TITLE PAGE

STATISTICAL ANALYSIS PLAN AMENDMENT 1.0

Version Number: Final Version 1.0

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

Protocol Number: ALXN2050-MG-201

Protocol Amendment Number: Amendment 1.0

Compound: ALXN2050

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

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VERSION HISTORY

This statistical analysis plan (SAP) Amendment 1.0 for Study ALXN2050-MG-201 is based on Protocol Amendment Version 1.0, dated 22 Jul 2021, and was amended from the original SAP Version 1.0.

SAP Version	Version Date	Change	Rationale
0.1	04 Jan 2022	Not applicable	Original version
0.2	07 Mar 2022	Revised with the Sponsor's comments	Added details for analyses 1 and 2 Added additional analysis sets
Final 1.0	23 Jun 2022	Corrected typo and finalized shells	Final version
Amendment 1.0	27 Feb 2023	Revised to include all available data beyond Week 16 at planned Analysis 1 and all available data during the Open-label Extension Period at planned Analysis 2 Updated relevant sections to reflect this change	Included all available data in the 2 planned analyses for the Phase 3 study design
		Added rerandomized set and ALXN2050-Treated Set	Added for use in relevant analyses
		Provided more details of biomarker analysis	Distinguished between secondary and exploratory biomarker endpoints, which will be reported in a clinical study report and in a separate document, respectively

APPROVAL SIGNATURES

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods for analyzing data for the protocol titled "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." Standard data presentation instructions and table, figure, and listing specifications are contained in the data presentation plan in a separate document.

Throughout the study, 3 analyses will be performed with different data cutoff and emphasis as follows:

- Analysis 1 (Week 8): The first analysis will be performed after the last randomized participant has completed the Primary Evaluation Period (PEP) or discontinued study treatment during the PEP. Specifically, this includes the PEP data for all participants, as well as the Extended Treatment Period (ETP) and Open-Label Extension (OLE) Period data, up to the data cutoff date or early discontinuation date, whichever occurs earlier. The primary, secondary, and select exploratory efficacy endpoints; safety endpoints; pharmacokinetic (PK) and pharmacodynamic (PD) endpoints; and baseline information (demographics and disease characteristics) will be analyzed. Biomarker endpoints will be analyzed if available at the first analysis.
- Analysis 2 (Week 34): The second analysis will be performed after the last randomized participant has completed the ETP or discontinued study treatment before the completion of the ETP. Specifically, this includes the PEP and ETP data for all participants, as well as the OLE Period data, up to the data cutoff date or early discontinuation date, whichever occurs earlier . Exploratory efficacy endpoints, additional safety, PK/PD, and biomarker data will be analyzed.
- Final analysis: The final analysis will be performed at the end of study (EOS) when all participants have completed the study or discontinued treatment early. The data in scope include efficacy, available PK/PD, biomarker, and safety data other than adverse events (AEs) of the OLE Period and aggregated AE data throughout the study, as defined in Section 5.9.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ALXN2050 compared with placebo in the treatment of generalized MG (gMG) based on improvement in the Myasthenia Gravis Activities of Daily Living (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	• 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

Objectives	Endpoints
Quantitative Myasthenia Gravis (QMG) total score	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 factor D inhibition on complement biomarkers	Plasma factor D 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
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

Objectives	Endpoints
	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 • 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 • Incidence of Clinical Deterioration of gMG over time • MGFA-PIS at Week 8 and Week 26 • Proportion of participants with a classification of Minimal Manifestations at Week 8 and Week 26 (as measured by the MGFA-PIS) • Proportion of participants who receive rescue therapy over time
To assess the effect of factor D inhibition on acetylcholine receptor (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

Objectives	Endpoints
	proteins and complement pathway regulators (eg, C5b-9, Properdin) • Change from baseline in biomarkers of inflammation and NMJ damage (eg, MMP-10, IL-6)

1.2. Study Design

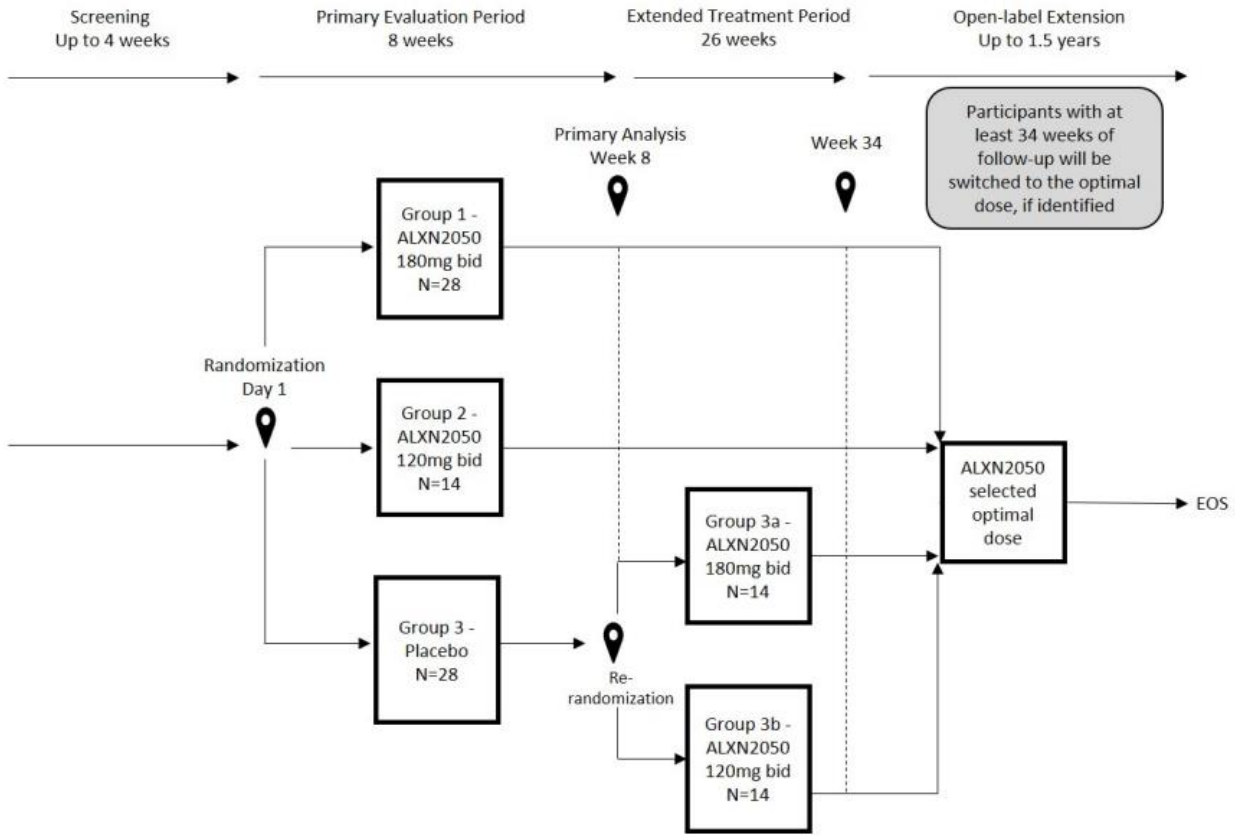
This is a Phase 2, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the efficacy and safety of ALXN2050 in adult participants (≥ 18 years of age at the time of signing the informed consent form [ICF]) diagnosed with gMG with a Myasthenia Gravis Foundation of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

Approximately 70 eligible participants will be stratified by the MG-ADL total score at Baseline (< 7 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 will receive the study intervention bid from Day 1 through Week 117.

Participants randomized to Group 1 and Group 2 will receive ALXN2050 during the PEP (8 weeks) and the ETP (26 weeks). Participants in Group 3 will receive placebo treatment during the PEP and will be rerandomized in a 1:1 ratio to receive either ALXN2050 180 mg bid (Group 3a) or ALXN2050 120 mg bid (Group 3b) at the end of the PEP. During the 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.

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 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. A schematic of the study design is included as 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

2. STATISTICAL HYPOTHESES

2.1. Primary Hypothesis

The primary hypothesis is that the ALXN2050 180 mg bid group is superior to the placebo group in the proportion of responders in the primary endpoint. The responders are defined as participants who achieved 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 received no rescue therapy. The hypothesis for assessing superiority with respect to the proportions of responders is as follows:

$$H_0: P_3 - P_1 \leq 0;\ H_1: P_3 - P_1 > 0$$

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.

2.2. Secondary Hypothesis

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 as follows:

$$H_0: P_1 = P_2 = P_3;\ H_1: P_1 \leq P_2 \leq P_3;\ \text{with at least 1 strict inequality}$$

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.

3. 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. For sample size determination, both trend analyses 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.

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 the Cochran Armitage test at a 2-sided type I error rate of 0.1.

Assuming approximately 5% non-evaluability, the study is planned to enroll 70 participants in total. The sample size calculations were performed in PASS 2020.

4. ANALYSIS SETS

Analysis Set	Description
Randomized Set	All randomized participants grouped by randomized treatment group.
Re-randomized Set	All re-randomized placebo arm (Group 3) participants grouped by re-randomized treatment group.
Full Analysis Set (FAS)	All randomized participants who received at least 1 dose of the 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 assessment and at least 1 evaluable postdose PK assessment.
PD Analysis Set	All randomized participants who have a baseline PD assessment and at least 1 evaluable postdose PD assessment.
Per Protocol Set (PPS)	All participants in the FAS without important protocol deviations. See Section 6.2.2 for the list of important protocol deviations.
Safety Set (SS)	All randomized participants who received at least 1 dose of the study intervention. Participants will be analyzed according to the study intervention they actually received. (Study intervention received is the same as planned study intervention if the participant has received at least 1 dose of planned study intervention. If planned study intervention is not received at all, the most frequently received study intervention will be the received study intervention).
ALXN2050-Treated Set	All randomized participants who received at least 1 dose of the ALXN2050. Participants will be analyzed according to the study intervention they actually received. (Study intervention received is the same as planned study intervention if the participant has received at least 1 dose of planned study intervention. If planned study intervention is not received at all, the most frequently received study intervention will be the received study intervention).
Open-label Extension Set (OLES)	All randomized participants who received at least 1 dose of ALXN2050 during the OLE Period.

5. STATISTICAL ANALYSES

5.1. General Considerations

Summary statistics will be computed and displayed by visit, by treatment group, and overall, where applicable. The summary statistics for continuous variables will include, but will not be limited to, the number of participants, mean, SD, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented.

Inference from efficacy analyses will be based on a 2-sided type I error rate of 10% unless stated otherwise. No multiplicity adjustment will be implemented. Statistical analyses will be performed using the Statistical Analysis Software (SAS®) Version 9.4 or higher.

Medications will be coded using the World Health Organization Drug Dictionary (WHO DD; March 2021 or higher). Therapies will be coded using Medical Dictionary for Regulatory Activities (MedDRA; Version 24.0 or higher).

AEs will be coded by primary System Organ Class (SOC) and Preferred Term (PT) using MedDRA (Version 24.0 or higher).

5.1.1. Data Presentation for the First Analysis at Week 8

Data summaries for the analyses on the PEP data will be presented by 3 treatment groups ("Group 1: ALXN2050 180 mg bid", "Group 2: ALXN2050 120 mg bid" and "Group 3: Placebo"). Baseline is defined as the last measurement on or prior to the first dose of study intervention. For analysis including data beyond week 8, data summaries will be presented by 5 treatment groups ("Group 1: ALXN2050 180 mg bid", "Group 2: ALXN2050 120 mg bid", "Group 3: Placebo", "Group 3a: ALXN2050 180 mg bid" and "Group 3b: ALXN2050 120 mg bid"). Placebo group may be dropped for some of the analyses as specified in the respective sections. For all groups other than Groups 3a and 3b, baseline is defined as the last measurement on or prior to the first dose of study intervention. For Group 3a and 3b, two baselines will be defined for efficacy analysis: the PEP baseline is defined as the last measurement on or prior to the first dose of the PEP (primary baseline) and the ETP baseline is defined as the last measurement on or prior to the first dose of the ETP (secondary baseline). The PEP baseline will be used in nonefficacy analysis for Group 3a and 3b.

5.1.2. Data Presentation for the Second Analysis at Week 34

Data summaries for the exploratory, safety, biomarker, and PK/PD analyses will be presented by 5 treatment groups. Placebo group may be dropped for some of the analyses as specified in the respective sections. For all groups other than Group 3a and 3b, baseline is defined as the last measurement on or prior to the first dose of study intervention. For Group 3a and 3b, 2 baselines will be defined for efficacy analysis: the PEP baseline is defined as the last measurement on or prior to the first dose of the PEP (primary baseline) and the ETP baseline is defined as the last measurement on or prior to the first dose of the ETP (secondary baseline). The PEP baseline will be used in nonefficacy analysis for Group 3a and 3b.

5.2. Study Participants

All participants who provided informed consent will be accounted for in this study.

The number of participants screened, screen failed, randomized, and re-randomized will be presented and grouped by treatment group. The number and percentage of participants who completed the study or discontinued treatment (along with reasons) and subsequently discontinued from the study (along with reasons) will be summarized. By-participant listing of the reasons for screen failure will also be produced. The number and percentage of participants in each analysis set will be tabulated, and a by-participant listing will be provided. The number and percentage of participants not meeting inclusion or exclusion criterion will be summarized and listed. The by-participant data listings of randomization information and consent status will also be provided.

If applicable, the impact of coronavirus disease 2019 on the study disposition will also be summarized and listed.

5.3. Primary Endpoints Analyses

The primary efficacy endpoint analysis will be performed based on the FAS. The PPS will also be used as a supplementary analysis of the primary endpoint. A sensitivity analysis will be performed by implementing participant-level imputation using the FAS. The supplementary analysis based on a logistic regression model will be additionally performed using the FAS. The primary endpoint analysis will be performed at the first analysis (Week 8).

The details of the statistical analyses of the primary endpoint are provided in the following sections and in Table 1.

5.3.1. Primary Endpoint

The primary endpoint is the proportion of participants with an MG-ADL total score reduction of ≥ 2 points from the Baseline in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy. To compute this, change from Baseline in the MG-ADL total score at each post-Baseline Visit of the first 8 weeks will be derived, where baseline is defined as the last nonmissing assessment prior to the first dose of study intervention. In general, this baseline assessment will be the Day 1 assessment. If the Day 1 assessment is missing, the latest observation during the Screening Period, where available, will be used as the baseline assessment.

Participants who discontinued early without achieving an MG-ADL total score reduction of ≥ 2 points from the Baseline in any 4 consecutive weeks during the first 8 weeks will be considered as nonresponders. Participants who received rescue therapy anytime during the first 8 weeks will be considered as nonresponders.

5.3.2. Main Analytical Approach

5.3.2.1. Primary Analysis for the Primary Endpoint

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 the 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. No imputation will be implemented.

5.3.2.2. 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.

A 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 the Cochran-Armitage test. No imputation will be implemented.

5.3.3. Sensitivity Analysis

To assess the robustness of the main analysis of this endpoint to missing data during the PEP, the following sensitivity analysis will also be performed:

For participants with completely missing (eg, all items are missing) or partially missing MG-ADL assessments (eg, certain items are missing) at any visit from Weeks 1 through 8, a total score will be derived after imputing the missing items. Missing items will be imputed by taking average of the most recent assessment of the particular items before and after the partially missing assessment if both assessments are present within the PEP. If only the assessment prior to the partially missing assessment is available, last observation carried forward approach will be used.

Once the imputed dataset is produced, the primary endpoint will be analyzed with imputed data using the same method as described in Section 5.3.2.1 and Section 5.3.2.2.

5.3.4. Supplementary Analysis

The supplementary analysis on the primary endpoint will be performed based on the PPS using the Barnard's unconditional exact test. The purpose of this supplementary analysis is to provide additional insights for the primary efficacy result in a more compliant subgroup of the study population.

In addition, a logistic regression model will be established with the primary endpoint as the dependent variable and the study arm and baseline MG-ADL total score as covariates using the FAS. The purpose of this supplementary analysis is to provide additional insights for the impact of baseline disease characteristics to the primary analysis.

The following statistics will be presented:

- Adjusted response rate per treatment group
- 90% CI
- Adjusted odds ratio (OR; 180 mg bid versus placebo, 120 mg bid versus placebo, and 180 mg bid versus 120 mg bid) and 90% CI of OR
- P-value

Table 1: Summary of Primary Endpoint

Endpoint	Analysis	Population	Method	Missing Data/Intercurrent Event Handling
Proportion of participants with an MG-ADL total score reduction of ≥ 2 points from the Baseline in any 4 consecutive weeks during the first 8 weeks and who did not receive rescue therapy	Primary	FAS	2-sided Barnard's unconditional exact test; 2-sided 90% CIs using Chan and Zhang method (Chan, 1999) for difference in proportions	Participants who discontinued early without achieving an MG-ADL total score reduction of ≥ 2 points from the Baseline in any 4 consecutive weeks during the first 8 weeks, will be considered as nonresponders. Participants who received rescue therapy anytime during the first 8 weeks will be considered as nonresponders.
	Secondary	FAS	2-sided Cochran-Armitage test for trend; 2-sided 90% CI using the Clopper-Pearson method for proportions	
	Supplementary	PPS	2-sided Barnard's unconditional exact test; 2-sided 90% CIs using Chan and Zhang method (Chan, 1999) for difference in proportions	
	Supplementary	PPS	2-sided Cochran-Armitage test for trend; 2-sided 90% CI using the Clopper-Pearson method for proportions	
	Supplementary	FAS	Logistic regression with the primary endpoint as the dependent variable and the study arm and baseline MG-ADL total score as covariates	

Table 1: Summary of Primary Endpoint

Endpoint	Analysis	Population	Method	Missing Data/Intercurrent Event Handling
	Primary Sensitivity 1	FAS	2-sided Barnard's unconditional exact test; 2-sided 90% CIs using Chan and Zhang method (Chan, 1999) for difference in proportions	LOCF for missing data after treatment discontinuation up to Week 8. Missing data during study treatment will be imputed by taking average of the most recent assessment before and after the missing assessment.
	Secondary Sensitivity 1	FAS	2-sided Cochran-Armitage test for trend; 2-sided 90% CI using the Clopper-Pearson method for proportions	

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; LOCF = last observation carried forward; MG-ADL = Myasthenia Gravis Activities of Daily Living; PPS = Per Protocol Set

5.4. Secondary Endpoints Analyses

The secondary efficacy endpoint analysis will be performed on the FAS. Analyses for change from Baseline to Week 8 in the QMG total score, MG-ADL total score, and Neuro-QoL Fatigue score will be performed using both the FAS and PPS. Unless otherwise specified, baseline is defined as the last available assessment prior to the first dose of study intervention. The analysis results will be reported by treatment group for the PEP. For QMG, in the event that cholinesterase inhibitor was not withheld for at least 8 hours prior to administration of the QMG test on Day 1, the Screening Visit assessment will be used as Baseline. If cholinesterase inhibitor was not withheld for at least 8 hours for these visits (both Day 1 and Screening Visits), the Day 1 assessment will be used as baseline.

All secondary endpoint analyses will be performed at the first analysis (Week 8).

5.4.1. Secondary Endpoints

5.4.1.1. Change From Baseline in the QMG Total Score at Week 8

The analysis will be performed on the FAS and PPS population.

A mixed-effects model with repeated measures (MMRM) will be used to estimate the treatment effect using all available data up to Week 8, irrespective of whether participants received rescue therapy. Missing data will not be imputed for the analysis.

The MMRM will include change from Baseline at each prespecified timepoint (Weeks 1, 2, 3, 4, 5, 6, 7, and 8) as the response variable; treatment group, study visit, and treatment-by-study visit

interaction as fixed categorical effects; and the baseline QMG 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. If a convergence issue occurs or the model performs poorly, alternative covariance matrix structures will be used in the following order until convergence or model performance issue is resolved: Toeplitz (TOEP), first order autoregressive (AR(1)), Compound symmetry (CS).

The Kenward-Rogers method will be used to estimate the denominator degrees of freedom.

The following statistics will be presented:

- Least-squares (LS) means per treatment group
- Standard error of LS means
- 90% CI
- LS mean difference (180 mg , 120 mg versus placebo, 180 mg versus 120 mg bid) and 90% CI of OR
- P-value for testing differences between treatment groups

Absolute levels and the change from Baseline in the QMG total score will be summarized in descriptive statistics by study visits and treatment groups.

A trend analysis to detect whether there is a decreasing (dose response) trend in the change from Baseline at Week 8 in the QMG total score will be presented, along with the p-value using the Jonckheere-Terpstra trend test.

5.4.1.2. Change From Baseline in the Neuro-QoL Fatigue Total Score at Week 8

The analysis method and missing data handling will be the same as described in Section 5.4.1.1. (with the baseline Neuro-QoL Fatigue total score as a covariate and change from Baseline to Week 4 and Week 8 as the response variable in the MMRM model)

5.4.1.3. Change From Baseline in the MG-ADL Total Score at Week 8

The analysis method and missing data handling will be the same as described in Section 5.4.1.1 (with the baseline MG-ADL total score as a covariate and change from Baseline at each prespecified timepoint as the response variable in the MMRM model).

5.4.1.4. Proportion of Participants With at Least a 3-, 4-, 5-, 6-, 7-, or 8-Point Improvement in the QMG Total Score at Week 8

The analysis will be performed on the FAS.

The proportions of participants with the various point improvement in QMG in each treatment group and study visit will be presented, along with exact 2-sided 90% CIs using the Clopper-Pearson method. The differences in proportions between each of the ALXN2050 dose groups (180 mg bid or 120 mg bid) and the placebo group will be presented, along with 2-sided 90% CIs using the Chan and Zhang method (Chan, 1999). No imputation will be implemented.

5.4.1.5. 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

The analysis method and missing data handling will be the same as described in Section 5.4.1.4.

5.4.1.6. 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

The analysis will be performed on the FAS.

The proportions of participants with the various point improvement in QMG in any 4 consecutive weeks during the first 8 weeks and who did not use rescue therapy will be presented by treatment group and study visit, along with exact 2-sided 90% CIs using the Clopper-Pearson method. The differences in proportions between each of the ALXN2050 dose groups (180 mg bid or 120 mg bid) and the placebo group will be presented, along with 2-sided 90% CIs using the Chan and Zhang method (Chan, 1999).

Participants who discontinued early without achieving the above specified response will be considered as nonresponders. Participants who received rescue therapy anytime during the first 8 weeks will be considered as nonresponders.

5.4.1.7. 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

The analysis method and missing data handling will be the same as described in Section 5.4.1.6.

5.4.1.8. Supplemental Analyses for the Secondary Endpoints

Supplemental analyses on select secondary endpoints (MMRM analysis as specified in Section 5.4.1.1, Section 5.4.1.2, and Section 5.4.1.3) will be performed based on the PPS in the same manner as done for the FAS. The purpose of these supplementary analyses is to provide additional insights for secondary efficacy results in a more compliant subgroup of the study population.

Table 2: Summary of Secondary Endpoints

Endpoint	Analysis	Population	Method	Missing Data/Intercurrent Event Handling
Change from Baseline in the QMG total score at Week 8	Primary	FAS	MMRM	No imputation will be implemented. Analyses will be performed regardless
	Secondary	FAS	Jonckheere-Terpstra trend test	
	Primary supplementary	PPS	MMRM	

Table 2: Summary of Secondary Endpoints

Endpoint	Analysis	Population	Method	Missing Data/Intercurrent Event Handling
	Secondary supplementary	PPS	Jonckheere-Terpstra trend test	of use of rescue therapy. For the responder endpoint (defined at various points of improvement) at a specific visit, only participants who have nonmissing assessment at the specific study visit will be included in the analysis for that particular visit.
Change from Baseline in the Neuro-QoL Fatigue total score at Week 8	Primary	FAS	MMRM	
	Secondary	FAS	Jonckheere-Terpstra trend test	
	Primary supplementary	PPS	MMRM	
	Secondary supplementary	PPS	Jonckheere-Terpstra trend test	
Change from Baseline in the MG-ADL total score at Week 8	Primary	FAS	MMRM	
	Secondary	FAS	Jonckheere-Terpstra trend test	
	Primary supplementary	PPS	MMRM	
	Secondary supplementary	PPS	Jonckheere-Terpstra trend test	
Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the QMG total score at Week 8	Primary	FAS	Exact 2-sided 90% CIs using the Clopper-Pearson method for proportions and 2-sided 90% CIs using the Chan and Zhang method (Chan, 1999) for difference in proportions	

Table 2: Summary of Secondary Endpoints

Endpoint	Analysis	Population	Method	Missing Data/Intercurrent Event Handling
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	Primary	FAS	Exact 2-sided 90% CIs using the Clopper-Pearson method for proportions and 2-sided 90% CIs using the Chan and Zhang method (Chan, 1999) for difference in proportions	
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	Primary	FAS	Exact 2-sided 90% CIs using the Clopper-Pearson method for proportions and 2-sided 90% CIs using the Chan and Zhang method (Chan, 1999) for difference in proportions	Participants who discontinued early without achieving the prespecified point improvement from the Baseline in any 4 consecutive weeks during the first 8 weeks will be considered as nonresponders. Participants who received rescue therapy anytime during the first 8 weeks will be considered as nonresponders.
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	Primary	FAS	Exact 2-sided 90% CIs using the Clopper-Pearson method for proportions and 2-sided 90% CIs using the Chan and Zhang method (Chan, 1999) for difference in proportions	

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; MG-ADL = Myasthenia Gravis Activities of Daily Living; PPS = Per Protocol Set; QMG = Quantitative Myasthenia Gravis

5.5. Tertiary/Exploratory Endpoints Analyses

All exploratory endpoint analyses will be performed on the FAS population, unless specified otherwise. For Group 1 and 2 (PEP, ETP and OLE Period, if applicable), baseline is defined as the last available assessment prior to the first dose of ALXN2050. For Group 3 (the PEP of the placebo arm), baseline is defined as the last available assessment prior to the first dose of placebo. For Groups 3a and 3b (ETP and OLE Period, if applicable, of placebo arm), 2 baselines are defined: the PEP baseline is defined as the last available assessment prior to the first dose of placebo and the ETP baseline is defined as the last available assessment prior to the first dose of ALXN2050. No formal hypothesis testing is planned. Unless otherwise specified, no imputation will be implemented.

5.5.1. Tertiary/Exploratory Endpoints Analyses at Analysis 1 (Week 8)

This section describes all exploratory analyses to be performed at the first analysis when all participants have completed the first 8 weeks of treatment or have discontinued from treatment.

5.5.1.1. Dual Responder in MG-ADL and QMG

The FAS will be used for this analysis.

Responder is defined as 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. The number and proportion of responders will be summarized by treatment group. The exact (Clopper-Pearson) 90% CI for each treatment group will be presented. The differences in proportions between each of the ALXN2050 dose groups (180 mg bid or 120 mg bid) and the placebo group will be presented, along with 2-sided 90% CIs using the Chan and Zhang method (Chan, 1999). The same intercurrent event handling approach will be followed as specified in the primary analysis of the primary endpoint in Table 1.

5.5.1.2. Proportion of Participants With 2-Point Improvement in the MG-ADL Total Score for 4 Consecutive Weeks and Who Did Not Use Rescue Therapy

The FAS will be used for this analysis.

This analysis includes MG-ADL data of the first 8 weeks (Groups 1, 2, and 3) and Week 8 to 16 data for Groups 3a and 3b participants who have completed Week 16 assessment or discontinued prior to Week 16 by the data cutoff date.

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 [PEP baseline] to Week 8 for Groups 1, 2, and 3 and from Week 8 [ETP baseline] to Week 16 for Groups 3a and 3b) and who did not receive any rescue therapy will be summarized. The exact (Clopper-Pearson) 90% CI for each group will be presented. Summaries using the PEP and ETP baselines will be both presented for Groups 3a and 3b. The same intercurrent event handling approach will be followed as specified in the primary analysis of the primary endpoint in Table 1.

For Groups 3a and 3b, this endpoint will be summarized in a shift table presenting the shift in responder status from the first 8 weeks to Weeks 8 to 16 (using the PEP and ETP baselines separately for Week 8 to 16 responder status). The observed frequencies and percentages, together with an exact (Clopper-Pearson) 90% CI for the true percentage of responders, will be presented for the first 8 weeks and Weeks 8 to 16 separately. The difference in percentages of responders (Weeks 8 to 16 [first 8 weeks]) and corresponding 90% CI for the true difference will also be presented for each group.

5.5.1.3. Change From Baseline in the MG-ADL Total Score at Week 8 for Groups 1, 2, and 3 and From Weeks 8 to 16 for Groups 3a and 3b

The FAS will be used for this analysis.

This analysis includes MG-ADL data of the first 8 weeks (Groups 1, 2, and 3) and Week 8 to 16 data (and beyond) for Group 3a and 3b participants by the data cutoff date.

Change from Baseline in the MG-ADL total score at Week 8 for Groups 1, 2, and 3 and change from the PEP and ETP baselines in the MG-ADL total score at Week 16 for Group 3a and 3b will be summarized in descriptive statistics. Change from Baseline in the MG-ADL total score by all study visits up to the data cutoff date and treatment group will be summarized in descriptive statistics.

Summaries using the PEP and ETP baselines will be presented separately for Group 3a and 3b.

5.5.1.4. Change From Baseline in the MG-ADL Total Score at Week 26 for Groups 1 and 2

This analysis will be covered in the analysis in Section 5.5.1.5.

5.5.1.5. Change From Baseline in the MG-ADL Total Score at Week 26 for Group 1 and 2 and From Weeks 8 to 34 for Groups 3a and 3b

This analysis includes MG-ADL data of the first 8 weeks (Group 1, 2, and 3) and Week 8 to 34 data for Group 1, 2, 3a, and 3b participants.

Change from Baseline in the MG-ADL total score at Week 26 for Groups 1 and 2 and change from Baseline in the MG-ADL total score at Week 34 for Group 3a and 3b will be summarized. Change from Baseline in the MG-ADL total score by all study visits up to the data cutoff date and treatment group will be summarized. Additional OLE Period data after Week 34 within the data cutoff date will be included, if applicable. Summaries using the PEP and ETP baselines will be both presented for Groups 3a and 3b.

Note that the output supporting this analysis will be covered in the output produced in Section 5.5.1.3.

5.5.1.6. Incidence of Clinical Deterioration of gMG Over Time

The FAS will be used for this analysis.

A detailed definition of clinical deterioration is in Section 6.3.1. Incidence of clinical deterioration of gMG during the first 8 weeks will be summarized by Groups 1, 2, and 3. The number and percentage of participants experiencing clinical deterioration, the total number of clinical deteriorations, and the difference in percentage of participants experiencing clinical deterioration between each ALXN treatment arm and placebo arm (along with 90% CIs) will be presented. Exact (Clopper-Pearson) 90% CIs for the true proportions will be presented.

5.5.1.7. MGFA-PIS at Week 8

The FAS will be used for this analysis.

A summary of the MGFA-PIS will be presented by treatment group and study visit (including Week 8 and all visits up to the data cutoff date), showing the number and percentage of participants in each category (ie, improved, unchanged, or worsened) and the number and percentage of participants who achieved MMs. The difference in the percentage of participants achieving “improved” status between each ALXN treatment arm and placebo arm will be presented, along with 90% CIs for the PEP study visits. The difference in the percentage of participants achieving MMs between each ALXN arm and placebo arm will be presented, along with 90% CIs.

5.5.1.8. Proportion of Participants Who Received Rescue Therapy Over Time

The FAS will be used for this analysis.

Proportion of participants who received rescue therapy during the first 8 weeks will be summarized by Group 1, 2, and 3. The number and percentage of participants who received rescue therapy, as well as the number of clinical deteriorations requiring rescue therapy, will be presented. Exact (Clopper-Pearson) 90% CIs for the true proportions will be presented.

5.5.2. Tertiary/Exploratory Endpoints Analyses at Analysis 2 (Week 34)

This section describes all analyses to be performed at the second analysis when all participants have completed the first 34 weeks of treatment or have discontinued treatment. All exploratory endpoint analyses will be performed on the FAS population, unless specified otherwise.

5.5.2.1. Proportion of Participants With 2-Point Improvement in the MG-ADL Total Score for 4 Consecutive Weeks and Who Did Not Use Any Rescue Therapy

This analysis includes MG-ADL data of the first 8 weeks (Groups 1, 2, and 3) and Week 8 to 16 data for all Group 3a and 3b participants.

The analysis described in Section 5.5.1.2 will be repeated with all available data as of the data cutoff date.

5.5.2.2. Change From Baseline in the MG-ADL Total Score at Week 8 for Group 1, 2, and 3 and From Weeks 8 to 16 for Groups 3a and 3b

This analysis includes MG-ADL data of the first 8 weeks (Groups 1, 2, and 3) and Week 8 to 16 data for all Group 3a and 3b participants.

The analysis described in Section 5.5.1.3 will be repeated with all available data as of the data cutoff date.

5.5.2.3. Change From Baseline in the MG-ADL Total Score at Week 26 for Groups 1 and 2

This analysis will be covered in the analysis in Section 5.5.2.4.

5.5.2.4. Change From Baseline in the MG-ADL Total Score at Week 26 for Groups 1 and 2 and From Weeks 8 to 34 for Groups 3a and 3b

This analysis includes MG-ADL data of first 8 weeks (Group 1, 2, and 3) and Week 8 to 34 data for Group 1, 2, 3a, and 3b participants.

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

Summaries using the PEP and ETP baselines will be both presented for Groups 3a and 3b.

5.5.2.5. Incidence of Clinical Deterioration of gMG Over Time

Incidence of clinical deterioration of gMG during the first 34 weeks for Group 1 and 2 and Weeks 8 to 34 for Group 3a and 3b will be summarized separately. The 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.

5.5.2.6. MGFA-PIS at Week 26

Analysis described in Section 5.5.1.7 will be repeated including assessments up to Week 34.

5.5.2.7. Proportion of Participants Who Received Rescue Therapy Over Time

Proportion of participants who received rescue therapy during the first 34 weeks for Groups 1 and 2 and Weeks 8 to 34 for Groups 3a and 3b will be summarized separately. The 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.

5.5.2.8. OLE Period Analyses

The following efficacy data collected during the OLE Period as of the data cutoff date will be listed and summarized in descriptive statistics by dose level, which is the dose received at the specific visit during the OLE Period:

- Change from Baseline in the MG-ADL total score
- Proportion of participants with at least a 2-, 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the MG-ADL total score
- Change from Baseline in the QMG total score
- Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the QMG total score
- MGFA-PIS status
- Change from Baseline in the Neuro-QoL Fatigue total score

For efficacy endpoints, baseline is defined as the last measurement on or prior to the first dose of the PEP.

5.6. Safety Analyses

The safety and tolerability of ALXN2050 will be assessed based on the incidence of AEs, clinical laboratory findings, electrocardiograms (ECGs), vital signs findings, and Columbia Suicide Severity Rating Scale (C-SSRS). The safety analyses to be produced during the Week 8 analysis and the Week 34 analysis will be detailed in each of the subsections below. No formal hypothesis testing is planned for safety data.

5.6.1. Safety Analyses at Analysis 1 (Week 8)

All outputs for safety outcomes of the Primary Treatment Period (first 8 weeks) will be based on the SS, unless otherwise specified. All safety analyses for participants during the ALXN2050 treatment period will be based on the ALXN2050-Treated Set. Safety data will be summarized

by the actual treatment received (Groups 1, 2, 3, 3a, and 3b, as applicable). Baseline is defined as the last available assessment prior to the first dose of study intervention.

5.6.1.1. Extent of Exposure

The cumulative and total drug exposure, dose intensity and relative dose intensity, treatment duration, treatment compliance, total time on study treatment and total patient-year of exposure during the Primary Treatment Period (first 8 weeks) will be summarized descriptively by treatment group. The SS will be used for the analysis. The same analysis will be performed, including all data up to the data cutoff date during the ALXN2050 treatment period using the ALXN2050-Treated Set.

Treatment duration will be calculated (in weeks) as the difference between the date of the last dose and the date of the first dose for the period plus 1. The duration will be summarized with descriptive statistics. In addition to a descriptive summary, the number and proportion of participants who have treatment duration for a specific period will be produced.

Planned total dose amount = assigned dose level of each tablet × daily frequency (bid) × duration in number of days of the period.

Received total dose amount = assigned dose level of each tablet × number of tablets received of the period. The number of tablets received is calculated as the difference between the number of tablets dispensed and the number of tablets returned.

Dose intensity is calculated as the total amount of the drug received divided by the treatment duration.

The **relative dose intensity** is calculated as the actual drug exposure of the period divided by the protocol-planned drug exposure of the period × 100%.

Expected total number of tablets for a specific period = 6 tablets/day × duration in the number of days of the period.

Actual total number of tablets received for a specific period = total number of tablets dispensed - total number of tablets returned of the period (based on electronic case report form [eCRF] collection).

Treatment compliance is defined as the actual total number of tablets received over the expected total number of tablets to be received for a participant × 100%.

Total time on study treatment for a specific period is calculated as the time in days from the first dose date until the last dose.

Total patient-years of exposure (years) for a specific period is calculated as the sum of total time on study treatment in a specific period across all participants who are treated.

In addition, the total number of participants with missed doses and reasons for missed doses will be summarized by treatment group and overall.

5.6.1.2. Adverse Events

AEs will be coded in MedDRA Version 24.0 or higher. The National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 will be used to grade the severity of the AEs. AEs during the Primary Treatment Period will be analyzed and reported in terms of

TEAEs, which are defined as any AEs that started or worsened in severity on or after the first dose of study intervention and before the first dose in the ETP (if the participant discontinues during the PEP, TEAEs are any AEs that started or worsened in severity on or after the first dose of study intervention through 30 days after the last dose of study intervention). The same analysis will be performed, including the aggregated PEP, ETP, and OLE Period (if applicable) AE data up to the cutoff date during the ALXN2050 treatment period by dose received using the ALXN2050-Treated Set.

See Section 6.1.6 for judging the TEAEs for AEs with partial dates. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case (ie, treatment emergent).

The incidence of TEAEs will be summarized with frequency and percentage by MedDRA SOC and PT. In addition, the incidence of TEAEs will be summarized by severity and relationship to study intervention. Should a participant experience multiple events within a category, the participant will be counted only once for that category. Percentages will be based on the number of treated participants in the analysis set within a treatment group. For the ALXN2050 treatment period analysis, an event rate per 100 patient-years will also be presented, which is defined as the number of events occurred within 100 patient-years.

Event rate= number of events / patient-years × 100

Patient-years = sum of all patient-years for all participants in a treatment, where patient-years is defined as time in days from the first ALXN2050 dose to the earliest date (eg, the last ALXN2050 dose + 30 days, data cutoff date, or study discontinuation/completion date).

TEAE summaries will be produced by treatment arm.

The frequency tables will be ordered by SOC and PT in descending order of the frequency by total ALXN2050-treated participants. For SOCs or PTs with the same frequency, categories will be sorted alphabetically.

All AEs (prior and TEAE) will be listed.

AEs will include the displays described in the following subsections.

5.6.1.2.1. Overall Summary of AEs

An overall summary table of TEAEs will be presented using summary statistics (n, %). The number of events (m), number and percentage of participants with events, and the event rate of TEAEs per 100 patient-years will be displayed for the following events subcategories:

- Total number of TEAEs and participants with TEAEs
- Related TEAEs
- Not related TEAEs
- TEAEs toxicity by grades (Grades 1 to 5)
- TEAEs leading to study intervention discontinuation
- TEAEs leading to death
- TESAEs

- Related TESAEs
- Not related TESAEs
- TEAEs leading to study intervention discontinuation

5.6.1.2.2. TEAEs and TESAEs by SOC and PT

The number of TEAEs, the number and percentage of participants with events, and the event rate of TEAEs per 100 patient-years will be presented by SOC and PT. Participants are counted once in each SOC and PT. TESAEs will be summarized similarly.

5.6.1.2.3. TEAEs and TESAEs by SOC, PT, and Relationship

The number of TEAEs, the number and percentage of participants with events, and the event rate of TEAEs per 100 patient-years will be presented by SOC and PT as described above by relationship to study treatment (related and not related). If a participant has > 1 occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. TESAEs will be summarized similarly.

5.6.1.2.4. TEAEs and TESAEs by SOC, PT, and Severity

The number of TEAEs, the number and percentage of participants with events, and the event rate of TEAEs per 100 patient-years will be presented by SOC and PT as described above by severity (Grades 1, 2, 3, 4, and 5). If a participant has > 1 occurrence of an AE, the highest grade will be used in the summary table.

5.6.1.2.5. Deaths and Other AEs

For TEAEs leading to study intervention discontinuation or death, the number of events, the number and percentage of participants with events, and the event rate of TEAEs per 100 patient-years will be presented by SOC and PT. Listings of TEAEs leading to study intervention discontinuation or death will be produced as well.

5.6.1.3. Additional Safety Assessments

All additional safety assessments will be reported by visit and treatment group.

5.6.1.3.1. Laboratory Tests

All laboratory data as of the data cutoff date will be included. Absolute values and changes from Baseline in central laboratory parameters (continuous variables) will be summarized descriptively at each visit by treatment group. Baseline is defined as the last nonmissing assessment value prior to the first dose of study intervention for the PEP. Shift tables over time will be presented for all laboratory values, where applicable, using normal, low, or high based on normal range values.

All central laboratory data will be presented in by-participant listings.

5.6.1.3.2. Vital Signs

All vital signs data as of the data cutoff date will be included.

Absolute values and changes from Baseline in vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) will be summarized descriptively at each visit and treatment group. A listing of vital signs will be presented.

The number and percentage of participants with at least 1 post-treatment vital sign measurement meeting any of the following criteria will be summarized by treatment group:

- Systolic blood pressure: < 90, > 140, and > 160 mmHg
- Diastolic blood pressure: < 50, > 90, and > 100 mmHg
- Heart rate: < 60 and > 100 bpm
- Body weight: decrease of ≥ 7% from Baseline and increase of ≥ 7% from Baseline
- Temperature: > 38.0°C and < 36.0°C
- Respiratory rate: < 12 and > 20 breaths/min

This analysis will be performed for the PEP data only using the SS and separately for the aggregated PEP, ETP, and OLE Period (if applicable) data during the ALXN2050 treatment period using the ALXN2050-Treated Set.

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

5.6.1.3.3. Electrocardiograms

Descriptive statistics by visit and treatment group will be presented for each ECG parameter (including PR, QRS, QT, corrected QT interval [QTc], and QTc using Fridericia's formula [QTcF]) value and for change from baseline values.

An outlier analysis that will summarize the frequency and percentage of participants who meet any of the following outlier criteria will be performed:

- QT and QTcF interval > 450 msec
- QT and QTcF interval > 480 msec
- QT and QTcF interval > 500 msec
- QT and QTcF interval increases from Baseline > 30 msec
- QT and QTcF interval increases from Baseline > 60 msec

This outlier analysis will be performed for the PEP data only using the SS and separately for the aggregated PEP, ETP, and OLE Period (if applicable) data during the ALXN2050 treatment period using the ALXN2050-Treated Set.

Overall ECG results will also be classified as normal, abnormal not clinically significant, and abnormal clinically significant. A summary table will be provided for clinically significant abnormalities by visit and treatment group.

A by-participant listing of ECG results will be presented.

5.6.1.3.4. C-SSRS

The following categories are C-SSRS categories and have binary responses (yes/no):

1. Wish to be dead
2. Nonspecific active suicidal thoughts
3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent
6. Preparatory acts or behavior
7. Aborted attempt
8. Interrupted attempt
9. Nonfatal suicide attempt
10. Completed suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined as follows:

Suicidal Ideation (1-5): A yes answer to any one of the five suicidal ideation questions (categories 1-5) on the C-SSRS

Suicidal Behavior (6-10): A yes answer to any one of the five suicidal behavior questions (categories 6-10) on the C-SSRS

Suicidal ideation or behavior: A yes answer to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

For each of the 3 composite endpoints, as well as the self-injurious behavior without suicidal intent, the number and percentage of participants who experienced an event at Baseline and at least once during the PEP will be summarized by treatment group. The Baseline C-SSRS assessment includes both (a) lifetime assessment (for both the suicidal ideation and the suicidal behavior categories) and (b) 1 year prior to treatment.

A shift tabulation from Baseline will be produced by treatment group during the PEP. A separate shift tabulation will be produced against the 3 composite endpoints. The 3 groupings for the shift tables are as follows: (a) no suicidal ideation or behavior, (b) composite endpoint of suicidal ideation, and (c) composite endpoint of suicidal behavior. Each participant is counted in 1 cell only for each of the 2 tabulations. Participants with both suicidal ideation and suicidal behavior are included in the suicidal behavior category for the particular tabulation.

5.6.1.3.5. Other Observations Related to Safety

All results for neurological examination and pregnancy tests will be presented in a by-participant listing.

Virus serology test results at Screening, including human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B virus, and hepatitis C virus, will be presented in a by-participant listing only.

5.6.2. Safety Analyses at Analysis 2 (Week 34)

All outputs for safety outcomes during the first 34 weeks and aggregated safety summary, including additional OLE Period data during the ALXN2050 treatment period, will be based on the ALXN2050-Treated Set, unless otherwise specified. Baseline is defined as the last available assessment prior to the first dose of study intervention. Baseline for Groups 3a and 3b is the last available assessment prior to the first dose of study intervention during the PEP.

5.6.2.1. Extent of Exposure

The same analyses as specified in Section 5.6.1.1 will be performed using the first 34 weeks of data (PEP and ETP) and the SS.

5.6.2.2. Adverse Events

AEs during the respective period for each group will be analyzed and reported in terms of TEAEs, which are defined as follows:

- Groups 3a and 3b: any AEs that started or worsened in severity on or after the first dose of study intervention in the ETP and before the first dose in the OLE Period or, if discontinued before the OLE Period, before the last dose + 30 days. The same analyses as specified in Section 5.6.1.2 will be performed using the first 34 weeks of data (PEP and ETP) and ALXN2050-Treated Set. Additional analyses will be performed, including the aggregated PEP, ETP, and OLE Period AE data up to the cutoff date by dose received ("ALXN2050 180 mg bid" and "ALXN2050 120 mg bid") at the time of the AE using the ALXN2050-Treated Set.

5.6.2.3. Additional Safety Assessments

The same analyses as specified in Section 5.6.1.3 will be performed using the first 34 weeks of data (PEP and ETP).

Additional safety data collected by study visit during the OLE Period (as specified in Section 5.6.1.3) will be listed and summarized by dose level, which is the dose received ("ALXN2050 180 mg bid" and "ALXN2050 120 mg bid") at the specific visit during the OLE Period.

5.7. Other Analyses

5.7.1. PK Analyses

For both of Analysis 1 (Week 8) and Analysis 2 (Week 34), the SS will be used for PK concentration listings and individual figures, and the PK set will be used for PK parameter listings, all summary tables, and mean figures.

5.7.1.1. Data Handling

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as 0 for calculation of descriptive statistics. When all concentrations are BLQ for a timepoint, the mean will be presented as BLQ, and the SD and coefficient of variation (CV) will be reported as not applicable; otherwise, the calculated mean will be presented.

For PK parameter calculations, BLQ values will be treated as 0.

Data rounding specifications for PK data are documented in the PK tables, listings, and figures (TLF) shells.

5.7.1.2. Plasma PK Concentrations

Blood samples for the analysis of concentrations of ALXN2050 in plasma for each of the treatments will be collected at the following timepoints:

- PEP of 8 weeks (Day 1 to Week 8): predose on Days 1, 29, and 57 and at 2 and 4 hours postdose on Days 1 and 57.
- ETP of 26 weeks (Weeks 9 to 34): predose on Days 85, 113, 183, and 239 and at 2 and 4 hours postdose on Days 85 and 113.

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

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

5.7.1.3. Plasma PK Parameters

The principal PK parameters for each participant will be derived using SAS Version 9.4 or higher. The following PK parameters will be determined for ALXN2050, where data permit:

C_{max}	Maximum observed concentration
C_{trough}	Pre-dose concentration prior to the administration of the next dose

Plasma PK parameters of ALX2050 will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) by period (PEP and ETP), treatment group, and day.

5.7.2. PD Analyses

For both Analysis 1 (Week 8) and Analysis 2 (Week 34), the SS will be used for all PD listings and individual absolute and change from baseline activity/concentration-time profiles, and the PD set will be used for PD summary tables and mean figures.

Baseline is defined as the last available assessment before the first dose of study intervention (predose Day 1 or Screening, whichever is the later and available). Baseline for Groups 3a and 3b is the last available assessment prior to the first dose of study intervention during the PEP.

5.7.2.1. Data Handling

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

Data rounding specifications for PD data are documented in the PK TLF shells.

5.7.2.2. Serum AP Activity and Plasma Bb Concentrations

Serum AP Activity

Blood samples for the analysis of serum AP activity over time for each of the treatments will be collected at the following timepoints:

- PEP of 8 weeks (Day 1 to Week 8): predose on Days 1, 29, and 57 and at 2 and 4 hours postdose on Days 1 and 57.
- ETP of 26 weeks (Weeks 9 to 34): predose on Days 85, 113, 183, and 239 and at 2 and 4 hours postdose on Days 85 and 113.

Plasma Bb Concentrations

Blood samples for the analysis of plasma Bb concentrations for each of the treatments will be collected at the following timepoints:

- PEP of 8 weeks (Day 1 to Week 8): predose on Days 1, 29, and 57 and at 2 hours postdose on Day 1.
- ETP of 26 weeks (Weeks 9 to 34): predose on Days 85, 113, 183, and 239.

The predose sample will be classified as the baseline value. Individual absolute values and change from Baseline in serum AP activity and plasma Bb concentrations will be presented in data listings and summarized separately using descriptive statistics (N, n [nonmissing values within the population], arithmetic mean, SD, CV%, median, minimum, and maximum) by group, period (PEP and ETP), day, and scheduled timepoint.

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

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

5.7.3. Population PK and PK/PD Analysis

In a separate analysis and report, ALXN2050 concentrations will be analyzed by both population PK and exposure-response approaches.

5.7.4. Biomarker Analyses

The following biomarker related objectives are defined in the protocol:

- Secondary objective: To assess the effect of FD inhibition on complement biomarkers
- Exploratory objective: To assess the effect of FD inhibition on AChR antibody titers in participants with gMG
- Exploratory objective: To characterize nongenetic biomarkers in adult participants with gMG

Samples will be collected for analyses that may include, but are not limited to, evaluation of complement components (eg, FD, C3, and CP activity), anti-AChR antibody, and other nongenetic exploratory biomarkers (eg, anti-MuSK antibodies, anti-LRP4 antibodies, MMP-10, and IL-6) in adult participants with gMG.

For the secondary endpoints (eg, FD, C3, and CP activity), absolute value and change from Baseline will be summarized descriptively. For the abovementioned exploratory biomarker endpoints, a stand-alone biomarker analysis plan will be developed with more details.

Baseline is defined as the last available assessment before the first dose of study intervention (predose Day 1 or Screening, whichever is the later and available).

If there is sufficient biomarker data for analysis, during Analysis 1 (Week 8), all biomarker results will be listed by treatment group and visit using the SS. Summary statistics for each variable (absolute and change from Baseline) will be provided by treatment group and visit using the FAS.

During Analysis 2 (Week 34), all biomarker results will be listed by treatment group and visit using the SS. Summary statistics for each variable (absolute and change from Baseline) will be provided by treatment group and visit using the FAS.

5.7.5. Hospitalizations

Hospitalization data will be listed by treatment group using the SS at Analyses 1 and 2.

5.8. Interim Analyses

Not applicable.

5.9. Final Analyses

The final analysis will be conducted at the end of the study. The OLES will be used for the final analysis, unless otherwise specified.

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 the OLE Period:

- Change from Baseline in the MG-ADL total score
- Proportion of participants with at least a 2-, 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the MG-ADL total score
- Change from Baseline in the QMG total score
- Proportion of participants with at least a 3-, 4-, 5-, 6-, 7-, or 8-point improvement in the QMG total score
- MGFA-PIS status
- Change from Baseline in the Neuro-QoL Fatigue total score
- For efficacy and nonefficacy endpoints, baseline is defined as the last measurement on or prior to the first dose of the PEP.

AEs will be analyzed and reported in terms of TEAEs, which are defined as any AEs that started or worsened in severity on or after the first dose of study intervention through 30 days after the last dose of study intervention.

AE data will be listed and summarized in an aggregated manner (combining data from the PEP, ETP, and OLE Period) by dose received using the 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 ("ALXN2050 180 mg bid" and "ALXN2050 120 mg bid") at the specific visit during the OLE Period.

Available PK, PD, and biomarker data during the OLE Period will be listed using the OLES.

Description of additional analyses may be provided in a SAP addendum before the conduction of the final analysis.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Technical Specifications for Derived Variables

The following derived data will be calculated prior to the analysis.

6.1.1. Age

Age will be presented as the number of years between the year of birth and the year of the reference date. The following ages (in years) may be computed using the formula (reference year - year of birth + 1), with reference dates indicated as follows:

Age	Reference Date
Age at informed consent	Year of signing ICF
Age at randomization	Year of randomization
Age at myasthenia gravis (MG) diagnosis	Year of MG diagnosis

6.1.2. Definition of Baseline Values

Baseline is defined as the last nonmissing assessment value prior to the first dose of study intervention for Group 1, 2, and 3. For Group 3a and 3b, 2 baselines are defined: the PEP baseline is defined as the last available assessment prior to the first dose of placebo and the ETP baseline is defined as the last available assessment prior to the first dose of ALXN2050.

For QMG, in the event that cholinesterase inhibitor was not withheld for at least 8 hours prior to administration of the QMG test at Day 1, the Screening Visit assessment will be used as Baseline. If cholinesterase inhibitor was not withheld for at least 8 hours for these visits (both Day 1 and Screening Visits), the Day 1 assessment will be used as baseline.

6.1.3. Change From Baseline

Change in values from Baseline will be calculated as follows:

Change in value = (subsequent value - baseline value), given that both the baseline value and the subsequent value are nonmissing.

6.1.4. Percent Change From Baseline

Percent change in values from Baseline will be calculated as follows:

% change in value = (subsequent value - baseline value) / (baseline value) × 100, given that the baseline value is nonmissing and nonzero and the subsequent value is nonmissing.

6.1.5. Analysis Visits

Summaries over post-Baseline timepoints or analyses at specific post-Baseline timepoints will be performed based on the nominal visits as collected from the eCRF and as described in the schedule of assessments in the protocol.

6.1.6. Adverse Events

The analysis of AEs is described in detail in Section 5.6.1.2.

TEAEs are any AEs that started or worsened in severity on or after the first dose of study intervention through 30 days after the last dose of study intervention. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE do not indicate that it occurred prior to the first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study intervention dose, then the AE is treatment emergent; else,
- If the start year is the same as the year of the first study intervention dose and The start month is missing, then the AE is treatment emergent, else if
    - The start month is present and is the same or after the month of the first study intervention dose, then the AE is treatment emergent; else,
- If the start date is completely missing, then the AE is treatment emergent.All other AEs are considered pretreatment AEs.

AEs with missing relationship will be assumed to be related to study treatment. AEs with missing toxicity grade will be summarized as a separate category.**Imputation rule for missing date**

Missing or incomplete partial start dates and/or stop dates will be imputed following the rules as defined below. The start date will be imputed first when the start date and stop date are both incomplete partial for a participant. If the field of year is missing, then no value will be imputed. The following rules will be applied to impute the incomplete partial start date, assuming that the year is available.

Missing or incomplete partial AE start dateIf the stop date is nonmissing and the imputed start date is after the stop date, the start date will be imputed by stop date.Missing day and month

- If the year is the same as the year of the first study treatment day, then the day and month of the first treatment day will be assigned to the missing fields.If the year is not equal to the year of the first study treatment day, then “January 01” will be assigned to the missing fields.Missing day onlyIf the month and year are the same as the year and month of the first study treatment day and the AE stop date is nonmissing, then the smaller AE stop day or the first study treatment day will be assigned to the missing day. If the month and year are the same as the year and month of the first study treatment day but the AE stop day is missing, then the first study treatment day will be assigned to the missing day.Otherwise, “01” will be assigned to the missing day.

3. Missing year onlyLeave as missing.

Missing or incomplete partial AE end date

- Leave as missing.

6.1.7. Concomitant Medication/Therapies

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

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

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

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

Missing or incomplete partial concomitant medication start date

If the stop date is nonmissing and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Imputation rule for missing date

The start date will be imputed first when the start date and stop date are both incomplete partial for a participant. If the stop date is nonmissing and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing or partial concomitant medication start date

1. Missing day only
   - If the month and year are not the same as the year and month of the first study treatment day, then “01” will be assigned to the missing day.
   - If the year is the same as the year of the first study treatment day
     - If the month is not the same as the month of the first study treatment day, then “01” will be assigned to the missing day.
     - If the month is the same as the month of the first study treatment day and the medication stop day is after the first study treatment day, then the first study treatment day will be assigned to the missing day.
     - If the month is the same as the month of the first study treatment day and the medication stop day is prior to the first study treatment day, then the medication start day will be assigned to the missing day.
2. Missing day and month

- If the year is not the same as the year of first study treatment day, then then "January 01" will be assigned to the missing fields.
- If the year is the same as the year of the first study treatment day
  - If the medication stop day is after the first study treatment day or the medication is "Meningococcal Vaccination," then the first study treatment day and month will be assigned to the missing fields.
  - If the medication stop day is prior to the year of first study treatment day, then medication stop day will be assigned to the missing fields.

3. Missing day, month, and year
   - If the medication is not "meningococcal vaccination," then the earliest date of informed consent date, the first study treatment date, or the AE end date will be assigned to the missing concomitant medication start date.
   - If the medication is "meningococcal vaccination," then the first study treatment date will be assigned to the concomitant medication missing start date.

Missing or incomplete partial concomitant medication end date

If the start date is nonmissing and the imputed stop date is before the start date, then the imputed stop date will be equal to the start date. If the "meningococcal vaccination" end date is missing, no imputation will be implemented.

1. Missing day only
   - If the month and year of the incomplete partial stop date are the same as the month and year of the last study treatment day, then the last study treatment day will be assigned to the missing day.
   - If the month and year of the partial incomplete stop date are not the same as the month and year of the last study treatment day, then the last day of the month will be assigned to the missing day.
2. Missing day and month
   - If the year of the partial incomplete stop date is the same as the year of the last study treatment day, then the day and month of the last treatment day will be assigned to the missing fields.
   - If the year of the partial incomplete stop date is not same as the year of the last study treatment day, then December 31 will be assigned to the missing fields.
3. Missing day, month, and year
   - If the medication is "ONGOING," no imputation will be implemented.

6.1.8. Actual Treatment

Safety data will be summarized by the actual treatment group. In case of study intervention dispensing error (eg, dispensing wrong kit), participants might receive a treatment other than the dose level they were randomized to receive. If dispensing error happens rarely, the participant

will remain in the original assigned treatment group, but a footnote should be added to describe the affected data point due to the dispensing error. If the dispensing error is recurrent and participant takes > 50% of the error treatment group over the study period, the participant should switch to the majority treatment group.

6.2. Appendix 2: Study and Participant Characteristics

6.2.1. Baseline Characteristics and Demographics

The following demographic variables will be summarized:

- Sex
- Race and ethnicity
- Age (years) at randomization: descriptive statistics (n, mean, SD, minimum, and maximum) and frequency of participants (< 65 and ≥ 65 years)
- Baseline weight: descriptive statistics (n, mean, SD, minimum, and maximum)
- Baseline weight: ≥ 40 and < 60, ≥ 60 and < 100, and ≥ 100 kg (n and percentage)Baseline height: descriptive statistics (n, mean, SD, minimum, and maximum)
- Baseline body mass index

The following disease characteristics will be summarized by descriptive statistics (n, mean, SD, minimum, and maximum) or by the number and percentage of participants in each category:MG-ADL total score at Baseline

- MG-ADL total score at Baseline (< 7 versus ≥ 7)
- QMG total score at Baseline Age (years) at MG diagnosisYears from MG diagnosis to informed consent
- Initial MG clinical presentation (ocular versus generalized)
- Time to gMG (if the initial clinical presentation was ocular MG): descriptive statistics (n, mean, SD, minimum, and maximum)
- Baseline MGFA clinical classification
- Maximum MGFA classification since diagnosis
- Ventilatory support since diagnosis (yes versus no)
- Experienced MG exacerbations or crisis (yes versus no)
- Type of MG event (exacerbation versus crisis)
- Any MG specific medications or therapies taken (yes versus no)

Summary statistics will be presented by treatment group and overall using the FAS and OLES. By-participant listings will be produced for all randomized participants.**Protocol Deviations**

All protocol deviations will be reviewed at the Blinded Data Review Meeting prior to the database lock. Any exclusion of participants from the PPS will be reviewed. Participants with the

following important protocol deviations (subset of all important protocol deviations) will be excluded from the PPS:

- Participants who did not meet inclusion criteria number 2, 3, 4 or 5
- Participants who violated exclusion criteria number 2, 3, 4, 19, 20, 21, 23 or 24.
- Participants who received any prohibited medication
- Participants who took a cholinesterase inhibitor within 8 hours prior to the QMG tests at Baseline and Week 8
- Participants who had changes in background MG medication in accordance with Section 6.5.1 of the protocol
- Participants who had unblinding of treatment allocation by the Investigator
- Participants who received incorrect randomized treatment

During Analysis 1 (Week 8), the number and percentage of participants with significant protocol deviations during the PEP will be summarized by treatment group and overall using the FAS. During Analysis 2 (Week 34), the number and percentage of participants with important protocol deviations during the PEP and ETP will be summarized by treatment group and overall using the ALXN2050-Treated Set. During the final analysis, the number and percentage of participants with important protocol deviations during the OLE Period will be summarized by treatment group and overall using the OLES. Protocol deviations from monitoring reports and other relevant sources will also be reviewed. All protocol deviations (important or not important) will be listed for all participants in the FAS.

6.2.3. Medical/Surgical History and Baseline Physical Examination

Medical history will be classified by SOC and PT using the latest available version of MedDRA and will be reported by treatment group and overall for the SS and OLES.

Baseline physical examination information will be summarized for the SS.

6.2.4. Prior/Concomitant Medication

Prior medications are defined as medications taken or received by participants prior to the first study treatment. Prior concomitant MG and non-MG medications will be summarized separately using the SS and OLES.

Concomitant medications are defined as medications taken or received by participants during the study after first study treatment. (Note: Some medications may be both prior and concomitant medications). During Analysis 1 (Week 8), concomitant MG and non-MG medications used in the PEP will be summarized separately using the SS. During Analysis 2 (Week 34), concomitant MG and non-MG medications used in the PEP or ETP will be summarized separately using the ALXN2050-Treated Set. During the final analysis, concomitant MG and non-MG medications used during the OLE Period will be summarized separately using the OLES.

Medications will be coded using the WHO DD (March 2021 or higher). Medication summaries by treatment group and overall using the number and percentage of participants will be presented

by WHO-DRUG Anatomical Therapeutic Chemical Level 4 class code and by WHO-DRUG generic name.

The number (percentage) of participants using prior nondrug therapies and procedures will be summarized by SOC and PT and will be reported by the treatment group for the SS. During Analysis 1 (Week 8), concomitant nondrug therapies and procedures performed in the PEP will be summarized by SOC and PT using the SS. During Analysis 2 (Week 34), concomitant nondrug therapies and procedures performed in the PEP or ETP will be summarized using the ALXN2050-Treated Set. During the final analysis, concomitant nondrug therapies and procedures performed during the OLE Period will be summarized separately using the OLES.

By-participant listings of prior and concomitant medications and nondrug therapies and procedures will be produced by treatment group using the SS.

6.3. Appendix 3: Additional Details on Statistical Methods

6.3.1. Clinical Deterioration

Clinical deterioration is defined as any of the following:

- Participants who experienced 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 participants; or
- Significant symptomatic worsening to 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; or
- Administration of rescue therapy to a participant whose, in the opinion of the Investigator or Investigator-designated physician, health would be in jeopardy if rescue therapy were not given (eg, emergent situations).

6.4. Appendix 4: Changes to Protocol-Planned Analyses

Not applicable in this version.

6.5. Appendix 5: List of Abbreviations

Abbreviation	Definition
AchR	acetylcholine receptor
AE	adverse event
AP	alternative pathway
Bb	completement factor Bb
bid	twice daily
BLQ	below the limit of quantification
C-SSRS	Columbia Suicide Severity Rating Scale
C3	complement component 3
CI	confidence interval
C_{max}	maximum observed concentration
CP	classical pathway
C_{trough}	concentration immediately prior to the administration of the next dose
CV	coefficient of variation
CV%	coefficient of variation percentage
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ETP	Extended Treatment Period
FAS	full Analysis Set
FD	factor D
gMG	generalized myasthenia gravis
HIV	human immunodeficiency virus
ICF	informed consent form
IL-6	interleukin 6
LRP4	low-density lipoprotein receptor-related protein 4
LS	least-squares
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-10	matrix metalloproteinase 10
MuSK	muscle-specific tyrosine kinase
Neuro-QoL Fatigue	Quality of Life in Neurological Disorders Fatigue questionnaire
OLE	Open-label Extension
OLES	Open-label Extension Set
OR	odds ratio
PD	pharmacodynamic(s)
PEP	Primary Evaluation Period
PK	pharmacokinetic(s)
PPS	Per Protocol Set
PT	Preferred Term
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 in an ECG
QTc	corrected QT interval
QTcF	corrected QT interval using Fridericia's formula
SAP	statistical analysis plan

Abbreviation	Definition
SAS	Statistical Analysis Software
SOC	System Organ Class
SS	Safety Set
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLF	table, listing, and figure
WHO DD	World Health Organization Drug Dictionary

7. REFERENCES

Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics. 1999;55(4):1202-9.

TITLE PAGE

STATISTICAL ANALYSIS PLAN ADDENDUM

Final Analysis

Version Number: Final v1.0

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

Protocol Number: ALXN2050-MG-201

Protocol Amendment Number: Amendment 3

Compound: ALXN2050

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

Sponsor Name: Alexion Pharmaceuticals Inc.

Legal Registered Address:

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USA

Author: [redacted]

Version Date: Final Version 1.0, 26Mar2024

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VERSION HISTORY

This Statistical Analysis Plan (SAP) Addendum for Study ALXN2050-MG-201 is based on Protocol Version Amendment 3, dated 15 Nov 2023.

SAP Version	Version Date	Change	Rationale
0.1	14 Mar 2024	Not applicable	Original version
1.0	26 Mar 2024	To address team comments on PK analysis	Final version

APPROVAL SIGNATURES

[redacted]

Biostatistician — Date dd Mmm yyyy

[redacted]

Biostatistics Functional Manager — Date dd Mmm yyyy

[redacted]

Medical Monitor — Date dd Mmm yyyy

1. STATISTICAL ANALYSIS PLAN ADDENDUM

Due to the lack of efficacy in ALXN2050 relative to Placebo based on the Week 8 interim analysis, Alexion decided to terminate Study ALXN2050-MG-201. There will be one final abbreviated CSR produced for the study including all applicable analyses.

The Statistical Analysis Plan (SAP) Addendum for final analysis details the changes from the planned analyses as described in the SAP Amendment Version 1.0 dated 27 Feb 2023 related to the analyses to be included in the final CSR. The original SAP was finalized on 23 Jun 2022. An SAP addendum was finalized on 20 Dec 2023 for Week 8 analysis.

1.1. Changes From Analyses Specified in the Protocol

See Section 1.2 for details.

1.2. Changes From Analyses Specified in the Previous Version of the SAP

- Primary endpoint: primary endpoint analyses will be performed as described in the SAP Amendment Version 1.0 Section 5.3.2. Sensitivity and supplementary analyses will not be performed.
- Secondary efficacy endpoints: only change from baseline in the QMG total score and change from baseline in the MG-ADL total score as described in the SAP Amendment Version 1.0 Section 5.4.1.1 and Section 5.4.1.3 (excluding the trend analysis to detect dose-response trend) will be performed. Descriptive summary of absolute and change from Primary Evaluation Period (PEP) baseline in MG-ADL and QMG total score will tabulate study visits through the entire study. Supplementary analyses will not be performed.
- PK/PD: PK parameter will not be reported as described in the SAP Amendment Version 1.0 Section 5.7.1.3. Population PK and exposure-response analysis will not be performed as described in the SAP Amendment Version 1.0 Section 5.7.3. All other PK/PD analyses will be performed.
- Biomarker: biomarker analysis will not be performed.
- Safety: All safety analyses will be performed as planned, as described in the SAP Amendment Version 1.0 Section 5.6 with all data collected until the end of study.
- No exploratory endpoint analyses will be performed.
- All other analyses (e.g., demographic, baseline disease characteristics, MG/non-MG medications/therapies, protocol deviation, etc), if not mentioned above, will be performed as planned.

Study exposure and adverse event data summaries will include the following two sets of analyses: (1) summary of the PEP data by Group 1, 2, 3; (2) summary of the ALXN2050 Treated Period data by Group 1, 2, 3a, 3b. Per-protocol Set and Re-randomized Set will be removed.

Medication summaries by treatment group and overall using the number and percentage of participants will be presented by WHO-DRUG Anatomical Therapeutic Chemical Level 3 class code and by WHO-DRUG generic name.
All planned listings other than the ones for exploratory biomarker endpoints will be produced.