity to any ingredient contained in the study intervention.
9. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the Screening Visit.
10. Evidence of hepatitis B (hepatitis B positive hepatitis surface antigen [HbsAg] or positive hepatitis B core antibody [anti-HBc]) with negative surface antibody [anti-HBs] or hepatitis C viral infection (hepatitis C virus [HCV] antibody positive, except for patients with documented successful treatment and documented sustained virologic response [SVR]) at Screening.
11. History of malignancy within 5 years of the Screening Visit, with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
12. History of persistent or recurrent infections prior to the Screening Visit.
13. Active systemic bacterial, viral, or fungal infection within 14 days prior to study intervention administration on Day 1.
14. Presence of fever as documented by a temperature ≥ 38°C (100.4°F) within 7 days prior to administration of study intervention on Day 1.
15. History or presence of any risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of Long QT Syndrome), a screening QT interval corrected using Fridericia's formula (QTcF) > 450 msec for males and > 470 msec for females, or receiving medications known to significantly increase the corrected QT interval (QTc).
16. Laboratory abnormalities at the Screening Visit, including:
    a. Alanine aminotransferase > 2 × the upper limit of normal (ULN)

b. Direct bilirubin > 2 × ULN

17. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 and/or are on dialysis.
18. Any other clinically significant laboratory abnormality that, in the opinion of the Investigator, would make the participant inappropriate for the study or put the participant at undue risk.

Prior/Concomitant Therapy

19. Use of the following within the time periods specified below:
    a. IVIg or subcutaneous immunoglobulin (SCIg) within the 4 weeks (28 days) prior to the Screening Visit
    b. Use of PE and PP within the 4 weeks (28 days) prior to the Screening Visit
    c. Use of rituximab within the 6 months (180 days) prior to the Screening Visit
    d. Use of tacrolimus or cyclosporine within the 4 weeks (28 days) prior to the Screening Visit
20. Any previous or current treatment with complement inhibitors (eg, eculizumab, ravulizumab).
21. Use of known cytochrome P450, family 3, subfamily A (CYP3A) sensitive substrates, moderate or strong CYP3A inducers, and/or moderate or strong CYP3A inhibitors from 2 weeks or 5 half-lives, whichever is longer, prior to the first administration of study intervention on Day 1 (randomization) (full list provided in Table 13).
22. Use of selected medications known to lower the seizure threshold and/or cause seizure (full list provided in Section 10.11).
23. Current treatment with a biologic medication that may affect immune system functioning or has stopped treatment with a biologic medication that may affect immune system functioning, and 5 terminal half-lives of the biologic medication have not elapsed by the time of the Screening Visit. Participants receiving prior treatment with an FcRn inhibitor ≥ 5 half-lives before the Screening Visit may be enrolled but the total immunoglobulin G (IgG) level must be above the lower limit of normal (LLN) before these participants can be randomized.

Prior/Concurrent Clinical Study Experience

24. Participation in another interventional treatment study or use of any experimental therapy within 30 days before the Screening Visit or within 5 half-lives of the study intervention, whichever is greater.

Other Exclusions

25. Pregnant, breastfeeding, or intending to conceive during the course of the study.
26. Inability to travel to the clinic for specified visits or fulfill the logistical requirements of study intervention administration.
27. Planned surgical procedure during the course of the study.

5.3. Lifestyle Considerations

5.3.1. Medications

If a participant is taking a cholinesterase inhibitor, the dose must be withheld for at least 8 hours prior to the QMG assessment at time points presented in the SoA (Section 1.3).

5.3.2. Meals and Dietary Restrictions

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

5.4. Screen Failures

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

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

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

- ALXN2050 drug product will be provided as tablets that are manufactured using a common blend.
  - The 60 mg formulation will be used in Study ALXN2050-MG-201.
- Matching placebo will be manufactured in the same fashion, without the active ingredient. ALXN2050 and placebo tablets will be identical in appearance.
- The participant will be provided with sufficient study intervention to last until their next study visit. Additional details will be provided in the interactive response technology (IRT) manual.
- In order to maintain the study blind for participants, Investigators, and site personnel, each of the 2 daily doses will consist of 3 tablets that in combination correspond to the assigned treatment group.
  - 180 mg: three 60 mg tablets
  - 120 mg: two 60 mg tablets and one placebo tablet
  - Placebo: 3 placebo tablets
- During in-clinic visits, the participant will be administered the first dose of study intervention. The second dose of study intervention is to be taken at home. Whether in the clinic or at home, the timing of administration should be consistent.
- In the event of a missed dose, the participant should be instructed to take the study intervention within 6 hours of the originally scheduled time. If more than 6 hours have passed, the missed dose should be skipped. In either scenario, the next dose should be taken according to the original dosing schedule.

The specific details of study intervention are presented in Table 8.

Table 8: Study Intervention

Study Intervention Name	ALXN2050 (Formerly ACH-0145228)	Placebo
Dose formulation	tablet	tablet
Unit dose strength(s)	60 mg	NA
Dose level(s) and frequency	120 mg bid or 180 mg bid	bid
Route of administration	oral	oral
IMP or AxMP	IMP	IMP
Sourcing	Alexion Pharmaceuticals, Inc.	Alexion Pharmaceuticals, Inc.

Abbreviations: AxMP = auxiliary medicinal product; bid = twice daily; IMP = investigational medicinal product; NA = not applicable

6.1.1. Study Intervention(s) Packaging and Labeling

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

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

6.1.2. Optional Dosing eDiary Tool

Participants will be provided with an optional dosing eDiary tool which is to be used as a reminder for taking the assigned study intervention throughout the duration of the study. Participants are advised to enter the date on which the assigned study treatment is scheduled and mark the chart each time the morning and evening dose is taken. As this is an optional tool, there will be no collection of data either by Alexion or the Investigator's site (ie, it will not be used for study intervention accountability).

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Preparation

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

6.2.2. Storage and Handling

- Study intervention must be stored in the containers as provided at 15ºC to 30ºC. Participants should be instructed to keep their study medications in the original container at room temperature at home.

- Study intervention will be shipped directly to each investigational site. When the medication is stored at the investigational site, the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit (a temperature monitor will accompany each shipment) for all study intervention received and that any discrepancies are reported and resolved before dispensation and use of the study intervention.
- Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. When the medication is stored at the investigational site, all study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

6.2.3. Accountability and Disposal

- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
  - This responsibility includes the reporting of any temperature excursions and product complaints to AlexionIMPTE@alexion.com and productcomplaints@alexion.com within 1 business day of awareness.

    A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.
- The pharmacist or other designated individual will maintain records of study intervention delivered to the study site, the inventory at the study site, the distribution to and use by each participant, and the return of materials to the Sponsor for storage or disposal/destruction of materials at the study site. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the study intervention and study participants.
- The Investigator will maintain records that adequately document that the participants were administered the correct study treatment kits and reconcile the products received from the drug dispensing center. Investigational product will not be returned to the Sponsor or disposed of until accountability has been fully monitored.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

All participants will be randomized on Day 1 in a ratio of 2:1:2 to ALXN2050 180 mg bid, ALXN2050 120 mg bid, or placebo, using a centralized IRT after the Investigator has verified that they are eligible to participate in the study (Section 4.1).

6.3.2. Blinding

All investigational site personnel, Alexion staff/designees, other staff directly associated with the conduct of the study, and all participants will be blinded to the treatment assignment during the PEP. The double-blind will be maintained by using identical study treatment kits and labels for all participants. The placebo tablet will have an identical appearance to that of ALXN2050. The randomization code will be maintained by the IRT provider. Select Alexion staff will be unblinded for the analyses of the PEP and will remain unblinded during the ETP and OLE. All participants, Investigators, and site personnel will remain blinded to treatment assignment from Day 1 through the end of the ETP (ie, Week 34). During the ETP, participants, Investigators, and site personnel will be informed that all participants are on active treatment but will remain blinded to the actual dose. After 34 weeks (ie, during the OLE Period), participants, Investigators, and site personnel will continue to be blinded to the actual dose received until an optimal dose is chosen (if this occurs during the study). If an optimal dose is chosen, then all participants will be moved to that dose, and participants, Investigators, and site personnel will no longer be blinded to treatment assignment/dose.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator will be able to unblind the participant's treatment allocation directly using the IRT. If a participant's intervention assignment is unblinded, Alexion or designee must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

In the event of a suspected unexpected serious adverse reaction (SUSAR), follow reporting guidance in Section 8.3.4. The blind will be maintained for persons responsible for the ongoing conduct of the study (eg, Monitors, Investigators) and those responsible for data analysis and interpretation of results, such as biometrics personnel.

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

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

6.4. Study Intervention Compliance

When participants are dosed at the investigational site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each

dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF).

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

A record of the quantity of study intervention dispensed and administered to/taken by each participant must be maintained and reconciled with study intervention records provided to the investigational site. Data from the optional dosing eDiary tool is **NOT** to be considered a source document nor to be used as record for reconciliation of study intervention. Intervention start and stop dates, including dates for planned and unplanned intervention delays will also be recorded in the eCRF.

6.5. Prior and Concomitant Therapies

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

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

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

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

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

6.5.1. Allowed Medications and Therapy

Participants receiving treatment with any of the medications listed in Table 9 must have been receiving treatment and on a stable dose for the time periods specified prior to the date of the Screening Visit.

Table 9: Allowed Medications and Therapies

Medication Name/Drug Class Name	Dosage Regimen Required Prior to the Screening Visit
AZA	≥ 6 months (180 days) on the medication, with a stable dose for ≥ 2 months (60 days)
Other immunosuppressive therapies, such as MMF, MTX, or cyclophosphamide	≥ 3 months (90 days) on the medication, with a stable dose for ≥ 1 month (30 days)
Corticosteroids (oral), maximum dose 20 mg/day prednisone or equivalent	stable dose for ≥ 4 weeks (28 days)
Acetylcholinesterase inhibitors[a]	stable dose for ≥ 2 weeks (14 days)

Note: If a participant has recently discontinued any of the above medications, a period of time equal to the stable dose requirement listed above for that medication (eg, ≥ 2 months for AZA or ≥ 4 weeks for corticosteroids) must have passed prior to the first day of the Screening Period.

[a] As needed or intermittent acetylcholinesterase inhibitor use is not permitted at any point during the study.

Abbreviations: AZA = azathioprine; MMF = mycophenolate mofetil; MTX = methotrexate

During the Screening, PEP, and ETP Periods, any stable regimen of AChEI, supportive ISTs, and/or corticosteroid therapy must not be discontinued or have a change in dose, and new AChEI, ISTs, and/or corticosteroid therapy must not be added, unless deemed medically necessary by the Investigator in order to maintain patient safety. During the OLE Period, changes in supportive AChEIs/ISTs/steroids can be made at the discretion of the Investigator.

Other concomitant medications used in the treatment of gMG may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor.

6.5.2. Disallowed Medications and Therapy

The following medications and therapies are prohibited during the study:

- Known CYP3A sensitive substrates, moderate or strong CYP3A inducers, and/or moderate or strong CYP3A inhibitors are prohibited throughout the study, until 1 week after the final administration of study intervention (see Table 13 for a full list of these medications)
- IVIg or SCIg as maintenance therapy (this is allowed acutely in the setting of a Clinical Deterioration of MG)
- PE/PP as maintenance therapy (this is allowed acutely in the setting of a Clinical Deterioration of MG)
- Rituximab
- Tacrolimus or cyclosporine
- Other complement inhibitors
- Biologic medications that may affect immune system functioning

- Experimental interventions or therapies
- Selected medications known to lower the seizure threshold and/or cause seizure (full list provided in Section 10.11)
- Medications known to significantly prolong the QTc

6.5.3. Rescue Medicine

Participants who experience Clinical Deterioration of MG (defined in Section 8.2.5) during the study may be administered rescue therapy (ie, high-dose corticosteroid, PE/PP, or IVIg) at the discretion of the Investigator. Alexion or designee should be notified within 24 hours of initiation of treatment with rescue therapy.

The name, date, and time of the dosage regimen will be recorded on the participant's eCRF.

Participants who require rescue medication may continue in the study at the discretion of the Investigator.

6.5.4. Vaccine and Antibiotic Prophylaxis

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

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

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

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

6.6. Dose Modification

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

If the optimal dose of ALXN2050 is determined during the study, all participants who have completed at least 34 weeks of treatment and are not already receiving the optimal dose will be switched.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Serious hypersensitivity reaction
- Pregnancy or planned pregnancy (Section 8.2.7)
- Severe uncontrolled infection
- Development of seizures (Section 10.7)
- Use of disallowed medication (defined in Section 6.5.2)
- Alexion or the Investigator deems it is necessary for the participant
- Adverse event that would, in the opinion of the Investigator, make continued participation in the study an unacceptable risk

Temporary discontinuation of study intervention is permitted (eg, in the event of an AE); however, the Medical Monitor should be notified if this occurs. If the study intervention is permanently discontinued, the participant should be discontinued from the study (described in Section 7.2).

All participants should complete an EOS visit 30 (±2) days after the last dose of study intervention as specified in the SoA (Section 1.3).

7.2. Participant Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.
- The study staff should notify Alexion or designee and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and eCRF.
- A participant may withdraw from the study at any time at his/her own request.
  - If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent, if permitted by local requirements.
  - If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- A participant can be withdrawn at any time in the best judgment of the Investigator for safety, behavioral, compliance, or administrative reasons, such as:
    - Pregnancy or planned pregnancy

- Lack of efficacy
- Participant noncompliance
- Intercurrent illness that would affect assessment of clinical status to a significant degree
- Unacceptable toxicity (including a clinically significant laboratory value) that compromises the participant's ability to continue study-specific procedures
- Loss of the ability to provide informed consent
- Any other condition or circumstance that would jeopardize the welfare of participants if they were to continue in the study

- At the time of discontinuing from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA (Section 1.3). Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Immediate safety concerns should be discussed with Alexion or designee immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Eligibility, study administrative, and screening assessments are further discussed in Section 8.11.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- See Section 10.2 for the list of clinical laboratory tests (that will be conducted at a central/specialty laboratory).

8.1. Efficacy Assessments

8.1.1. MG-ADL

The MG-ADL profile is an 8-item participant-reported scale that focuses on relevant symptoms and functional performance of ADL in patients with MG. The 8 items of the MG-ADL questionnaire were derived from symptom-based components of the original 13-item QMG scale to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects of MG. In this functional status instrument, each response is graded 0 (normal) to 3 (most severe). The MG-ADL total score ranges from 0 to 24, with higher scores indicating worse function. The recall period for the MG-ADL profile is the preceding 7 days or since the last visit if the visit interval is less than 7 days. A 2-point change in the MG-ADL total score is considered clinically meaningful.

The MG-ADL assessment should be administered by a properly trained Clinical Evaluator (preferably the same evaluator) throughout the study. It is anticipated that the form should take no more than 10 minutes to complete. The MG-ADL is required to be performed first, followed by the QMG.

8.1.2. QMG

The QMG Score for Disease Severity is an objective evaluation of therapy for MG and is based on quantitative testing of sentinel muscle groups. The MGFA task force has recommended that the QMG Score be used in prospective studies of therapy for MG (Benatar, 2012). The QMG instrument consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item); each graded 0 to 3, with 3 being the most

severe. The QMG total score ranges from 0 to 39, with higher scores indicating more severe disease. The QMG assessment should be performed by a properly trained Clinical Evaluator (preferably the same evaluator) throughout the study.

If a participant is taking a cholinesterase inhibitor, the dose must be withheld for at least 8 hours prior to the assessment and, whenever possible, the time from the last dose to the QMG assessment should be kept similar between visits.

8.1.3. MGFA-PIS

The gMG clinical state will be assessed using a modified version of the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) (Jaretzki, 2000). Change in status categories of Improved, Unchanged, or Worse, as well as the minimal manifestation (MM) state will be assessed and recorded by the Investigator or the same neurologist skilled in the evaluation of participants with gMG throughout the study. The subscores of MM, ie, MM-0, MM-1, MM-2, and MM-3, will not be used in this study.

8.1.4. Neuro-QoL™ Fatigue

The Quality of Life in Neurological Disorders Fatigue questionnaire (Neuro-QoL™ Fatigue) is a reliable and validated brief 19-item survey of fatigue, completed by the participant (Cella, 2010). Higher scores indicate greater fatigue and greater impact of MG on activities.

8.2. Safety Assessments

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, musculoskeletal, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- An abbreviated physical examination will be performed, if necessary, on the basis of the participant's health status and the clinical judgment of the Investigator.
- A symptom-based neurologic examination should be performed if the participant has any complaints or clinical findings attributable to the central nervous system, and if positive for findings, a full neurologic examination should be performed at that assessment time point and at future time points as needed (determined by the Investigator). If a full neurologic examination is required, the Investigator should perform the following evaluations:
  - Mental status
  - Cranial nerve examination
  - Motor examination
  - Gait examination
  - Coordination examination
  - Sensory examination

8.2.2. Vital Signs

- Body temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg) will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine or seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.
- Vital signs (to be taken before blood collection for laboratory tests) will consist of a single pulse check and a single blood pressure measurement.

8.2.3. Electrocardiograms

- A single 12-lead electrocardiogram (ECG) will be performed to obtain heart rate, PR interval (time from the onset of the P wave to the start of the QRS complex), combination of the Q wave, R wave, and S wave (QRS) interval, interval between the start of the Q wave and the end of the T wave (QT), and the QTc. QT interval will be corrected for heart rate using Fridericia's formula.
- Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- The Investigator will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results.
- Results will be recorded on the eCRF. Clinically significant findings should be recorded on the AE form.

8.2.4. Clinical Safety Laboratory Assessments

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.

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

- Repeat or unscheduled laboratory tests may be obtained for safety reasons or for technical issues with the samples.

8.2.4.1. Virus Serology

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

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

8.2.4.2. Urinalysis

Urine samples will be analyzed for the parameters listed in Section 10.2. A microscopic examination of urine samples will be performed if the results of the macroscopic analysis are abnormal.

8.2.4.3. Follicle-Stimulating Hormone

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

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

8.2.5. Clinical Deterioration of Myasthenia Gravis

Clinical Deterioration of MG is defined as any of the following:

- Patients who experience an MG Crisis, which is defined as weakness from MG that is severe enough to necessitate intubation or to delay extubation following surgery. The respiratory failure is due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness often accompanies the respiratory muscle weakness, or may be the predominant feature in some patients; or,
- A score of 3 or a 2-point worsening from baseline on any one of the individual MG-ADL items other than double vision or eyelid droop that, in the Investigator's assessment, is associated with significant symptomatic worsening; or,

- Administration of rescue therapy for MG to a patient whose, in the opinion of the Investigator or Investigator-designated clinician, health would be in jeopardy if rescue therapy were not given (eg, emergent situations).

Alexion or designee should be notified within 24 hours of initiation of treatment with rescue therapy for Clinical Deterioration of MG.

Evaluation of Clinical Deterioration of MG must be performed as soon as possible (ie, within 48 hours of notification to the Investigator of symptom onset). If a participant experiences Clinical Deterioration of MG during a scheduled study visit or presents to the clinic after an event of Clinical Deterioration of MG, refer to the SoA (Section 1.3) for assessments/procedures to be obtained. Additional tests may be performed in the best judgment of the Investigator.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

The National Institute of Neurological Disorders and Stroke in collaboration with regulatory agencies have developed a set of common data elements to be considered when implementing clinical studies for a neurologic indication (ie, in participants with gMG).

Participants being treated with study intervention should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing study intervention in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Families and caregivers of participants being treated with study intervention should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the Investigator.

Baseline assessment of suicidal ideation and behavior/intervention emergent suicidal ideation and behavior will be monitored during Study ALXN2050-MG-201 using the Columbia-Suicide Severity Rating Scale (C-SSRS).

There are 2 types of C-SSRS assessments that will be conducted during the study: “C-SSRS at Baseline/Screening” and “C-SSRS-Since Last Visit”. The C-SSRS will be performed by the Treating Physician or an appropriately trained designee at visits specified in the SoA (Section 1.3) to ensure that participants who are experiencing suicidal thoughts or behavior are properly recognized and adequately managed or referred for further evaluation. Additional C-SSRS assessments will be permitted as needed.

8.2.7. Pregnancy

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

Pregnancy data from female participants and female spouses/partners of male participants will be collected from the first dose of study intervention and at the time points specified in the SoA (Section 1.3). Any female participant who becomes pregnant during the study will be

discontinued from the study intervention and withdrawn from the study. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.5.3.

8.2.8. Participant Safety Card

Before the first dose of the study intervention, a Participant Safety Card will be dispensed during the Day 1 Visit. The safety card is provided to increase participant awareness of the risk of meningococcal infections, promote rapid recognition and disclosure of any potential signs or symptoms of infection experienced during the course of the study, and to inform participants of what actions must be taken if they are experiencing signs or symptoms of an infection.

At each visit/contact throughout the study, the study staff will ensure that the participant has the Participant Safety Card and review the content of the safety card with the participant. Participants are required to carry the safety card until 30 days after the final dose of study intervention.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

All AEs and SAEs will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to Alexion immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of the date the investigational site became aware of the event.

Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- Alexion or designee is required to submit individual SUSAR reports (defined in Section 10.3.2) in the format of MedWatch 3500 or CIOMS I Form to health authorities and Investigators as required. Forms submitted to Investigators will be blinded to treatment assignment. In limited circumstances, the blind may be broken in the case of urgent safety issues that could compromise participant safety.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Under the EU CTR 536/2014, events other than SAEs (eg, unexpected events) that may impact the benefit-risk balance should be reported. See definitions in Section 10.3.5.

8.3.5. Medication Error, Drug Abuse, and Drug Misuse

8.3.5.1. Timelines

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

The full definitions and examples of medication error, drug abuse, and drug misuse can be found in Section 10.4.

8.3.5.2. Medication Error

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

8.3.5.3. Drug Abuse

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

8.3.5.4. Drug Misuse

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

8.4. Treatment of Overdose

For this study, any dose of IMP or Alexion AxMP greater than that specified in the protocol will be considered an overdose. Any blinded dose greater than that specified in the protocol will be considered a suspected overdose.

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

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

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

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

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

8.5. Pharmacokinetics

- Biomatrix samples (eg, plasma, serum, or whole blood) will be collected for measurement of concentrations of ALXN2050 as specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of ALXN2050.
- PK data may be used for research to develop methods, assays for prognosis, diagnostics, and/or treatment monitoring related to gMG, pathways associated with the disease state, and/or mechanism of action of ALXN2050.
- Study intervention concentration information that would unblind the study will not be reported to investigational sites or blinded personnel until the study has been unblinded.

8.6. Pharmacodynamics

- Biomatrix samples (eg, plasma, serum, and whole blood) will be collected for measurement of AP activity and Bb as specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PD of ALXN2050. Samples collected for analyses of ALXN2050 (plasma, serum, whole blood) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

- Samples will be collected for analyses that may include but are not limited to evaluation of complement components (eg, FD, C3, CP activity), anti-AChR antibody, and other nongenetic exploratory biomarkers (eg, anti-MuSK antibodies, anti-low density lipoprotein receptor-related protein 4 [LRP4] antibodies, matrix metalloproteinase 10 [MMP-10], interleukin 6 [IL-6]) in adult participants with gMG.
- Blood samples for biomarker research will be collected from all participants in this study.
- Additional details regarding how biomarkers will be collected and analyzed are provided in Section 10.6.

8.9. Immunogenicity Assessments

Immunogenicity is not applicable in this study.

8.10. Health Economics Data and/or Medical Resource Utilization

Medical resource utilization and/or health economics data will not be collected during this study.

8.11. Other Assessments and Procedures

8.11.1. Informed Consent

Participants or their legally authorized representative must be consented per the informed consent process outlined in Section 10.1.3.

8.11.2. Demographics

A review of demographic parameters, including age, gender, race, and ethnicity, will be performed if allowed per country-specific regulations.

8.11.3. Inclusion and Exclusion Criteria

All inclusion (Section 5.1) and exclusion (Section 5.2) criteria must be reviewed by the Investigator or qualified designee to ensure the participant qualifies for study participation.

8.11.4. Medical History and MG History

The participant's MG history and relevant medical history, including prior and concomitant conditions/disorders, treatment history, substance usage, and history of medical conditions and surgeries will be evaluated by the Investigator and documented in the source documents and eCRF.

Myasthenia gravis history will include diagnosis date; initial MG clinical presentation (ocular myasthenia gravis [oMG] or gMG); time to gMG, if initial clinical presentation was oMG; maximum MGFA classification since diagnosis; ventilatory support since diagnosis; dates of MG exacerbation or crisis since diagnosis and prior to Day 1; and any MG-related hospitalizations within 2 years prior to the Screening Visit. Myasthenia gravis-specific medication or therapy taken within 2 years prior to the Screening Visit should also be recorded.

8.11.5. MGFA Classification

The MGFA Clinical Classification, a universally accepted grading system for patients with MG, will be also used to determine participant eligibility. This system was developed to identify subgroups that share distinct clinical features or disease severity that may necessitate different prognoses or responses to treatment (Jaretzki, 2000).

Table 10: MGFA Classification System

Class I	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
Class II	Mild weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity.
Class IIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
Class IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class III	Moderate weakness affecting other than ocular muscle; may also have ocular muscle weakness of any severity.
Class IIIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
Class IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class IV	Severe weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity.
Class IVa	Predominantly affecting limb and/or axial muscles. May also have lesser involvement of oropharyngeal muscles.
Class IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. Use of a feeding tube without intubation places the patient in Class IVb.

Source: Jaretzki, 2000

8.11.6. Vaccination or Antibiotic Prophylaxis

All participants must be vaccinated against meningococcal infections within 3 years or before the administration of study intervention on Day 1. Participants who initiate study intervention treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination.

8.11.7. Rerandomization

All participants who are determined to be eligible for Study ALXN2050-MG-201 by the Investigator will be randomized to treatment via an IRT system on Day 1 (Section 4.1). Participants randomized to placebo will be further randomized to 1 of the 2 active treatment groups (ie, ALXN2050 120 or 180 mg) at Week 8.

9. STATISTICAL CONSIDERATIONS

Statistical methods for this study will be further detailed in a separate statistical analysis plan (SAP). The SAP will be developed and finalized prior to the database lock. Statistical analyses will include tabulations of summary data, inferential analyses, by-participant listings, and figures. Inference from efficacy analyses will be based on a 2-sided type I error rate (α) of 10% unless stated otherwise. The summary statistics for continuous variables will include, but not be limited to, the number of participants, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented.

All efficacy analyses will be based on the Full Analysis Set (FAS). Supplemental per-protocol analyses for primary and secondary efficacy endpoints will be performed based on the Per Protocol Set (PPS) in the same manner as done for the FAS. Safety analyses will be performed on the Safety Set (SS).

The baseline value for analysis and reporting will be based on the last nonmissing measurement on or prior to the first dose of study intervention unless stated otherwise.

Analyses will be performed using the Statistical Analysis System (SAS®) software Version 9.4 or higher.

Given that this is a proof-of-concept Phase 2 study, all results will be interpreted as exploratory in nature.

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

The primary hypothesis is that the ALXN2050 180 mg bid group is superior to the placebo group in the proportions of responders in the primary endpoint. The responders are defined as participants who achieve an MG-ADL total score reduction of at least 2 points in any 4 consecutive weeks during the first 8 weeks of the PEP and who did not receive rescue therapy. The hypothesis for assessing superiority with respect to the proportions of responders is:

$H_0: p_3 - p_1 \leq 0;\ H_1: p_3 - p_1 > 0$

Where p_1 and p_3 are the proportions of responders in the primary endpoint for the placebo and ALXN2050 180 mg bid groups, respectively.

9.1.2. Secondary Hypotheses

The secondary hypothesis is that there is an increasing trend in the proportions of responders in the primary endpoint among the 3 treatment groups. The hypothesis for assessing the increasing trend is:

$H_0: p_1 = p_2 = p_3; H_1: p_1 \leq p_2 \leq p_3$; with at least 1 strict inequality

Where p_1, p_2, and p_3 are the proportions of responders in the primary endpoint in the placebo group, ALXN2050 120 mg bid group, and ALXN2050 180 mg bid group, respectively.

9.2. Sample Size Determination

The study has 3 treatment groups: ALXN2050 180 mg bid, ALXN2050 120 mg bid, and placebo. The goals of this study are to establish proof of concept for the treatment of gMG with ALXN2050 and to select a dosage for further development of ALXN2050 in gMG. Both trend analysis among the 3 treatment groups and differences in proportions of responders between the ALXN2050 180 mg bid group and the placebo group in the primary endpoint are used for sample size determination.

Data from the Argenx ADAPT study and the Momenta Vivacity-MG study were used to estimate the response rate on placebo with background standard-of-care treatment. Based on the data from both studies, the response rate for the placebo group is assumed to be 25%. A sample size of 54 evaluable participants with a randomization ratio of 1:1 to the placebo group and the ALXN2050 180 mg bid group results in approximately 80% power to detect a treatment effect (difference in the proportions of responders) of 35% between the 2 treatment groups, using a 2-sided type I error rate of 0.1 and the exact binomial computation method. An additional 13 evaluable participants will be enrolled to the ALXN2050 120 mg bid group, for a total of 67 evaluable participants.

Assuming that the response rate for the ALXN2050 120 mg bid group is 45%, with a total of 67 evaluable participants, the study has approximately 80% power to detect the increasing trend in the proportions of responders, using Cochran Armitage test at a 2-sided type I error rate of 0.1.

Assuming about 5% non-evaluability, the study is planned to enroll 70 participants in total.

The sample size calculations were performed in PASS 2020.

9.3. Populations for Analyses

For the purpose of analyses, the following populations are defined. The primary efficacy analyses will be based on the FAS and safety analyses will be based on the SS.

Population	Description
Randomized Set	All randomized participants grouped by randomized treatment group.
FAS	All randomized participants who receive at least 1 dose of study intervention and have a baseline and at least 1 postbaseline efficacy assessment. Participants will be analyzed as randomized.
PK Analysis Set	All randomized participants who have a baseline PK value and at least 1 evaluable postdose PK assessment.
PD Analysis Set	All randomized participants who have a baseline PD value and at least 1 evaluable postdose PD assessment.
PPS	All participants in the FAS without any important protocol deviations.
SS	All randomized participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received.
OLE Set	All randomized participants who receive at least 1 dose of ALXN2050 at the start of the OLE Period.

Abbreviations: FAS = Full Analysis Set; OLE = Open-label Extension; PD = pharmacodynamic; PK = pharmacokinetic; PPS = Per Protocol Set; SS = Safety Set

9.4. Statistical Analyses

9.4.1. Enrollment and Disposition

The number of participants screened, screen failed, and randomized will be presented. Enrollment information will be grouped by stratification factor and treatment allocation. The number of participants discontinued (along with reasons) from the PEP, ETP, OLE Period, and the overall study will be summarized.

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

All demographic information and baseline characteristics will be reported by treatment group and overall. No statistical test will be performed for homogeneity among treatment groups.

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

9.4.3. Medical/Surgical History, Physical Examination, and Myasthenia Gravis History

Medical and surgical history will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23 or later, System Organ Class (SOC) and Preferred Term. Myasthenia gravis history and abnormal physical examination findings will also be summarized.

9.4.4. Prior and Concomitant Medications

For analysis and reporting purposes, any medication started prior to first dose of study intervention will be considered prior medication, and medications that were received on or after the first dose of study intervention will be considered concomitant medications. All prior and concomitant medications including MG-specific medications and rescue therapy during the study, if any, will be summarized.

9.4.5. Extent of Drug Exposure

The cumulative and total drug exposure, dose intensity and relative dose intensity, and treatment duration will be summarized by treatment group and study periods. The relative dose intensity will be calculated as the percentage of the actual drug exposure divided by the protocol planned drug exposure by study period.

9.4.6. Efficacy Analyses

All efficacy analyses will be based on the FAS. Supplemental per-protocol analyses for primary and secondary efficacy endpoints will be performed based on the PPS in the same manner as the FAS.

9.4.6.1. Analyses of Primary Efficacy Endpoint

9.4.6.1.1. Primary Analysis for the Primary Endpoint

The primary endpoint is the proportion of participants with an MG-ADL total score reduction of ≥ 2 points in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy.

The differences in proportions, along with 2-sided 90% confidence intervals (CIs) using Chan and Zhang method (Chan, 1999), will be presented between the ALXN2050 180 mg bid group and the placebo group. P-value using Barnard's unconditional exact test to determine whether there is a difference in the proportions of responders between the 2 treatment groups will be presented.

9.4.6.1.2. Secondary Analysis for the Primary Endpoint

The differences in proportions, along with 2-sided 90% CIs using Chan and Zhang method (Chan, 1999), will be presented for the following pairwise comparisons: between the ALXN2050 120 mg bid group and the placebo group, and between the ALXN2050 180 mg bid group and the ALXN2050 120 mg bid group.

In addition, the proportions of responders in each treatment group will be presented along with exact 2-sided 90% CIs using the Clopper-Pearson method.

Trend analysis to detect whether there is an increasing trend in the proportions of responders in the primary endpoint will be presented along with the p-value using Cochran Armitage test.

9.4.6.2. Analyses of Secondary Efficacy Endpoints

For all continuous secondary endpoints (QMG total score, MG-ADL total score, Neuro-QoL™ Fatigue score) related to the change from baseline at Week 8, the mixed-effects model with repeated measures (MMRM) will be used to estimate the treatment effect using all available data, irrespective of whether participants received rescue therapy. Missing data will not be imputed for the analysis. For each of the continuous secondary endpoints, the MMRM will include change from baseline at each prespecified time point as the response variable, treatment group, study visit, and treatment-by-study visit interaction as fixed categorical effects, and baseline total score as a covariate. The treatment effect will be evaluated via contrast for the treatment-by-visit term at Week 8. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each participant. Other covariance structures will be implemented if a convergence issue occurs (details to be provided in the SAP). The Kenward-Rogers method will be used to estimate the denominator degrees of freedom.

Trend analysis to detect whether there is a decreasing trend in the change from baseline at Week 8 in MG-ADL total score will be presented along with the p-value using Jonckheere-Terpstra trend test.

For the categorical secondary endpoints:

- Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the QMG score at Week 8

- Proportion of participants with a QMG score reduction of ≥ 3 points in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy
- Proportion of participants with at least a 2-, 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the MG-ADL total score at Week 8
- Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the MG-ADL total score in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy
- Proportion of participants with at least a 4-, 5-, 6-, 7-, or 8-point improvement in the QMG total score in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy

The proportions of responders in each treatment group will be presented along with exact 2-sided 90% CIs using Clopper-Pearson method. The differences in proportions between each of the ALXN2050 dosage groups (180 mg bid or 120 mg bid) and the placebo group will be presented, along with 2-sided 90% CIs using Chan and Zhang method (Chan, 1999).

9.4.6.3. Multiplicity Adjustment

This is a Phase 2 study. Multiplicity adjustments are not planned.

9.4.6.4. Analyses of Exploratory Endpoints

Proportion of participants with both an MG-ADL total score reduction of ≥ 2 points and a QMG total score reduction of ≥ 3 points in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy:

Number and proportion of responders will be summarized by treatment group. Exact (Clopper-Pearson) 90% CI for each treatment group will be presented. The differences in proportions between each of the ALXN2050 dosage groups (180 mg bid or 120 mg bid) and the placebo group will be presented, along with 2-sided 90% CIs using Chan and Zhang method (Chan, 1999).

Proportion of participants with at least 2-point improvement in the MG-ADL total score for 4 consecutive weeks and who did not receive rescue therapy (measured from Day 1 to Week 8 for Groups 1, 2, and 3 and from Week 8 to Week 16 for Groups 3a and 3b):

The proportion of participants with at least a 2-point improvement in the MG-ADL total score for 4 consecutive weeks (measured from Day 1 to Week 8 for Group 1, Group 2, Group 3 and from Week 8 to Week 16 for Group 3a and 3b) and who did not receive any rescue therapy will be summarized. Exact (Clopper-Pearson) 90% CI for each group will be presented.

Change from baseline in MG-ADL total score at Week 8 for Groups 1, 2, 3 and from Week 8 to Week 16 for Groups 3a and 3b:

Change from baseline in MG-ADL total score at Week 8 for Group 1, 2, 3 and change from baseline in MG-ADL total score at Week 16 for Group 3a and 3b will be summarized in descriptive statistics. Change from baseline in MG-ADL total score by study visit up to Week 16 and treatment group will be summarized in descriptive statistics.

Change from baseline in MG-ADL total score at Week 26 for Groups 1 and 2, and from Week 8 to Week 34 for Groups 3a and 3b:

Change from baseline in MG-ADL total score at Week 26 for Group 1 and 2 and change from baseline in MG-ADL total score at Week 34 for Group 3a and 3b will be summarized. Change from baseline in MG-ADL total score by study visit up to Week 34 and treatment group will be summarized.

Incidence of Clinical Deterioration of gMG over time:

Incidence of clinical deterioration of gMG during the first 8 weeks for Group 1, 2, 3, and during the first 34 weeks for Group 1, 2 and 3/3a/3b will be summarized separately. The number and percentage will be presented. Exact (Clopper-Pearson) 90% CIs for the true proportions will be presented.

MGFA-PIS and Minimal Manifestations at Week 8 and Week 26:

A summary of the MGFA-PIS will be presented by treatment group and study visit (including Week 8 and up to Week 26), showing the number and percentage of participants in each category (ie, improved, unchanged, or worsened).

A summary table of the number and percentage of participants who achieved MM will be presented by treatment group and study visit.

Proportion of participants who received rescue therapy over time:

Proportion of participants who received rescue therapy during the first 8 weeks for Group 1, 2, 3, and during the first 34 weeks for Group 1, 2 and 3/3a/3b will be summarized separately. FAS will be used for this analysis. The number and percentage will be presented. Exact (Clopper-Pearson) 90% CIs for the true proportions will be presented.

OLE data analysis:

The following efficacy data collected during the OLE period will be listed and summarized in descriptive statistics by dose level which is the dose received at the specific visit during OLE period:

- Change from baseline in MG-ADL total score
- Change from baseline in QMG total score
- MGFA-PIS status
- Change from baseline in Neuro-QoL Fatigue total score

AE data will be listed and summarized in an aggregated manner (combining data from PEP, ETP, OLE) by dose received using SS. Additional safety data collected by study visit during the OLE period will be listed and summarized by dose level which is the dose received at the specific visit during OLE period ("ALXN2050 180 mg" and "ALXN2050 120 mg"). Available PK, PD and biomarker data during OLE will be listed using OLES.

Detailed analyses of tertiary (exploratory) endpoints will be discussed in the SAP.

9.4.7. Safety Analyses

All safety analyses will be performed on the SS.

The safety and tolerability of ALXN2050 will be assessed based on AEs, clinical laboratory findings, ECGs, and vital signs findings. Safety analyses will be performed on the SS and OLE Set based on the study period under consideration.

9.4.7.1. Analysis of Adverse Events

Analysis and reporting for AEs will be based on treatment-emergent adverse events (TEAEs), including treatment-emergent serious adverse events (TESAEs), defined as an AE with onset on or after the first dose of study intervention in the PEP, and TEAEs leading to discontinuation of study intervention. TEAEs, TESAEs, and TEAEs leading to discontinuation of study intervention will be summarized using MedDRA SOC and Preferred Terms, by severity, and by relationship to the study intervention. Participant-year-adjusted event rates will be generated to characterize the long-term safety profile.

9.4.7.2. Analysis of Clinical Laboratory Parameters, Vital Sign Measurements, and Electrocardiogram Parameters

Laboratory measurements, changes from baseline at each visit, and shifts from baseline, if applicable, will be summarized descriptively. Significant findings related to ECGs and vital sign measurements will also be summarized using descriptive analyses.

9.4.7.3. Other Safety Analyses

The number and percentage of participants in each of the C-SSRS categories and shift analyses will be produced descriptively.

Results from pregnancy tests will be summarized descriptively.

9.4.8. Analyses of Pharmacokinetics and Pharmacodynamics

Blood samples will be collected for the determination of plasma ALXN2050 concentrations, serum AP activity, and plasma Bb concentrations as specified in the SoAs (Table 2, Table 3, and Table 4). Trough and peak concentrations (predose concentration [C_{trough}] and C_{max}) of ALXN2050 will be summarized using descriptive statistics. Absolute values and change from baseline in serum AP activity and plasma Bb concentrations will be summarized using descriptive statistics.

Blood samples for additional complement biomarkers (eg, FD, C3, CP activity) and nongenetic exploratory biomarkers (eg, MuSK, LRP4, MMP-10, IL-6) will be collected as specified in the SoAs (Table 2, Table 3, and Table 4). Absolute values and changes from baseline will be summarized using descriptive statistics.

Population PK and exposure-response analyses will be conducted and reported separately.

9.5. Interim Analysis

An early interim analysis may be conducted at the discretion of Alexion (based on feasibility) when approximately 50% of participants have been randomly assigned to study treatment and

have had the opportunity to complete the 8-week Primary Evaluation Period or have discontinued from the study treatment before Week 8. This early interim analysis, if performed, will be conducted by a separate unblinded team and will be for Phase 3 planning purposes only with no impact on the progression of the study.

9.5.1. Other Analyses

Data at 2 predefined time points will be locked for analysis: the first will be after the last randomized participant has completed the Week 8 Visit during the PEP, and the second will be after the last randomized participant has completed the Week 34 Visit during the ETP. Additional analyses may be performed after the PEP. Final analyses and reporting will be performed at the end of the study.

The SAP will describe the planned analyses in greater detail.

9.6. Data Monitoring Committee

A Data Monitoring Committee will not be convened for Study ALXN2050-MG-201.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments (ie, modifications), ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion, and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any substantial amendments (ie, modifications) to the protocol will require IRB/IEC and regulatory/health authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- For studies to be approved by the Medicines and Healthcare products Regulatory Agency: The Investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by UK legislation as a serious breach or as required by IRB/IEC procedures.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, EU CTR 536/2014 for clinical studies, and all other applicable local regulations.
  - Promptly notifying Alexion of any (potential) serious breach of the protocol or regulations (including if a data breach compromises the integrity, confidentiality, or availability of the personal data of participants) so that legal and ethical obligations are met. A ‘serious breach’ means a breach likely to affect to a

significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

- In certain regions/countries, Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - Alexion will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority (including data protection authorities and, if applicable, affected participants in case of a personal data breach), IRB/IEC, and Investigators. Under EU CTR 536/2014, Alexion is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trials Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach, including personal data breaches.
  - A (potential) serious breach is promptly reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator or designee to obtain signed (written or electronic signature) informed consent from all study participants, prior to performing any study-related procedures including screening assessments.
- The Investigator or designee will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Patients in vulnerable populations (including those placed in an institution due to an official or judicial order) and patients who are dependent on the Sponsor or the institution/investigational site are prohibited from providing informed consent in this study and are therefore excluded from participation.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent or a certified translation, if

applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation, ICH GCP guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

- The participant's medical record must include a statement that signed (written or electronic) informed consent was obtained before any screening procedures were performed with a participant, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study, as applicable.
- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant, as applicable. This document may require translation into the local language. Original signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened outside of the Screening window (Table 2) are required to sign a new ICF (Section 5.4).

10.1.4. Recruitment Strategy

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

10.1.5. Data Protection

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

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

10.1.6. Dissemination of Clinical Study Data

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

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

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed CRF or eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
  - Remote source data verification may be employed where permitted by local regulations.
  - The scope of the source data verification will be described in detail in the Clinical Monitoring Plan.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 25 years after study completion (or per local or institutional policy record retention requirements). No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate

and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.

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

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

10.1.9. Study and Site Start and Closure

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

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

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or ICH GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development
- Withdrawal of the local ethics committee/health authority favorable opinion or approval

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

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

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

10.1.10. Publication Policy

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

10.1.11. Good Clinical Practice Compliance

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

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

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

10.2. Clinical Laboratory Tests

- The tests listed in Table 11 will be performed by the central or specialty laboratory as appropriate for all participants unless otherwise noted. However, if a participant is not able to present to the clinic, a local laboratory may be used to collect the protocol-required samples.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Women of childbearing potential should only be enrolled after a negative serum pregnancy test result at the Screening Visit and a negative urine pregnancy test at Day 1. Additional serum or urine pregnancy testing will be employed as required by site policies, local regulations, or per the requirements of the IRB/IEC and should be performed per the time points specified in the SoA (Table 2, Table 3, and Table 4).
- Investigators must document their review of each laboratory report. Clinically significant findings resulting in an assessment of a TEAE should be recorded on the AE eCRF.
- Laboratory/analyte results that could unblind the study will not be reported to investigational sites or other blinded personnel until the study has been unblinded.

Table 11: Protocol-Required Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: Distribution width Mean corpuscular volume Mean corpuscular hemoglobin % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	BUN C-reactive protein Creatinine Chloride Potassium Bicarbonate Sodium Glucose (nonfasting) Creatine kinase	AST/SGOT ALT/SGPT Alkaline phosphatase Gamma glutamyltransferase Total and direct bilirubin Total protein Albumin Uric acid	Lipids: Total cholesterol Triglycerides LDL-c HDL-c
Coagulation	International normalized ratio, partial thromboplastin time, prothrombin time		

Table 11: Protocol-Required Laboratory Assessments

Laboratory Assessments	**Parameters**
Urinalysis	Appearance, color, specific gravity, pH, glucose, protein, leukocyte esterase, blood, ketones, bilirubin, urobilinogen, nitrite, microscopic examination (if blood or protein is abnormal)
Screening tests	Serum/urine beta-hCG pregnancy test (as needed for female participants of child-bearing potential) Serum follicle-stimulating hormone test (as needed for female participants who consider themselves postmenopausal) HIV-1 and HIV-2 antibodies Hepatitis B surface antigen Hepatitis C antibody
Complement activity	Pharmacodynamic assays (AP activity and Bb concentration) Complement biomarkers (Factor D, C3, C5b-9, Properdin, and CP activity)
Other	Biomarker assay (anti-AChR antibody) Pharmacokinetic assay (serum ALXN2050 concentration) Nongenetic exploratory biomarkers (eg, MuSK, LRP4, MMP-10, IL-6)

Abbreviations: AChR = acetylcholine receptor; ALT = alanine aminotransferase; AP = alternative pathway; AST = aspartate aminotransferase; Bb = Bb fragment of complement factor B; BUN = blood urea nitrogen; C = complement component; C5b-9 = terminal complement complex; CP = classical pathway; eCRF = electronic case report form; hCG = human chorionic gonadotropin; HDL-c = high-density lipoprotein cholesterol; HIV-1 = human immunodeficiency virus type 1; HIV-2 = human immunodeficiency virus type 2; IL = interleukin; LDL-c = low-density lipoprotein cholesterol; LRP4 = low density lipoprotein receptor-related protein 4; MMP-10 = matrix metalloproteinase-10; MuSK = muscle-specific tyrosine kinase; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells

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

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).
- **Note**: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease [new or exacerbated] temporally associated with the use of the study intervention, whether or not considered related to the study intervention.

Events Meeting the AE Definition

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

Events Not Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before signing the ICF, admissions for social reasons or for convenience).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error.
- Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

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

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-

An SAE is defined as any untoward medical occurrence that, at any dose:
threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A SUSAR is defined as:
An event that is assessed as serious by the Investigator and/or Alexion that is not listed in the appropriate Reference Safety Information (IB) and has been assessed that there is at least a reasonable possibility that the event is related to the study intervention by the Investigator and/or Alexion. Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents. Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable.

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

Recording of AE and/or SAE
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. • It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the Alexion AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017: • Grade 1: Mild (awareness of sign or symptom, but easily tolerated) • Grade 2: Moderate (discomfort sufficient to cause interference with normal activities) • Grade 3: Severe (incapacitating, with inability to perform normal activities) • Grade 4: Life-threatening • Grade 5: Fatal

Recording of AE and/or SAE

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study intervention.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate

Follow-up of AEs and SAEs

the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection Tool

1. All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness.
2. The primary mechanism for reporting an SAE to Alexion will be the EDC system.
3. If the electronic system is unavailable or site staff is unable to process the SAE via the EDC system at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE Reporting via facsimile or email. Facsimile transmission or email may also be used in the event of electronic submission failure.
   - Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347
4. The site will enter the SAE data into the EDC system as soon as it becomes available.
5. When further information becomes available, the EDC should be updated immediately with the new information and an updated SAE report should be submitted to Alexion Global Drug Safety (GDS) within 24 hours of Investigator/site awareness.
6. After the participant has completed the study, no new data or changes to existing data are expected to be entered in the EDC system.
   a. If a site receives a report of a new SAE from a study participant which the Investigator considers to be related to the study intervention, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via facsimile or email.

10.3.5. Unexpected Events

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

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

10.4. Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

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

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

Medication error includes situations where an error:

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

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

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/Randomization and Trial Supply Management [RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM – including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose, see Section 8.4)
- Participant failed to return unused medication or empty packaging

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired non-therapeutic effect.

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

Examples of drug abuse include but are not limited to:

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

Drug Misuse

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

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

Examples of drug misuse include but are not limited to:

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

10.5. Contraceptive Guidance and Collection of Pregnancy Information

10.5.1. Definitions

Woman of Childbearing Potential (WOCBP)

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

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

Women in the Following Categories Are Not Considered WOCBP

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

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

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

10.5.2. Contraception Guidance

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

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

10.5.2.1. Guidance for Female Participants

Female participants of childbearing potential must have a negative serum pregnancy test as required by local regulations at the Screening Visit and a negative urine pregnancy test before the first dose of study intervention on Day 1. Additional requirements for pregnancy testing during and after dosing with study intervention are indicated in the SoAs (Table 2, Table 3, and Table 4).

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

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

Female participants of childbearing potential must use a highly effective method of contraception, including at least 1 of the following until at least 30 days after the final dose of study intervention.

1. Intrauterine device in place for at least 6 weeks prior to first dose of study intervention.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of study intervention.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of study intervention.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of study intervention.
5. Combined (estrogen- and progestogen containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study intervention.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of study intervention). Male partner is still required to use condom during sexual intercourse.
7. Sexual abstinence for female participants:
    a. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent female participants must refrain from heterosexual intercourse for at least 30 days after the final dose of study intervention.

Female participants must not donate ova from the Day 1 Visit at least until 30 days after their final dose of study intervention.

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

- Periodic abstinence (calendar, symptothermal, or post-ovulation methods)

- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Female condom and male condom should not be used together

10.5.2.2. Guidance for Male Participants

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

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

10.5.2.2.1. Sexual Abstinence for Male Participants

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

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

Male participants must not donate sperm from the Day 1 Visit until 90 days after their final dose of study intervention.

10.5.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants, and female spouses/partners of male participants, from the first dose of study intervention until the last study visit. Any female participant who becomes pregnant during the study will be discontinued from the study intervention and withdrawn from the study. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study intervention via semen following paternal exposure. If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

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

Pregnancy is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of

pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

10.5.3.1. Male Participants with Partners Who Become Pregnant

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

10.5.3.2. Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial Information will be recorded on the appropriate form and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- For all Alexion products, both in development or postapproval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Pregnancy is not considered as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of a TESAE through spontaneous reporting.

- Any female participant who becomes pregnant during the study will discontinue study intervention and be discontinued from the study.

10.6. Biomarkers

- Blood biomarker matrix samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to study intervention or gMG and related diseases. The samples may also be used to develop tests/assays including diagnostic tests related to study intervention and gMG.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to the study intervention or to understand gMG or related conditions.
- The results of biomarker analyses may be reported in the clinical study report or in a separate report.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention continues but no longer than 5 years after all data have been collected for the study or other period/time point per local requirements.

10.7. Management of Seizures

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

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

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

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

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

- Seizure start date and time
- Description of the seizure

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

10.8. Participant-Reported Outcome Instruments

Participant-reported Outcomes or Clinician-reported Outcomes (Clinical Outcome Assessments) may be collected electronically.

10.9. COVID-19 Risk Assessment

Generalized MG is a debilitating chronic disease sometimes associated with severe generalized weakness requiring intubation for mechanical ventilation or the prevention of aspiration (Jaretzki, 2000). As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. In this particular case, the fact that the study contains an ETP and an OLE Period, where every participant is treated with the study intervention, also contributes to the potential benefit a participant may derive from partaking in the study. Given that treatment for gMG does involve immunosuppression in many patients, there is a theoretical concern that the risk for infection may be higher than in participants not receiving immunosuppressants. However, there is no specific data to further inform this risk. The site Investigator will therefore balance the risk/benefit considerations in the study participant taking these factors into account.

Table 12: Potential Risks and Mitigation Measures due to COVID-19

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

Table 12: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
	missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

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

10.10. Prohibited Inducers, Inhibitors, and Substrates of CYP3A

Table 13: List of Prohibited Inducers, Inhibitors, and Substrates of CYP3A

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

[a] Table number from the US FDA Table of Clinical CYP Inhibitors and Inducers

Note: This list is complete as of 25 Jan 2021. Please visit the link below for the most up-to-date information.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Abbreviation: CYP3A = cytochrome P450, family 3, subfamily A

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

The following medications are PROHIBITED while on the study:

- Meperidine/pethidine
- Tramadol
- Typical (1st generation) antipsychotics
- Clozapine
- Olanzapine
- Lithium
- Tricyclic antidepressants
- Bupropion
- Aminophylline/Theophylline

10.12. COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, and Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant ALXN2050 administration, based on ALXN2050's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ALXN2050. The same precautions should be taken as described in Section 6.5.4.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. If possible, consider vaccination when the underlying complement mediated disease is clinically controlled. Patients should be closely monitored for disease symptoms after recommended vaccination.

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

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

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

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

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

10.13. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly after the List of Figures.

DOCUMENT HISTORY		
Document	**Date**	**Overall Rationale for the Amendment**
Original Protocol	28 Apr 2021	Not applicable
Protocol Amendment 1 (Global)	22 Jul 2021	Update the list of exclusion criteria with a renal impairment criterion and to indicate that medications known to significantly prolong the corrected QT interval are not allowed during the study
Protocol Amendment 1.1 (Germany)	02 Jun 2022	Germany-specific amendment to incorporate, where appropriate, the changes made at the request of the Ethics Committee of the State of Berlin. The informed consent process, participant withdrawal, study/site closure, statistical interpretation and primary analyses were clarified further or modified.
Protocol Amendment 1.2 (Serbia)	26 Jul 2022	Serbia-specific amendment to update the informed consent process, participant withdrawal, study/site closure, statistical interpretation, and primary analyses.
Protocol Amendment 2 (Global)	09 Mar 2023	The primary reason for this amendment was to address the requirements for conducting a clinical study under the EU CTR.
Protocol Amendment 3 (Global)	15 Nov 2023	The primary reason for this amendment was to address the requirements for transitioning a clinical study under the EU CTR.

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