Janssen Research & Development

Statistical Analysis Plan

Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Nipocalimab Administered to Adults with Generalized Myasthenia Gravis

Protocol MOM-M281-011; Phase 3

JNJ-80202135 (nipocalimab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	16 November 2022	Not Applicable	Initial release
2	14 July 2023	Revisions to key secondary and other secondary endpoints throughout	To reflect updates in protocol amendment 2
		Revisions in Study Design section (Section 1.2)	To reflect updates in protocol amendment 2
		Add Appendix 18 (sample SAS code for implementing MMRM analysis in Section 5.3.3) and Appendix 19 (details for defining ICEs and ICE dates)	To address FDA comments on SAP version 1
		Add test of study intervention-by-subgroup interaction term in the autoantibody seropositive/seronegative subgroup analysis, define supportive assessment criterion for the seronegative subgroup (Section 5.5.1.1)	Additional analysis to support evaluation of the treatment effect in the seronegative population
		Added summaries of response using the full analysis set; added plots depicting distribution of levels of improvement (Section 5.5.2)	To support assessment of treatment in the overall population; to enhance presentation of data in reports/publications.
		Added exposure duration definitions in terms of days (Section 5.6.1)	To clarify what the x-month exposure categories mean in terms of days
		Added three AEs of clinical interest (activation of latent virus, potentially abuse-related, hyperlipidemia) (Section 5.6.2, Section 6.8 [Appendix 8])	To characterize the safety profile of nipocalimab more fully.
		Added summaries of AEs potentially associated with glucocorticoid toxicity by concomitant steroid use (yes, no); by relationship to steroids; and by steroid dose reduction in OLE (Section 5.6.2)	To estimate incidence of potentially glucocorticoid toxicity events in participants with steroid use.
		Removed Colombia, Russia, and UK from list of countries/territories for subgroup analysis (Section 5.7.8)	Colombia, Russia, and UK did not enroll any participants.
		Added subgroup analysis based on age at onset of MG (≤50 years, >50 years) (Section 5.5.1; Section 5.7.8)	To evaluate consistency of treatment effect in early- versus late-onset MG
		Added summaries of concomitant medications started within a phase (Section 6.5 [Appendix 5])	To differentiate from concomitant medication use that may have started before the first dose of a phase.
3	8 December 2023	Modified Pharmacodynamics analysis set to include subjects	To allow for comparisons between nipocalimab and placebo

SAP Version	Approval Date	Change	Rationale
		randomized to placebo (Section 4).	in the double-blind phase on PD parameters
		Modified nipocalimab arm label to: Nipocalimab 30 mg/kg LD + 15 mg/kg q2w (Section 5.1)	Addition of loading dose more accurately describes the planned dosing.
		Removed sensitivity analysis in which delta-adjustment is made to imputed observations in both the placebo and nipocalimab groups (Section 5.3.3.2)	Sensitivity analysis in which only imputed observations in the nipocalimab arm are adjusted is sufficient and more conservative.
		Added Neuro-QoL Fatigue short form total score (Section 5.4.2.1.2, Section 5.5.3)	Addition of validated total score for Neuro – QoL Fatigue
		Remove subgroup analysis under primary estimand for EU (Section 5.5.1)	Subgroup analysis under primary estimand for US is sufficient for assessing consistency of treatment effect across subgroups. Analysis under primary estimand for EU (500 imputations) is excessively computationally intensive.
		Added subgroup analysis based on specific autoantibody for QMG change from baseline and MG-ADL response (Section 5.5.1.1)	For comparison to similar analysis on MG-ADL change from baseline
		Added new responder parameters based on MG-ADL and QMG (Section 5.5.2)	To pre-specify additional parameters that may be of interest.
		Removed cumulative total dose from exposure summaries (Section 5.6.1)	Cumulative total dose is not an informative parameter.
		Myasthenia gravis added as an AE of clinical interest (Section 5.6.2, Appendix 6.8)	To have an overall summary of the occurrence of this event which may be reported under multiple MedDRA preferred terms.
		Added a summary of MACE adjudication committee decisions (Section 5.6.2)	For a complete summary of adjudication committee findings.
		Additional vital signs and weight summaries based on FDA-suggested criteria (Section 5.6.3.2)	For consistency with FDA requests.
		Defined weight subgroup for summary of serum nipocalimab concentrations. Added summary of serum nipocalimab concentrations by sex (Section 5.7.1)	For consistency with factors considered for PK modeling.
		Updates to methods for analysis of pharmacodynamics parameters (Section 5.7.3)	To clarify observations to be included and excluded. Add geometric mean as a descriptive statistic and change figures to median (IQR) to use more robust measures.

SAP Version	Approval Date	Change	Rationale
		Added summary of rescue medication use (Appendix 6.5)	To present overall use of rescue medications in one summary table.
		Added summaries of changes in corticosteroid use during the OLE (Appendix 6.5)	Changes in steroid use during OLE are of clinical interest.
		Added appendix with additional details for implementing multiple imputations (Appendix 20)	To document details of imputation models and provide example SAS code.

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety for study MOM-M281-011.

Analyses for both the double-blind phase and open-label extension (OLE) phase are described. A database lock and unblinding will occur after the last participant completes the double-blind phase. The final analysis of the double-blind phase will be conducted after that database lock and a clinical study report (CSR) will be written. That CSR will include summaries of OLE phase data available at the time of the database lock.

A final database lock will occur after the last participant, last visit of the OLE phase and a final analysis of the OLE phase will be conducted.

1.1. Objectives and Endpoints

The primary and secondary objectives of the study as stated in the protocol are summarized below. Statistical hypotheses for the primary and key secondary objectives are in Section 2.

Objective	Endpoint(s)
Primary Objective	
To evaluate the efficacy of nipocalimab compared to placebo based on the Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale, in seropositive generalized myasthenia gravis (gMG) participants when treatment is taken as directed.	Average change from baseline in MG-ADL score over Weeks 22, 23, and 24 of the double-blind placebo-controlled phase.
Key Secondary Objectives	
To evaluate the efficacy of nipocalimab compared to placebo based on the Quantitative Myasthenia Gravis (QMG) scale, in seropositive gMG participants when treatment is taken as directed.	Average change in QMG score over Weeks 22 and 24 of the double-blind placebo-controlled phase.
To evaluate effect of nipocalimab compared to placebo in achieving the minimum clinically important difference (MCID) or better based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed.	Percentage of participants whose average improvement in MG-ADL total score over Weeks 22, 23, and 24 of the double-blind placebo-controlled phase is at least a 2-point improvement compared to baseline.
To evaluate the efficacy of nipocalimab loading dose compared to placebo based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed.	Percentage of participants with improvement in MG-ADL total score ≥ 2 points at Week 1 and/or Week 2 of the double-blind placebo-controlled phase.
To evaluate sustainability of therapeutic response of nipocalimab compared to placebo based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed.	Percentage of participants with improvement in MG-ADL total score ≥ 2 points at Week 4 through Week 24 of the double-blind placebo-controlled phase with no more than 2 non-consecutive excursions allowed between Week 6 through Week 23 (excursion defined as loss of improvement in MG-ADL score ≥ 2 points from baseline).
To evaluate the effect of nipocalimab compared to placebo on the percentage of participants achieving ≥50% symptom improvement based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed.	Percentage of participants whose average improvement in MG-ADL total score over Weeks 22, 24, and 24 of the double-blind placebo-controlled phase is at least a 50% improvement from baseline.
Other Secondary Objectives	
To evaluate safety and tolerability of treatment with nipocalimab.	• Proportion of participants with adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs:

Objective	Endpoint(s)
	severe or serious infections and hypoalbuminemia < 20g/L). • Change in vital signs and clinical laboratory values. • Change in Columbia-Suicide Severity Rating Scale (C-SSRS) score.
To evaluate sustainability of therapeutic response of nipocalimab compared to placebo based on the QMG scale, in seropositive gMG participants, when treatment is taken as directed.	Percentage of participants with improvement in QMG of ≥3 points from baseline at Week 2 through Week 24 of the double-blind placebo-controlled phase with no more than 2 non-consecutive excursions allowed at Weeks 4 through 22 (excursions defined as loss of improvement in QMG score of ≥3 points from baseline).
To evaluate the effect of nipocalimab compared to placebo on fatigue based on the Quality of Life in Neurological Disorders (Neuro-QoL) Fatigue scale, in seropositive gMG participants when treatment is taken as directed.	Average change from baseline in the Neuro-QoL Fatigue total score over Weeks 22 and 24 of the double-blind placebo-controlled phase.
To evaluate the effect of nipocalimab compared to placebo on health-related quality of life based on the15-item Myasthenia Gravis – Quality of Life (revised) instrument (MG-QoL15r) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) scale, in seropositive gMG participants when treatment is taken as directed.	• Average change from baseline in the MG-QoL15r score over Weeks 22 and 24 of the double-blind placebo-controlled phase. • Change from baseline in the visual analog scale and health status index of the EQ-5D-5L over 24 weeks of the double-blind placebo-controlled phase.
To evaluate the effect of nipocalimab compared to placebo on gMG minimum symptom expression based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed.	• Percentage of participants with MG-ADL score of 0 or 1 over time in the double-blind, placebo-controlled phase. • Percentage of participants with MG-ADL score of 0 or 1 at any time during the double-blind, placebo-controlled phase. • Percentage of participants with MG-ADL score of 0 or 1 at 50% of timepoints during the double-blind, placebo-controlled phase. • Percentage of participants with MG-ADL score of 0 or 1 at 75% of timepoints during the double-blind, placebo-controlled phase.
To evaluate pharmacokinetics (PK) and immunogenicity of nipocalimab.	• Serum nipocalimab concentrations over time • Incidence and titers of anti-drug antibodies (ADA) to nipocalimab and presence of neutralizing antibodies (NAb) to nipocalimab
To evaluate pharmacodynamic (PD) activity of nipocalimab.	PD outcome measure: Effects on total serum immunoglobulin G (IgG) concentrations
To explore the effects of nipocalimab treatment on biomarkers of MG disease biology and response.	• Effects on levels of autoantibodies associated with gMG. • Assessment of relationship between IgG lowering and MG-ADL and QMG. • Evaluate the potential relationship between change in MG-ADL and/or QMG score and change in autoantibody levels in seropositive participants (anti-

Objective	Endpoint(s)
	AChR, anti-MuSK, anti-LRP4) treated with nipocalimab.
Exploratory Objectives	
To further evaluate clinically relevant response to treatment with nipocalimab compared to placebo in seropositive gMG participants when treatment is taken as directed.	• Number of participants with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥8 point improvement in total MG-ADL score over time in the double-blind placebo-controlled phase. • Number of participants with a 3-, 4-, 5-, 6-, 7-, 8-, or ≥9 point improvement in total QMG score over time in the double-blind placebo-controlled phase. • Time to first response (MG-ADL total score improvement of ≥2 points) in the double-blind placebo-controlled phase. • Time to treatment discontinuation during the double-blind placebo-controlled phase for any reason. • Time to treatment discontinuation during the double-blind placebo-controlled phase due to Clinical Deterioration requiring hospitalization or rescue medication use. • Percentage of responders as measured by QMG (improvement on QMG of ≥3 points) over time in the double-blind placebo-controlled phase. • Number of participants with a total MG-ADL score of 0 or 1 over time in the double-blind placebo-controlled phase. • Number of emergency room (ER) visits; number of hospitalizations; average Length of Stay (LOS) from hospitalization due to Clinical Deterioration over time in the double-blind placebo-controlled phase.
To evaluate the efficacy of nipocalimab compared to placebo in seronegative gMG participants when treatment is taken as directed.	• Average change from baseline in MG-ADL score over Weeks 22, 23, and 24 of the double-blind placebo-controlled phase. • Average change from baseline in QMG score over Weeks 22 and 24 of the double-blind placebo-controlled phase. • Percentage of participants whose average MG-ADL total score over weeks 22, 23 and 24 of the double-blind, placebo-controlled phase is at least a 2-point improvement compared to baseline.
To explore the effects of nipocalimab on biomarkers of MG disease biology in gMG participants when treatment is taken as directed.	• Evaluate exploratory biomarkers[a] (including but not limited to IgG subtypes, IgM, IgA, IgE, MG-associated RNAs, complement proteins, proteomic, glycoprotein, and metabolomic markers).
To explore the changes in physical activity, mobility, and sleep, as measured by accelerometry,	• Change in Actigraphy watch-collected continuous data on physical activity, mobility, and sleep (including but

[a] Exploratory biomarkers (including but not limited to IgG subtypes, IgM, IgA, IgE) are not applicable for collection in China

Objective	Endpoint(s)
in nipocalimab compared to placebo in seropositive gMG participants when treatment is taken as directed (at selected sites)	not limited to step count, activity count, sleep time, sleep efficiency, and percent mobile time) during the double-blind placebo-controlled phase (at selected sites).
To explore the effects of nipocalimab compared to placebo on fatigue based on the meaningful change threshold (MCT) of the Neuro-QoL Fatigue scale, in seropositive gMG participants when treatment is taken as directed.	• Estimation of MCT threshold using anchor-based, and distribution- based approaches. • Cumulative Distribution Function curves of change from baseline in Neuro-QoL Fatigue over time. • Patient Global Impression of Change (PGI-C) and Patient Global Impression of Severity (PGI-S) frequency distribution of responses over time (anchoring for Neuro-QoL Fatigue) during the double-blind placebo-controlled phase.
To explore the long-term efficacy of nipocalimab 15 mg/kg q2w during the open-label extension phase.	• Change from baseline in the total MG-ADL score over time during the open-label extension phase. • Number of participants with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥8 point improvement in total MG-ADL score over time during the open-label extension phase. • Change from baseline in total QMG score over time during the open-label extension phase. • Percentage of responders as measured by QMG (improvement on QMG of ≥3 points) over time during the open-label extension phase. • Change from baseline in Neuro-QoL Fatigue scores over time during the open-label extension phase. • Number of participants with a total MG-ADL score of 0 or 1 over time during the open-label extension phase. • Change from baseline in the MG-QoL15r score over time during the open-label extension phase. • Change from baseline in the visual analog scale and health status index of the EQ-5D-5L over time during the open-label extension phase. • Number of participants having Clinical Deterioration requiring hospitalization or rescue therapy during the open-label extension phase. • PGI-C and PGI-S frequency distribution of responses over time (anchoring for Neuro-QoL Fatigue) during the open-label extension phase. • Changes in individualized concomitant medications for gMG over time during the open-label extension phase.

1.2. Study Design

This study is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of nipocalimab compared to placebo in participants with gMG who are inadequately controlled with standard of care therapy (or have discontinued corticosteroids and/or

immunosuppressants >4 weeks prior to screening due to intolerance or lack of efficacy). Participants who have completed the double-blind placebo-controlled phase of the study have an option to receive open-label treatment of nipocalimab to evaluate long-term safety and efficacy of nipocalimab.

The study will consist of a screening phase of up to 4 weeks, a 24-week double-blind placebo-controlled phase and an OLE phase. The OLE will be of variable duration per participating country or territory. Participants may continue until 2 years after marketing authorization in a participant's local country or territory, or until nipocalimab becomes available commercially or via other continued access program, whichever comes first. Participants who discontinue study intervention during the double-blind placebo-controlled phase for any reason other than Clinical Deterioration requiring hospitalization or rescue therapy will be required to complete study procedures per the Schedule of Activities until the completion of the 24-week period. Participants who discontinue study intervention administration or withdraw at any point during the study will be requested to complete a follow-up assessment 8 weeks after their last infusion of study intervention.

Approximately 190 participants will be enrolled into the double-blind placebo-controlled phase of the study, including approximately 150 seropositive participants (anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive). Seronegative participants will also be enrolled. Participants will be randomly assigned in a 1:1 ratio to receive either placebo or nipocalimab (30 mg/kg for the first infusion followed by 15 mg/kg every 2 weeks [q2w]) during the first 24 weeks. Randomization will be stratified by autoantibody status (anti-AChR and/or anti-MuSK positive, anti-AChR negative and anti-MuSK negative), Day 1 MG-ADL total score (≤9, >9), and region (East Asia, United States [US], rest of world).

Participants who complete the double-blind placebo-controlled phase will continue to the OLE phase where treatment with nipocalimab will continue until 2 years after marketing authorization in a participant's local country or territory, or until nipocalimab becomes available commercially or via other continued access program, whichever comes first. After protocol amendment 2, all participants entering the OLE phase will receive open label nipocalimab treatment of 15 mg/kg q2w. CCI

Due to the COVID-19 pandemic, the MOM-M281-005 study, an OLE study was placed on hold and subsequently terminated. As a result, some participants from the MOM-281-004 study, a Phase 2 double-blind, placebo-controlled study, were unable to enroll into the MOM-M281-005 study. Participants affected by this study termination (either those who were ongoing in the MOM-M281-005 study at the time of the hold or those who were unable to enroll from MOM-M281-004) will have the opportunity to directly enter the OLE phase of study MOM-M281-011 (bypassing the

double-blind placebo-controlled phase). These return participants will undergo a screening assessment to confirm eligibility for entry into the OLE phase of the study.

Procedures for randomization and stratification

Eligible participants will be randomized on Day 1 to a treatment assignment according to a randomization schedule generated by the sponsor or designee. The study personnel will use an interactive web response system (IWRS) to obtain the randomization number for each eligible participant.

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups (nipocalimab or placebo) based on a computer-generated randomization schedule prepared before the study under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by autoantibody status (anti-AChR positive and/or anti-MuSK positive, anti-AChR negative and anti-MuSK negative), Day 1 MG-ADL total score (≤9 >9), and region (East Asia, US, rest of world). The IWRS will assign a unique intervention code, which will dictate the intervention. The requestor must use his or her own user identification and personal identification number when contacting the IWRS which will then give the relevant participant details to uniquely identify the participant.

Blinding

The participant, investigator, and sponsor will be blinded to study treatment for the duration of the blinded periods. An unblinded site pharmacist will be responsible for storage, preparing, and documentation of the study intervention for infusion while all other site personnel will remain blinded. Selected data will be handled with special care to minimize any potential impact on blinding/bias. This can include masking/segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. The following measurements obtained after screening will remain blinded during study conduct: nipocalimab concentrations, total serum IgG and IgG subtypes (IgG1, IgG2, IgG3, and IgG4), IgA, IgM, IgE, anti-AChR/anti-MuSK/anti-LRP4 autoantibodies, anti-nipocalimab antibodies, total serum protein, and serum albumin. The following measurements will remain blinded during the double-blind placebo-controlled phase: serum lipid profiles, c-reactive protein, complement proteins (C4, C4, CH50, C5a), circulating immune complexes (CIC), and striational antibodies.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Under normal circumstances, the blind must not be broken until the database is finalized. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. The date and reason for the unblinding must be documented by the IWRS and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner. Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

A separate code break procedure will be available for use by the sponsor's Global Medical Safety group to allow for unblinding of individual participants to comply with specific requests from regulatory or health authorities.

The blind will be maintained until the last participant completes the double-blind phase Week 24 evaluations at which time the data will be locked. Investigative sites and participants will remain blinded to initial intervention assignment until after the final database is locked after the last participant completes the last visit of the open-label extension phase.

2. STATISTICAL HYPOTHESES

The primary efficacy endpoint is the average change from baseline in MG-ADL total score over Weeks 22, 23 and 24.

For submissions in the US and other non-EU regions, the null hypothesis that is to be tested to address the primary objective of the study is that there is no difference between nipocalimab and placebo in the treatment of gMG in seropositive participants, when study intervention is taken as directed, based on the primary efficacy endpoint.

For submissions in the EU, the null hypothesis that is to be tested to address the primary objective of the study is that there is no difference between nipocalimab and placebo in the treatment of gMG in seropositive participants, regardless of whether study intervention is taken as directed or not, based on the primary efficacy endpoint.

Similar null hypotheses will be tested in a pre-specified hierarchical order (see Section 5.4) to address the key secondary objectives based on the endpoints specified for those objectives in Section 1.1.

For submission in Japan, two families of 3 null hypotheses will be tested with a serial gatekeeping strategy (see Section 5.3.2.3 for details):

Family 1

1. No difference between nipocalimab and placebo in the treatment of gMG in seropositive participants, when study intervention is taken as directed, based on the primary efficacy endpoint.
2. No difference between nipocalimab and placebo in the treatment of gMG in anti-AChR positive participants, when study intervention is taken as directed, based on the primary efficacy endpoint.

Family 2

3. No difference between nipocalimab and placebo in the treatment of gMG in seropositive and seronegative participants, when study intervention is taken as directed, based on the primary efficacy endpoint.

Family-wise Type 1 error is controlled at 0.05 within estimand and testing hierarchy for each region separately.

3. SAMPLE SIZE DETERMINATION

A sample size of 75 seropositive participants per group is needed to provide at least 90% power to detect standardized effect sizes of at least 0.57 at a two-sided significance level of 0.05, assuming a drop-out rate of 20% at Week 24. A standardized effect size of 0.57 is based on estimates of between-group differences (≥1.7) and standard deviations (approximately 3) from clinical trial simulations of the MG-ADL total score. The sample size is based on a mixed effects model for repeated measures (MMRM) assuming 12 post-baseline assessments over 24 weeks and a constant within-participant correlation of 0.5 (Lu 2008; Donohue 2020). At least 150 eligible seropositive participants will be enrolled. Seronegative participants will also be enrolled.

The sample size of 75 participants per group also provides at least 90% power to detect a standardized effect size of at least 0.57 for the QMG key secondary endpoint. Based on estimates of the standard deviation of changes from baseline in this endpoint in published gMG studies (approximately 5 [Howard 2017, 2019, 2020],), a standardized effect size of 0.57 translates to a between-group difference of approximately 2.9.

Table 2 below summarizes the between-group differences in proportions that can be detected with at least 90% (80%) power for the key secondary endpoints of response, assuming 75 participants per group, two-sided significance level of 0.05, and a Pearson chi-square test. The assumed percent responders in the placebo group were derived from clinical trial simulations.

Table 2: Between-group Differences in Proportions That can be Detected With at Least 90% (80%) Power for the Key Secondary Endpoints

Key secondary endpoint	Percent in placebo arm	Smallest difference in proportions (percent in nipocalimab arm) that can be detected with the given power (N/group = 75; two-sided α = 0.05)	
		Power = 90%	Power = 80%
Response	45%	0.26 (71%)	0.23 (68%)

Type I error is controlled over the primary and key secondary objectives at two-sided 0.05 by employing a fixed sequence testing approach described below (see Section 5.4.1).

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	**Description**
Enrolled	All participants who sign the ICF.
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Full Analysis Set	The full analysis set includes all randomized participants who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase
Full Analysis Set (OL)	The full analysis set (OL) includes all participants who received at least 1 dose (partial or complete) of nipocalimab in the OLE phase
Primary Efficacy Analysis Set	The primary efficacy analysis set includes all randomized seropositive participants who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase

Analysis Sets	Description
Anti-AChR Positive Efficacy Analysis Set	The anti-AChR positive efficacy analysis set includes all randomized anti-AChR positive participants who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase
Seropositive Efficacy Analysis Set (OL)	The seropositive efficacy analysis set (OL) includes all seropositive participants who received at least 1 dose (partial or complete) of nipocalimab in the OLE phase
Safety (DB)	The safety analysis set includes all randomized participants who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase
Safety (OL)	The safety analysis set (OL) includes all participants who received at least 1 dose (partial or complete) of nipocalimab in the OLE phase
Safety	The safety analysis set includes all participants who received at least 1 dose (partial or complete) of any study intervention in either the double-blind or OLE phase
All Nipocalimab	The all nipocalimab analysis set includes all participants who received at least 1 dose (partial or complete) of nipocalimab in either the double-blind or OLE phase
Pharmacokinetics (PK) Analysis Set	The PK analysis set is defined as all participants who received at least 1 complete dose of nipocalimab in either the double-blind or OLE phase and have at least 1 valid post-dose blood sample drawn for PK analysis
Immunogenicity Analysis Set	The immunogenicity analysis set is defined as all participants who received at least 1 dose (partial or complete) of nipocalimab in either the double-blind or OLE phase and have at least 1 post-dose serum sample evaluable for antibodies to nipocalimab
Pharmacodynamic (PD) Analysis Set	The PD analysis set is defined as all participants who received at least 1 dose (partial or complete) of any study intervention in either the double-blind or OLE phase and have at least 1 valid post-dose blood sample drawn for PD analysis

5. STATISTICAL ANALYSES

5.1. General Considerations

The reference start date for the calculation of study day is the date of the first infusion of study intervention. Study day of a visit or an event start or end date is defined as the visit/start/end date – reference start date + 1 for dates on or after the reference start date, and visit/start/end date – reference start date for dates before the reference start date. There is no study day 0.

Start and end dates for the study phases are defined below.

Double-blind phase

- Start date: Date of first infusion in the double-blind phase.
- End date:

- Double-blind participants who enter the OLE phase: Date of first infusion in OLE phase – 1 day.
- Double-blind participants who do not enter the OLE phase: Study termination date.

OLE phase

- Start date: Date of first infusion in the OLE phase.
- End date: Study completion or termination date.

Results in the double-blind phase will be summarized by randomized study intervention groups:

- Placebo
- Nipocalimab 30 mg/kg LD + 15 mg/kg q2w

Results that include the OLE phase will be summarized by 3 intervention groups:

- Placebo/Nipocalimab (participants randomized to placebo in the double-blind phase)
- Nipocalimab/Nipocalimab (participants randomized to nipocalimab in the double-blind phase)
- Nipocalimab (OL) (participants who had participated in MOM-M281-004 or MOM-M281-005 and entered the OLE phase directly)

5.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits for all efficacy assessments in the double-blind period except MGFA classification. Analyses in the double-blind phase for these efficacy assessments will use the analysis visit. Analyses for MGFA classification and all other assessments in the double-blind phase, and all analyses in the OLE phase, will use the nominal visit.

Listed below are the visit windows and the target days for each analysis visit. The reference day is Study Day 1. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 3) are the analysis visit windows and the target days for each double-blind visit defined in the protocol for the given parameter.

Table 3: Visit Windows

Parameter	Analysis Period	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
MG-ADL	Double-blind	10000	Screening	-28 to -1	-1
		20001	DB Day 1	1	1
		20010	DB Week 1	2 to 11	8
		20020	DB Week 2	12 to 18	15
		20030	DB Week 3	19 to 25	22
		20040	DB Week 4	26 to 36	29
		20060	DB Week 6	37 to 50	43
		20080	DB Week 8	51 to 71	57
		20120	DB Week 12	72 to 99	85
		20160	DB Week 16	100 to 127	113
		20140	DB Week 20	128 to 148	141
		20220	DB Week 22	149 to 158	155
		20230	DB Week 23	159 to 165	162
		20240	DB Week 24	>165	169
QMG, Neuro-QoL-Fatigue, PGI-S, PGI-C, EQ-5D-5L	Double-blind	10000	Screening	-28 to -1	-1
		20001	DB Day 1	1	1
		20020	DB Week 2	2 to 22	15
		20040	DB Week 4	23 to 43	29
		20080	DB Week 8	44 to 71	57
		20120	DB Week 12	72 to 99	85
		20160	DB Week 16	100 to 127	113
		20200	DB Week 20	128 to 148	141
		20220	DB Week 22	149 to 162	155
		20240	DB Week 24	>162	169
MG-QoL-15r	Double-blind	10000	Screening	-28 to -1	-1
		20001	DB Day 1	1	1
		20020	DB Week 2	2 to 22	15
		20040	DB Week 4	23 to 36	29
		20060	DB Week 6	37 to 50	43
		20080	DB Week 8	51 to 71	57
		20120	DB Week 12	72 to 99	85
		20160	DB Week 16	100 to 127	113
		20200	DB Week 20	128 to 148	141
		20220	DB Week 22	149 to 162	155
		20240	DB Week 24	>162	169

*Relative to Study Day 1

5.1.2. COVID-19

Summaries related to COVID-19 medical history (including vaccination), participant disposition related to COVID-19, study intervention and protocol disruptions because of COVID-19, adverse events related to COVID-19, and medications taken for COVID-19 are described in Section 6.11 (Appendix 11).

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received double-blind study intervention
- Participants who received open-label study intervention
- Participants who completed double-blind study intervention
- Participants who completed the study
- Participants who discontinued double-blind study intervention
- Reasons for discontinuation of double-blind study intervention
- Participants who discontinued open-label study intervention
- Reasons for discontinuation of open-label study intervention
- Participants who terminated study prematurely
- Reasons for termination of study

The distribution of the time to discontinuation of double-blind study intervention will be displayed with Kaplan-Meier curves. Participants who discontinue double-blind study intervention at any time will be considered an 'Event' and their date of double-blind study intervention discontinuation + 14 days will be used in the time to event calculation (14 days are added to account for the q2w dosing interval). Participants who complete double-blind study intervention will be censored and the date of last dose of double-blind study intervention + 14 days will serve as the time of censoring. The distribution of the time to discontinuation of open-label study intervention will also be displayed with Kaplan-Meier curves in the same manner, with time calculated relative to the OLE phase start date.

Listings of participants will be provided for the following categories:

- Participants who discontinued double-blind study intervention
- Participants who discontinued open-label study intervention
- Participants who terminated study prematurely
- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study intervention.

5.3. Primary Endpoint(s) Analysis

The significance level for the primary endpoint analysis is two-sided $\alpha = 0.05$.

5.3.1. Definition of Endpoint

The MG-ADL is an 8-item questionnaire administered by a qualified healthcare professional that assesses the severity of the impairment of 8 activities (talking, chewing, swallowing, breathing, impairment of ability to brush teeth or comb hair, impairment of ability to arise from a chair, double vision, and eyelid droop) on a 4-point scale (0 = normal, 1, 2, or 3 = severe) (Wolfe 1999). See Section 6.12 (Appendix 12) for definitions of each score for each function. The MG-ADL is assessed at Screening, Day 1, Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 22, 23, and 24 (or end of phase visit) during the double-blind phase. Participants who prematurely discontinue treatment or modify or discontinue their stable gMG therapy during the double-blind phase for reasons other than initiation of rescue therapy, are expected to continue the double-blind visit schedule until Week 24.

During the OLE phase the MG-ADL is assessed every 2 weeks through Week 8, every 4 weeks through Week 24, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

The MG-ADL total score is defined as the sum of the 8 individual items (range: 0 to 24). The total score is missing if any item is missing. Higher scores indicate greater impairment.

Baseline is defined as the average of the Screening and Day 1 total scores. Change from baseline in MG-ADL total score will be calculated for each post-Day 1 visit.

The primary efficacy endpoint is the average change from baseline in the MG-ADL total score over Weeks 22, 23, and 24 of the double-blind phase.

5.3.2. Estimands

After interaction with health authorities in US (FDA), Europe (EMA), and Japan (PMDA), different primary estimands for the primary endpoint are defined for submissions to European Union (EU) countries, Japan, and US/Rest of World (US/ROW).

For a given estimand, the attributes, including strategies for ICEs, will apply to all participants from every region. The primary estimand(s) of a given region will be supplementary estimands for the other regions.

5.3.2.1. Primary Estimand: US/ROW

Study Intervention

- Nipocalimab 30 mg/kg loading dose followed by 15 mg/kg every 2 weeks in addition to stable gMG therapy (or who discontinued MG therapy due to intolerance or lack of efficacy)
- Placebo every 2 weeks in addition to stable gMG therapy

Population: Seropositive participants with gMG who are on stable gMG therapy

Variable: Average change from baseline in MG-ADL total score over Weeks 22, 23, and 24 of the double-blind phase

Population level summary: The difference in mean average change from baseline over Weeks 22, 23, and 24 of the double-blind phase between the nipocalimab and placebo intervention groups

Intercurrent events (ICEs) and strategies: ICEs of study intervention discontinuation, discontinuation of stable gMG therapy (with or without study intervention discontinuation), and change in stable gMG therapy, whether the ICE occurred because of initiation of rescue therapy or not, are addressed with a hypothetical strategy, as if these ICEs would not have occurred.

5.3.2.2. Primary Estimand: EU

The study intervention, population, variable, and population level summary attributes are the same as for the US/ROW primary estimand.

The primary estimand for EU differs from the US/ROW primary estimand in the strategy applied to certain ICEs. ICEs of discontinuation of study intervention or stable gMG therapy that **are not** due to initiation of rescue therapy, or changes in stable gMG therapy (for any reason), are addressed with a treatment policy strategy targeting the effect of the assignment to the study intervention group regardless of the occurrence of the ICEs. ICEs of discontinuation of study intervention or stable gMG therapy that **are** due to initiation of rescue therapy, are addressed with a hypothetical strategy as if the rescue therapy had not been available.

Rescue therapy refers to the use of IVIg or plasmapheresis for the treatment of myasthenia gravis exacerbation or crisis.

5.3.2.3. Primary Estimands: Japan

For submission in Japan, two primary endpoint families of three statistical hypotheses will be tested.

The estimands for each hypothesis have the same study intervention, variable, population level summary, ICEs, and ICE strategy attributes as for the US/ROW primary estimand, but different population attributes for 2 of the 3 hypotheses:

Primary Endpoint Family 1

1. Efficacy of 24 weeks of nipocalimab treatment compared to placebo for gMG based on the MG-ADL total score **in seropositive participants** when treatment is taken as directed (same as Primary Estimand for US/ROW).
2. Efficacy of 24 weeks of nipocalimab treatment compared to placebo for gMG based on the MG-ADL total score **in anti-AChR positive participants** when treatment is taken as directed.

Primary Endpoint Family 2

3. Efficacy of 24 weeks of nipocalimab treatment compared to placebo for gMG based on the MG-ADL total score **in seropositive and seronegative participants** when treatment is taken as directed.

Type I error over the two families of three hypotheses is controlled at the two-sided 0.05 level through a serial gatekeeping strategy. The primary analyses for Japan will be conducted at the two-sided 0.05 level for both the seropositive and anti-AChR positive analysis sets. If both are statistically significant, the null hypotheses for the Primary Endpoint Family 1 will be rejected and the analysis for the full analysis set (including both seropositive and seronegative participants) will be conducted at the two-sided 0.05 level. If the analysis for either the seropositive analysis set or the anti-AChR analysis set is not statistically significant (at two-sided 0.05), then the analysis for the full analysis set will not be conducted.

5.3.2.4. Supplementary Estimands

The primary estimand(s) for one region will be supplementary estimands for other regions. For example, the primary estimand with the 'seropositive and seronegative' population attribute for Japan is a supplementary estimand for US/ROW and EU.

5.3.3. Analysis Methods

Descriptive statistics of the actual values and change from baseline to each post-baseline timepoint in the double-blind phase will be presented for MG-ADL total score by intervention group. Descriptive statistics include N, mean, standard deviation (SD), median, minimum, and maximum.

Under each estimand, the primary efficacy endpoint, the average change from baseline in MG-ADL total score over Weeks 22, 23, and 24 of the double-blind phase, will be analyzed using a mixed effects model for repeated measures (MMRM) with weekly change from baseline as the dependent variable, factors for study intervention group, autoantibody status ("anti-AChR positive or anti-MuSK positive" or "anti-AChR negative and anti-MuSK negative", as randomized), region, week, and study intervention group-by-week interaction; baseline MG-ADL total score as a covariate; and participant as a random effect. An unstructured variance-covariance matrix will be used first. In case of convergence problems, alternative variance-covariance structures will be used in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1). The Kenward-Roger method will be used for approximating the denominator degrees of freedom. The between-group difference of the average change over Weeks 22, 23, and 24 will be tested with an F-test of the linear contrast that averages the change from baseline over those time points. The estimate of this contrast and its 95% confidence interval will be provided. Least squares mean estimates, with 95% confidence intervals, of change from baseline at each time point will be provided and displayed graphically over time by intervention group. Sample SAS code for implementing this analysis is provided in Section 6.18 (Appendix 18).

The analysis sets used, the data to be included or excluded, and the methods applied for missing or unobserved data under each primary estimand are summarized in the table below. Further details about how to identify an ICE in the data and defining the participant ICE date are provided in Section 6.19 (Appendix 19).

Estimand	Analysis set[a]	Data to be included/excluded	Method for missing or unobserved data[b]	Sensitivity analysis[b]
Primary Estimand for US/ROW	Primary efficacy	Included: Observations before any ICE. Excluded: Observations after any ICE are deemed missing.	No imputation. Estimation by MMRM, with MAR (Missing at Random) assumption	Multiple imputation with serial delta adjustment (tipping point analysis; see Section 5.3.3.2)
Primary Estimand for EU	Primary efficacy	For ICE of change in gMG therapy for any reason or other ICEs not due to initiation of rescue therapy: Included: Observations before or after the ICE. Excluded: No observations are excluded.	Multiple imputation by "Copy Reference" method (see Section 5.3.3.1)	Multiple imputation by "Jump to Reference" method (see Section 5.3.3.2)
		For ICEs that are due to initiation of rescue therapy: Included: Observations before the ICE Excluded: Observations after the ICE are deemed missing		
Primary Estimand 1 for Japan	Primary efficacy	Included: Observations before any ICE. Excluded: Observations after any ICE are deemed missing.	No imputation. Estimation by MMRM, with MAR assumption	Multiple imputation with serial delta adjustment (tipping point analysis; see Section 5.3.3.2)
Primary Estimand 2 for Japan	Anti-AChR positive efficacy			
Primary Estimand 3 for Japan	Full			

[a] See Section 4 for analysis set definitions.
[b] When multiple imputation is employed, non-monotone missing observations (intermediate missing) are imputed by MCMC with MAR assumption

The number and percentage of participants with post-intercurrent event observations at each visit will be summarized.

5.3.3.1. Analysis Method for Primary Estimand for EU

Step 1 – Multiple Imputation

If there are participants with a non-monotone missing data pattern, datasets with only monotone missing data patterns will be created first by imputing the intermediate missing values using methods such as the MCMC (Markov Chain Monte Carlo) method. Five hundred (500) imputations will be performed to create 500 datasets which now have monotone missing data patterns (i.e., missing data after the last value to be included in the analysis).

Analysis assumptions: MAR is assumed for intermediate missing data. Missing not at random (MNAR) is assumed for monotone missing data in the nipocalimab group after the last observed value for participants who experienced an intercurrent event. MAR is assumed for the placebo group.

The "Copy Reference" multiple imputation (MI) estimator will be used to impute missing data in the nipocalimab group after the last observed value for participants who experienced an intercurrent event. By this method, the model-expected mean for imputations is derived as if the participant had always been a member of the placebo group. Insofar as a nipocalimab participant's observed values are better (or worse) than those of participants in the placebo group, the mean for imputations for that participant at the imputed visit will tend to be better (or worse) than those observed for the placebo group at the imputed visit.

Step 2 – Analysis

The MMRM described above will be performed for each of the 500 imputed datasets.

Step 3 – Pooling

Rubin's methodology will be applied to the MMRM results from the 500 imputed datasets to produce final inferences (Rubin 1987).

5.3.3.2. Sensitivity analyses

The robustness of the primary analyses with respect to deviations from the assumptions pertaining to data that is either deemed missing under the hypothetical strategy or missing under the treatment policy strategy will be evaluated with the sensitivity analyses described below.

Primary estimands for US/ROW and Japan

Step 1 – Multiple Imputation

Analysis assumptions: If there are participants with a non-monotone missing data pattern, datasets with only monotone missing data patterns will be created first by imputing the intermediate missing values using methods such as the MCMC (Markov Chain Monte Carlo) method. Five hundred (500) imputations will be performed to create 500 datasets which now have monotone missing data patterns (i.e., missing data after the last value to be included in the analysis). Monotone missing data will first be imputed by MAR-based MI regression, and the imputed scores in the nipocalimab intervention group will be adjusted to be worse than the other participants in the same group with non-missing data as discussed below. Additional details pertaining to the multiple imputation methods are in Section 6.20 (Appendix 20).

The imputed value will be adjusted by adding δ_A to the imputed values for participants randomized to the nipocalimab group with δ_A ranging from 0 to Δ^* in increments of 0.5.

Adding positive values results in higher (worse) scores. Δ^* represents the adjustment leading to the 'tipping point' or the smallest delta adjustment value at which conclusions change from

favorable (i.e., statistically significant: 2-sided p-value ≤0.05 in favor nipocalimab) to *unfavorable* (fail to reject the null hypothesis of no intervention difference).

Five-hundred (500) delta-adjusted fully imputed datasets will be generated for each δ_A.

Step 2 – Analysis

The MMRM described above will be performed for each set of 500 imputed datasets.

Step 3 – Pooling

Rubin's methodology will be applied to the MMRM results from each set of 500 imputed datasets to produce final inferences (Rubin 1987).

Between-group differences for the average change from baseline over Weeks 22, 23, and 24 (2-sided p-values and point estimates for the intervention difference) will be displayed graphically for each considered δ_A, up to the 'tipping point' adjustment.

Primary estimand for EU

Step 1 – Multiple Imputation

Analysis assumptions: If there are participants with a non-monotone missing data pattern, datasets with only monotone missing data patterns will be created first by imputing the intermediate missing values using methods such as the MCMC (Markov Chain Monte Carlo) method. Five hundred (500) imputations will be performed to create 500 datasets which now have monotone missing data patterns (i.e., missing data after the last value to be included in the analysis). Missing not at random (MNAR) is assumed for monotone missing data in the nipocalimab group after the last observed value for participants who experienced an intercurrent event. MAR is assumed for the control group.

The "Jump to Reference" multiple imputation (MI) estimator will be used to impute missing data in the nipocalimab group after the last observed value for participants who experienced an intercurrent event. By this method, the model-expected mean for imputations is derived under the nipocalimab group, but then shifted to be relative to the placebo group of the imputed visit, instead of relative to the nipocalimab group at the visit. Under this approach, nipocalimab participants are considered as not being treated any longer (and therefore being similar to placebo participants). Insofar as a nipocalimab participant's observed values are better (or worse) than those of participants in the nipocalimab group, the mean for imputations for that participant at the imputed visit will tend to be better (or worse) than those observed for the placebo group at the imputed visit.

Additional details pertaining to the multiple imputation methods are in Section 6.20 (Appendix 20).

Step 2 – Analysis

The MMRM described above will be performed for each of the 500 imputed datasets.

Step 3 – Pooling

Rubin's methodology will be applied to the MMRM results from each of the 500 imputed datasets to produce final inferences (Rubin 1987).

5.4. Secondary Endpoints Analysis

5.4.1. Key Confirmatory Secondary Endpoints

For US/ROW and EU, a fixed sequence approach will be applied to adjust for multiplicity and to control Type 1 error across the primary and 5 key secondary endpoints.

For Japan, Type 1 error is controlled over the 3 primary efficacy hypotheses described in Section 5.3.2.3. The testing procedure described here does not apply to Japan.

The 5 key secondary endpoints will be analyzed sequentially and will be considered statistically significant at the 2-sided 0.05 level only if the endpoint is individually significant at the 2-sided 0.05 level and previous endpoints in the hierarchy were significant at the 2-sided 0.05 level, including the primary efficacy endpoint. If the primary efficacy endpoint is statistically significant, the key secondary endpoints will be assessed in the order listed below. Details of definitions and analysis methods are provided in the subsequent sections.

1. Average change from baseline in Quantitative Myasthenia Gravis (QMG) score over Weeks 22 and 24 of the double-blind phase.
2. Percentage of participants whose average MG-ADL total score over Weeks 22, 23, and 24 of the double-blind phase is at least a 2-point improvement compared to baseline.
3. Loading dose response, defined as the percentage of participants with improvement in MG-ADL total score of ≥2 points at Week 1 and/or Week 2 of the double-blind phase.
4. Sustainability of therapeutic response, defined as the percentage of participants with improvement in MG-ADL total score of ≥2 points at Week 4 through Week 24, with no more than 2 non-consecutive excursions allowed at Weeks 6 through 23 (excursions defined as loss of improvement in MG-ADL total score of ≥2 points from baseline).
5. Percentage of participants whose average MG-ADL total score over Weeks 22, 23, and 24 of the double-blind phase is at least a 50% improvement compared to baseline.

5.4.1.1. Definition of Endpoints

5.4.1.1.1. Quantitative Myasthenia Gravis (QMG) Test

The QMG test is a standardized quantitative strength assessment with 13 components (Barohn 1998). It is administered by a trained qualified healthcare professional. For each item a raw score is measured, for example, the number of seconds before double vision occurs on lateral gaze, or the right-hand grip strength in kilograms. The raw score is converted to a 4-point scale score (0 = none, 1 = mild, 2 = moderate, and 3 = severe). See Section 6.13 (Appendix 13) for the definition of each item and how the raw score is converted to a scale score. The QMG is assessed at Screening, Day 1, Weeks 2, 4, 8, 12, 16, 20, 22, and 24 (or end of phase) during the double-

blind phase. Participants who discontinue treatment or modify or discontinue their stable gMG therapy, are expected to continue the double-blind visit schedule until Week 24.

During the OLE phase the QMG is assessed very 4 weeks through Week 24, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

The QMG total score is defined as the sum of the 13 individual item scale scores (range: 0 to 39). If a right or left leg item (seconds leg can be outstretched) score is missing, the missing score will be imputed with the score of the other leg. The total score is missing if any other item is missing. Higher scores indicate greater impairment.

Baseline is defined as the average of the Screening and Day 1 total scores. Change from baseline in QMG total score will be calculated for each post-baseline visit.

The **first** key secondary endpoint is the average change from baseline in the QMG total score over Weeks 22 and 24 of the double-blind phase.

5.4.1.1.2. MG-ADL Key Secondary Endpoints

The **second** key secondary endpoint is the percentage of participants whose average MG-ADL total score over Weeks 22, 23, and 24 of the double-blind phase is at least a 2-point improvement compared to baseline. The average score for a participant is the average of the non-missing values at Weeks 22, 23, and 24. A participant must have a non-missing value at Week 24 and at least 1 non-missing value at Weeks 22 or 23 to have a non-missing average score. A participant with a missing average score will be considered a non-responder.

The **third** key secondary endpoint is the loading dose response, defined as the percentage of participants with improvement in MG-ADL total score of ≥2 points at Week 1 and/or Week 2 of the double-blind phase. A participant with a missing assessment at either Week 1 or Week 2, but not both time points, is defined as a responder if improvement at the non-missing time point is ≥2 points. Participants with missing assessments at both Week 1 and Week 2 will be considered non-responders.

The **fourth** key secondary endpoint is sustainability of therapeutic response, defined as the percentage of participants with improvement in MG-ADL total score of ≥2 points at Week 4 through Week 24, with no more than 2 non-consecutive excursions allowed at Weeks 6 through 23 (excursions defined as loss of improvement in MG-ADL total score of ≥2 points). A participant with a missing assessment at a time point will be considered a non-responder at that time point.

The **fifth** key secondary endpoint is the percentage of participants whose average MG-ADL total score over Weeks 22, 23, and 24 of the double-blind phase is at least a 50% improvement compared to baseline. The average score is calculated in the same way as for the second key secondary endpoint above. A participant with a missing average score will be considered a non-responder.

5.4.1.2. Estimands

5.4.1.2.1. Estimands for QMG Key Secondary Endpoint

Estimands are defined for the QMG key secondary endpoint in the same way as the Primary Estimand for US/ROW, Primary Estimand for EU, and Primary Estimands for Japan are defined for the primary efficacy endpoint (see Section 5.3.2).

5.4.1.2.2. Estimands for MG-ADL Key Secondary Endpoints

The estimands defined below are applicable for all regions.

Study Intervention

- Nipocalimab 30 mg/kg loading dose followed by 15 mg/kg every 2 weeks in addition to stable gMG therapy (or who discontinued MG therapy due to intolerance or lack of efficacy)
- Placebo every 2 weeks in addition to stable gMG therapy

Population: Seropositive participants with gMG who are on stable gMG therapy

Variable: As defined in Section 5.4.1.1.2 for each endpoint

Population level summary: The difference in proportions between the nipocalimab and placebo intervention groups

Intercurrent events (ICEs) and strategies: ICEs of study intervention discontinuation, discontinuation of stable gMG therapy (with or without study intervention discontinuation), and change in stable gMG therapy, whether the ICE occurred because of initiation of rescue therapy or not, are addressed with a composite strategy, with the endpoint defined as "non-response" at timepoints after the ICE according to the definitions in Section 5.4.1.1.2.

5.4.1.3. Analysis Methods

Analysis methods, including sensitivity analyses, for the QMG key secondary endpoint will follow the same approaches defined in Section 5.3.3 for the Primary Estimand US/ROW, Primary Estimand for EU, and Primary Estimands for Japan. Baseline QMG total score will replace baseline MG-ADL total score in the MMRM.

For each of the MG-ADL key secondary endpoints, the percentage of participants who were responders according to the endpoint criteria will be analyzed by Cochran-Mantel-Haenszel tests controlling for the baseline MG-ADL total score randomization strata (≥9, <9), autoantibody status, and region. Between-intervention differences in proportions and 95% Wald confidence intervals (based on the normal approximation) will be provided.

5.4.2. Supportive Secondary Endpoints

5.4.2.1. Definition of Endpoints

5.4.2.1.1. Sustained therapeutic QMG response

Sustained therapeutic QMG response is defined as improvement in the QMG total score from baseline of ≥3 points at Week 2 through Week 24 of the double-blind phase with no more than 2 non-consecutive excursions allowed at Weeks 4 through Week 22 (excursions defined as loss of improvement in QMG total score of ≥3 points from baseline).

5.4.2.1.2. Quality of Life in Neurological Disorders (Neuro-QoL) Fatigue Scale

The Neuro-QoL Fatigue version 1.0 is a 19-item questionnaire developed and validated for use in common neurological conditions which assess patient-reported fatigue and associated impact on physical, mental, and social activities during the past 7 days (Health Measures n.d.). Each item is graded on a 5-point scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always). The Neuro-QoL Fatigue scale is assessed at Day 1; Weeks 2, 4, 8, 12, 16, 20, 22, and 24 (or end of phase) during the double-blind phase. During the OLE phase the Neuro-QoL Fatigue scale is assessed very 4 weeks through Week 24, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

The Neuro-QoL Fatigue total score is defined as the sum of the 19 individual items (range: 19 – 95) and the Neuro-QoL Fatigue short-form total score is the sum of the first 8 items (range: 8 – 40). A total score is missing if any item is missing. Higher scores indicate more fatigue.

Change from baseline (Day 1) in Neuro-QoL Fatigue total score and short-form total score will be calculated for each post-baseline visit.

The secondary endpoint is the average change from baseline in the Neuro-QoL Fatigue total score over Weeks 22 and 24 of the double-blind phase.

5.4.2.1.3. Myasthenia Gravis – Quality of Life (Revised) Instrument (MG-QOL-15r)

The MG-QoL-15r is a 15-item, health-related quality of life measure designed to assess limitations related to living with MG (Burns 2016). Responses to each item are rated by the patient, using a reflection period of "over the past few weeks" on a 3-point scale (0 = not at all, 1 = somewhat, and 2 = very much). See Section 6.14 (Appendix 14) for a list of the 15 items. The MG-QoL-15r is assessed at Day 1, Weeks 2, 4, 6, 8, 12, 16, 20, 22, and 24 (or end of phase) during the double-blind phase. During the OLE phase MG-QoL-15r is assessed every 4 weeks through Week 24, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

The MG-QoL-15r total score is defined as the sum of the 15 individual items (range: 0 – 30). The total score is missing if any item is missing. Higher scores indicate more limitation.

Change from baseline (Day 1) in MG-QoL-15r total score will be calculated for each post-baseline visit.

The secondary endpoint is the average change from baseline in MG-QoL-15r total score over Weeks 22 and 24 of the double-blind phase.

5.4.2.1.4. European Quality of Life Group, 5 Dimension, 5 Level Questionnaire (EQ-5D-5L)

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It is a descriptive system comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (Level 1 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating severe problems, and Level 5 indicating extreme problems) (EuroQol 2021, EuroQol 2019). The EQ-5D-5L is assessed at Day 1, Weeks 2, 4, 8, 12, 16, 20, 22, and 24 (or end of phase) during the double-blind phase. During the OLE phase the EQ-5D-5L is assessed very 4 weeks through Week 24, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

Participants select an answer for each of the 5 dimensions considering the response that best matches their health "today". Individual scores from the 5 dimensions will be used to obtain a weighted health status index as follows:

- Scores from each dimension will be combined to obtain a 5L profile score, e.g., a score of 1 for each dimension will give a 5L profile score of 11111. Dimension scores will be combined in the following order: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression.
- A participant's HSI will be determined by matching the participant's 5L profile score with the HSI score for that profile using the value set developed for Canada (Xie 2016).

EQ-5D-5L also includes a visual analog scale (VAS) on which participants rate their health from 0 = "Worst imaginable health state" to 100 = "Best imaginable health state".

Change from baseline (Day 1) will be calculated for the HSI and the VAS at each post-baseline time point.

5.4.2.2. Analysis Methods

Supportive secondary endpoints will be summarized with descriptive statistics, estimates, and 95% confidence intervals using the primary efficacy analysis set and the full analysis set. Descriptive statistics for categorical parameters include N and percent (%). Descriptive statistics for continuous parameters include N, mean, SD, median, minimum, and maximum.

Between-intervention differences in proportions of participants with sustained therapeutic QMG response will be calculated and 95% Wald confidence intervals of the difference (based on the normal approximation) will be provided.

Analysis of the Neuro-QoL Fatigue total score, Neuro-QoL Fatigue short-form total score, and the MG-QoL-15r total score will follow the approach described for the primary efficacy endpoint under the Primary Estimand for US/ROW (hypothetical strategy for ICEs and MAR assumption).

That is, an MMRM with factors for study intervention group, autoantibody status ("anti-AChR positive or anti-MuSK positive" or "anti-AChR negative and anti-MuSK negative", as randomized), region, week, and study intervention group-by-week interaction; the endpoint baseline score as a covariate; and participant as a random effect. The between-group difference of the average change over Weeks 22 and 24 and its 95% confidence interval will be estimated by a linear contrast that averages the change from baseline over those time points. Least squares mean estimates, with 95% confidence intervals, of change from baseline at each time point will be provided and displayed graphically over time by intervention group.

For EQ-5D-5L, the frequency distribution of scores for each item (Mobility, Self-Care, etc.) will be summarized at each time point in the double-blind phase by study intervention group. Values and changes from baseline at each time point in the double-blind phase for the HSI and the VAS will be summarized with descriptive statistics by study intervention group

5.5. Tertiary/Exploratory Endpoint(s) Analysis

Tertiary/exploratory endpoints will be summarized with descriptive statistics and will use the primary efficacy analysis set unless specified otherwise. Descriptive statistics for categorical parameters include N and percent (%). Descriptive statistics for continuous parameters include N, mean, SD, median, minimum, and maximum.

5.5.1. Subgroup Analyses

See Section 5.7.8 for the definition of subgroup variables. Subgroup analyses of MG-ADL total score will be performed under the Primary Estimand for US/ROW. For each subgroup analysis, the subgroup variable will be added as a main effect to the MMRM model defined in Section 5.3.3 and study intervention-by-subgroup variable and study intervention-by-time point-by-subgroup variable interaction terms will also be added. The between-intervention difference of the average change from baseline over Weeks 22, 23, and 24 at each level of the subgroup variable, and its 95% confidence interval, will be estimated from the MMRM with a linear contrast. Estimates and 95% confidence intervals will be displayed with forest plots, including only those levels of the subgroup variables with ≥5 participants in each study intervention group. When country/territory is the subgroup variable, region will be removed from the MMRM. When specific autoantibody status (negative, anti-AChR+, anti-MuSK+, or anti-LRP4+) is the subgroup variable, autoantibody status as randomized ("anti-AcHR positive or anti-MuSK positive" vs. "anti-AChR negative and anti-MuSK negative') will be removed from the MMRM. When specific autoantibody status (negative, anti-AChR+, anti-MuSK+, or anti-LRP4+) or autoantibody positive/negative is the subgroup variable, the full analysis set will be used.

5.5.1.1. Subgroup analysis based on serostatus

Additional analyses will be performed based on the serostatus subgroup variables (autoantibody status [seropositive or seronegative]; and specific autoantibody [anti-AChR+, anti-MuSK+, anti-LRP4+, or seronegative]).

Subgroup analysis of QMG total score (first key secondary endpoint; see Section 5.4.1.1.1 for definition) will be performed under the Primary Estimand for US/ROW in a similar manner as described above for MG-ADL.

Subgroup analysis will also be performed for MG-ADL response over Weeks 22, 23, and 24 (second key secondary endpoint; see Section 5.4.1.1.2 for definition). The between-intervention difference in proportions and 95% Wald confidence interval will be calculated for each subgroup.

The following additional approaches to assess the consistency of the study intervention difference for MG-ADL total score in the seronegative subgroup compared to the seropositive and overall populations (Alosh 2017) will be conducted if the study intervention difference under the primary estimand, with seropositive participants as the population, and under the estimand with seropositive and seronegative participants as the population (the 'overall' population) are both statistically significant in favor of nipocalimab:

- A one-sided test of the study intervention-by-subgroup interaction effect in the MMRM model specified in Section 5.5.1 (with the alternative hypothesis being that the study intervention difference in the seropositive group is greater than in the seronegative group) will be conducted with significance level of 0.15. The larger significance level is chosen to account for the reduced power of this test.
- An MMRM analysis for the seronegative subgroup will be conducted using the same methodology described for the primary estimand for US/ROW (Section 5.3.3). The one-sided p-value for the primary efficacy endpoint in this analysis will be compared to a supportive assessment criterion, α_s. The supportive assessment criterion is based on the proportion of seronegative participants in the overall population and the pre-specified significance level and power for the study (0.05 and 0.90, in this case) and is calculated as:

$$\alpha_s = 1 - \Phi\left((N_s/N)^{1/2} * \left(z_{1-\alpha} + z_{1-\beta}\right) - z_{1-\beta}\right)$$

  Where N_s is the number of seronegative participants, N is the number of participants in the overall population, $z_{1-\alpha}$ = 1.96 (for one-sided 0.025 significance level), $z_{1-\beta}$ = 1.28 (for power of 0.90) and $\Phi(.)$ is the cumulative distribution function of the normal distribution. The final criterion will be based on the actual sample sizes. Assuming seronegative participants are approximately 25% of the overall population, the supportive assessment criterion (α_s) would be 0.367. If the p-value of the between-group difference in the seronegative subgroup is less than α_s, it can be concluded that the study intervention difference in the seronegative subgroup is supportive of the overall population.

5.5.2. Response in the Double-blind Phase

Consistent with the composite strategy for addressing ICEs for the response key secondary endpoints, participants will be considered "non-responders" or "without symptom remission" at timepoints after an ICE and for any other timepoint with a missing assessment for each of the endpoints defined below.

Summaries of response in the double-blind phase will use both the primary efficacy analysis set and the full analysis set.

The number and percentage of participants with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥8 point improvement in MG-ADL total score, as well as the number and percent of participants with ≥2 point improvement ("MG-ADL responder"), will be summarized at each timepoint in the double-blind phase by study intervention group. Similar summaries will be provided for QMG total score based on categories of 3-, 4-, 5-, 6-, 7-, 8-, or ≥9 point improvement as well as for ≥3 point improvement ("QMG responder"). The distribution of improvement in MG-ADL and QMG total scores will be displayed graphically using "Christmas tree" plots (cumulative distribution) and bar charts (frequency distribution). Figures will be provided for Weeks 1, 2, 22, 23, and 24 for MG-ADL, and Weeks 1, 22 and 24 for QMG.

The number and percentage of participants who were both an MG-ADL responder and a QMG responder will be summarized at each time point when both assessments were performed.

An additional QMG responder parameter is defined as the average QMG total score over Weeks 22 and 24 of the double-blind phase being at least a 3-point improvement compared to baseline. The average score for a participant is the average of the non-missing values at Weeks 22 and 24. A participant must have a non-missing value at Week 24. A participant with a missing average score will be considered a non-responder.

Additional sustained response parameters for MG-ADL and QMG are defined similar to the definitions above (Section 5.4.1.1.2 and Section 5.4.2.1.1, respectively), but starting from Week 2 for MG-ADL and starting from Week 4 for QMG. No more than 2 non-consecutive excursions are allowed from Week 4 to Week 23 for MG-ADL and from Week 8 to Week 22 for QMG.

The number and percentage of participants who were MG-ADL responders at both Week 2 and Week 24 will be summarized. Observations at these time points that are after an ICE or are otherwise missing will be considered as not meeting the 2-point improvement criteria.

The number and percentage of participants with <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100% improvement in MG-ADL total score, as well as the number and percentage of participants with ≥50% improvement, will be summarized at each timepoint in the double-blind phase by study intervention group. Similar summaries will be provided for QMG total score. The distribution of percent improvement in MG-ADL and QMG total scores will be displayed graphically using "Christmas tree" plots (cumulative distribution) and bar charts (frequency distribution). Figures will be provided for Weeks 1, 2, 22, 23, and 24 for MG-ADL, and Weeks 1, 22 and 24 for QMG.

The cumulative distribution functions (CDF) of change and percent change from baseline in the MG-ADL total score and the QMG total score will be displayed graphically by intervention group at Weeks 1 (MG-ADL only), 2, 22, 23 (MG-ADL only), and 24.

The distribution of the time to first occurrence of an MG-ADL total score improvement of ≥2 points in the double-blind phase will be displayed with Kaplan-Meier curves. The visit date of the first occurrence will be used in the time to event calculation. Participants who did not have MG-ADL total score improvement of ≥2 points in the double-blind phase will be censored and the date

of last visit in the double-blind phase will serve as the time of censoring. Participants with an intercurrent event will be censored at the last visit date before the ICE. A similar analysis will be conducted for time to first occurrence of an MG-ADL total score of 0 or 1 in the double-blind phase; this analysis will be performed stratifying by baseline MG-ADL total score (≤9, >9).

The number and percentage of participants with an MG-ADL total score of 0 or 1 (minimum symptom expression) will be summarized at each timepoint in the double-blind phase by study intervention group. The number and percentage of participants with minimum symptom expression at any time point, at ≥50% of all time points, and at ≥75% of all time points during the double-blind phase will also be summarized.

5.5.3. Fatigue

The Patient Global Impression of Severity (PGI-S) of fatigue asks the participant to rate the severity of fatigue over the past 7 days on a 5-point scale (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe). The Patient Global Impression of Change (PGI-C) asks the participant to rate the overall change in fatigue since the first visit on a 7-point scale (1 = much better, 2 = moderately better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = moderately worse, 7 = much worse). PGI-S is assessed at Day 1, Weeks 2, 4, 8, 12, 16, 20, 22, and 24 during the double-blind phase. During the OLE phase, PGI-S is assessed every 4 weeks through Week 24, then every 12 weeks, at the end of treatment visit, and at the end of study visit. PGI-C is assessed at the same visits, except not at Day 1.

The frequency distribution of PGI-S and PGI-C scores will be provided for each timepoint in the double-blind phase by intervention group. Observations after an ICE will not be included.

At selected timepoints during the double-blind phase participants will be classified as none/mild or moderate/severe/very severe based on the PGI-S and improved (much, moderately, or a little better) or not improved (no change, a little worse, moderately worse, or much worse) based on the PGI-C. At each timepoint, descriptive statistics of the Neuro-QoL Fatigue total score change from baseline and the Neuro-QoL Fatigue short-form total score change from baseline will be provided by PGI-S or PGI-C category and intervention group.

The cumulative distribution function (CDF) of the change from baseline in the Neuro-QoL Fatigue total score and the Neuro-QoL Fatigue short-form total score will be displayed graphically by intervention group at selected time points.

5.5.4. Myasthenia Gravis Foundation of America (MGFA) Classification

The MGFA system classifies a patient's MG severity into one of 5 classifications of increasing severity from Class I (ocular muscle weakness only) to Class V (the patient is intubated) (Jaretzki 2000). Classes II through IV are each further divided into 2 subclasses ('a' or 'b') based on which muscle groups are primarily affected (see Section 6.16 [Appendix 16]). The MGFA classification is assessed at Screening, Day 1, Week 12, and Week 24 (or end of phase) in the double-blind phase and every 12 weeks in the OLE phase.

The distribution of the MGFA classification in the double-blind phase will be summarized with the number and percentage of participants with each value at each time point by intervention group. The shift from baseline MGFA classification to the classification at each post-baseline time point will also be summarized.

5.5.5. Open-label Extension (OLE) Phase

Summaries of results for participants who entered the OLE phase will be presented by the Placebo/Nipocalimab, Nipocalimab/Nipocalimab, and Nipocalimab (OL) groups based on the seropositive efficacy analysis set (OL) and the full analysis set (OL) and will include double-blind and OLE phase time points.

Baseline for randomized participants is always the double-blind phase baseline. Baseline for participants who entered the OLE phase directly is the OLE phase Day 1 visit.

MG-ADL total score, QMG total score, Neuro-QoL Fatigue total score, PGI-S, MG-QoL-15r total score, EQ-5D-5L HSI, and EQ-5D-5L VAS will be summarized with descriptive statistics of the value and change from baseline over time. Plots of means and mean changes over time from baseline through the OLE phase (including double-blind phase timepoints for randomized participants) will be provided. CCI [redacted]

The number and percentage of participants with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥8 point improvement in MG-ADL total score, as well as the number and percent of participants with ≥2 point improvement ("MG-ADL responder") will be summarized at each timepoint. Similar summaries will be provided for QMG total score based on categories of 3-, 4-, 5-, 6-, 7-, 8-, or ≥9 point improvement as well as for ≥3 point improvement ("QMG responder"). CCI [redacted]

The number and percentage of participants with an MG-ADL total score of 0 or 1 (minimum symptom expression) will be summarized at each timepoint.

The frequency distribution of PGI-S, PGI-C, MGFA classification, and level of responses for each of the EQ-5D-5L health dimensions will also be summarized at each time point.

5.6. Safety Analyses

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

The number and percentage of participants who receive study intervention will be summarized for both the double-blind and OLE phases.

Descriptive statistics for duration of double-blind study intervention (N, mean, SD, median, and range (minimum, maximum)) using the safety (DB) and primary efficacy analysis sets; total duration of nipocalimab treatment over the double-blind and OLE phases using the "all nipocalimab" analysis set; and duration of follow-up using the safety (DB) analysis set, will be summarized. Participant-years of intervention are calculated as days of intervention/365.25 and will be calculated based on double-blind study intervention duration and total nipocalimab duration over the double-blind and OLE phases. Each definition of participant-years will be presented by intervention group using the safety (DB) and primary efficacy analysis sets for participant-years in the double-blind period and using the "all nipocalimab" analysis set for participant-years of total nipocalimab duration.

Double-blind study intervention duration is defined as (date of last dose of double-blind study intervention – date of first dose of double-blind study intervention) +1.

Total duration of nipocalimab treatment is defined as (date of last dose of nipocalimab in the study – date of first dose of nipocalimab in the study (either in the double-blind or OLE phase)) + 1.

Follow-up duration is defined as (date of last study visit or last study contact (whichever is later) – date of first dose of study intervention) +1.

Descriptive statistics will be presented for the following parameter based on double-blind study intervention and based on total nipocalimab treatment over both the double-blind and OLE phases:

- Number of administrations

Total nipocalimab duration in categories of ≤3 months [≤90 days]; >3 to <6 months [>90 days to <180 days]; ≥6 to <12 months [≥90 days to <360 days]; ≥12 to <18 months [≥360 days to <540 days]; ≥18 to <24 months [≥540 days to <720 days]; or ≥24 months [≥720 days] will be summarized. The total number of participants with ≥6 months [≥180 days] and ≥12 months [≥360 days] total nipocalimab duration will also be summarized.

A listing of participants with an infusion interruption or change in infusion flow rate will be provided.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summary tables will be provided for treatment-emergent adverse events (TEAEs) separately for each phase (double-blind or OLE) and for AEs that were treatment-emergent after any nipocalimab exposure in either phase (using the "all nipocalimab" analysis set):

- AEs
- Serious AEs (SAEs)
  - Related SAEs
- AEs leading to discontinuation of study intervention/termination of study participation
- AEs by severity
  - Severe AEs
- AEs by relationship to study intervention
- AEs of special interest (AESI)
  - Infections that are severe or require IV anti-infective or operative/invasive intervention
  - Hypoalbuminemia with albumin <20 g/L
- AEs of clinical interest
  - Infusion reactions
  - Infusion site reaction
  - Opportunistic infections
  - Hypersensitivity reactions
  - Anaphylactic reactions or serum sickness reactions
  - Suicidal ideation/behavior
  - Potentially associated with glucocorticoid toxicity
  - Activation of latent virus
  - Potentially abuse-related
  - Hyperlipidemia
  - Myasthenia gravis

Additional summaries of adverse events potentially associated with glucocorticoid toxicity by concomitant steroid use (yes/no) and by relationship to steroids (as recorded in the CRF by the investigator) will be provided. For participants who were taking steroids at the start of the OLE the following additional summaries of adverse events potentially associated with glucocorticoid toxicity will be provided:

- The number and percentage of participants with AEs in the OLE by onset of the event relative to the first steroid dose reduction (before or after) in participants with a steroid dose reduction.
- The number and percentage of participants with AEs in the OLE by subgroups of participants defined by the occurrence of a steroid dose reduction in the OLE (yes or no).

In addition to the summary tables, listings will be provided for the following:

- SAEs
- AEs leading to discontinuation of study intervention/termination of study participation
- Deaths
- AEs of special interest
- Infusion reactions
- Infusion site reaction
- Opportunistic infections
- Anaphylactic reactions or serum sickness reactions
- Suicidal ideation/behavior
- Potentially associated with glucocorticoid toxicity
- Activation of latent virus
- Potentially associated with abuse liability
- Hyperlipidemia
- Myasthenia gravis
- Major cardiovascular events (non-fatal myocardial infarction, stroke, and cardiovascular death, identified through independent adjudication committee)

See Section 6.8 (Appendix 8) for the definitions of adverse events in each special interest and clinical interest categories.

A summary of the independent MACE adjudication committee's classification of the events provided to them for review will also be provided.

Since safety should be assessed relative to exposure and follow-up, most AE summary tables will include average number of study agent administrations and average weeks of follow-up for each intervention group.

Treatment-emergent AEs, SAEs, and AESI will be summarized by minimum decreases from baseline in IgG (≤25%, >25% to ≤50%, >50% to ≤75%, >75%) and by minimum IgG levels <1, ≥1 to <3, ≥3 to ≤6, >6 g/L). Events that are summarized are those that occurred since previous dosing prior to the date of minimum IgG level until the end of the phase. Additionally, IgG values over time will be plotted for those participants who experience an AESI or had a treatment-emergent AE of "Myasthenia gravis" or "Myasthenia gravis crisis".

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety (DB), safety (OL), safety, and "all nipocalimab" analysis sets.

The following analytes will be collected:

- Hematology: hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH)%, corpuscular volume (MCV), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils).
- Clinical chemistry: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, creatine phosphokinase (CPK), gamma-glutamyltransferase (GGT), glucose, lactic acid dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein.
- Lipid panel: total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides. The ratio of HDL to total cholesterol (HDL/total cholesterol) will be calculated. Only fasting lipid samples will be included in summaries.
- Urinalysis: dipstick (blood, glucose, protein).

The descriptive statistic summaries by time point described below will be presented for the double-blind and OLE phases by the Placebo/Nipocalimab, Nipocalimab/Nipocalimab, and Nipocalimab (OL) groups based on the safety analysis set.

Baseline for randomized participants is always defined as the double-blind phase Day 1 visit. Baseline for participants who entered the OLE phase directly is the OLE phase Day 1 visit.

Descriptive statistics will be presented for chemistry and hematology laboratory tests at scheduled time points.

Change from baseline to each scheduled time point will be summarized for chemistry and hematology tests and displayed by intervention group. Descriptive statistics will be provided for percent change from baseline to each scheduled time point for albumin, cholesterol, HDL, LDL, HDL/cholesterol ratio, and triglycerides by intervention group. Boxplots and plots of mean (±SE) value, change, and percent change from baseline to each scheduled time point will be provided for albumin, cholesterol, HDL, LDL, HDL/cholesterol ratio, and triglycerides. Plots of mean (±SE) value and change to each scheduled time point will be presented for ALT, AST, and total bilirubin.

For the categorical shifts and frequency of markedly abnormal values described below, summaries based on the safety (DB) analysis set will involve only double-blind phase time points; summaries based on the safety (OL) analysis set will involve only OLE phase time points; and summaries based on the "all nipocalimab" analysis set will involve all time points when nipocalimab was an assigned intervention in either the double-blind or OLE phases.

Shift tables will be provided summarizing the shift in select laboratory values from baseline to the maximum post-baseline value and to the minimum post-baseline value with respect to the normal range criteria (low, normal, high).

Markedly abnormal criteria will be applied to baseline and post-baseline values and are provided in Section 6.10 (Appendix 10). The number and percentage of participants with treatment-emergent markedly abnormal values at any time, and by time point, will be presented by intervention group. A listing of markedly abnormal laboratory values will be provided. Additionally, abnormal laboratory findings to be reported for albumin and liver enzyme tests are described below. For criteria that do not include an increase or decrease from baseline, postbaseline abnormalities will be compared with their corresponding baseline result. Specifically, if the postbaseline value is above the upper limit and the baseline value is below the upper limit (e.g., Normal or Low), then the postbaseline abnormality will be considered treatment-emergent (TE). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (e.g., Normal or High). If the baseline value is missing, a postbaseline abnormality will always be considered TE.

- Albumin: <20 g/L
- ALT, AST: >1xULN; ≥3xULN; ≥5xULN; ≥10xULN; ≥20xULN
- ALP: >1xULN; ≥3xULN; ≥5xULN; ≥10xULN; ≥20xULN
- Bilirubin: ≥2xULN

A listing of participants meeting biochemical Hy's law criteria will be provided:

- ALT or AST ≥3xULN and
- ALP <2xULN and
- Total bilirubin ≥3xULN or INR >1.5 (if measured)

5.6.3.2. Vital Signs and Physical Examination Findings

Continuous vital signs parameters including temperature, weight, pulse, and blood pressure (systolic and diastolic) will be summarized at each assessment time point. Change from baseline will be summarized at each assessment time point. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for the double-blind and OLE phases by the Placebo/Nipocalimab, Nipocalimab/Nipocalimab, and Nipocalimab (OL) groups based on the safety analysis set.

Baseline for randomized participants is always defined as the double-blind phase Day 1 visit. Baseline for participants who entered the OLE phase directly is the OLE phase Day 1 visit.

For the frequency of markedly abnormal values described below, summaries based on the safety (DB) analysis set will involve only double-blind phase time points; summaries based on the safety (OL) analysis set will involve only OLE phase time points; and summaries based on the "all

nipocalimab" analysis set will involve all time points when nipocalimab was an assigned intervention in either the double-blind or OLE phases.

Abnormality criteria (based on criteria in Table 4) will be applied to baseline and postbaseline values. For baseline values, increase or decrease criteria are not applied.

Postbaseline values will be considered treatment-emergent (TE) if they meet both value and change criteria in Table 4.

For criteria that do not include an increase or decrease from baseline:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (e.g., Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (e.g., Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Incidence of TE markedly abnormal vital signs during intervention will be summarized. A listing of participants with markedly abnormal vital signs will be presented. Markedly abnormal criteria are defined in Table 4 below.

Table 4: Markedly Abnormal Vital Signs Criteria

Vital Sign	Criteria
Pulse	≥120 bpm and with ≥15 bpm increase from baseline
	≤50 bpm and with ≥15 bpm decrease from baseline
Systolic blood pressure	160 mm Hg and with ≥20 mm Hg increase from baseline
	≤90 mm Hg and with ≥20 mm Hg decrease from baseline
Diastolic blood pressure	≥100 mm Hg and with ≥15 mm Hg increase from baseline
	≤50 mm Hg and with ≥15 mm Hg decrease from baseline
Temperature	>38°C
	< 36°C

The number and percentage of participants with at least one post-baseline pulse <60 bpm and >100 bpm; post-baseline systolic blood pressure <90 mmHg, >140 mmHg, and >160 mmHg; and post-baseline diastolic blood pressure <50 mmHg, >90 mmHg, and >100 mmHg will also be summarized.

The number and percentage of participants with ≥7% increase from baseline weight and with ≥7% decrease from baseline weight will be summarized.

A listing of abnormal findings on physical examination will be provided.

5.6.3.3. Electrocardiogram

The ECG parameters that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: Bazett's formula (QTcB) and Fridericia's formula (QTcF).

- Bazett's formula: QTcB (msec) = QT (msec) / (RR (msec)/1000)$^{1/2}$; if RR is missing, use QT (msec) * (HR (bpm)/60)$^{1/2}$
- Fridericia's formula: QTcF (msec) = QT (msec) / (RR (msec)/1000)$^{1/3}$; if RR is missing, use QT (msec) * (HR (bpm)/60)$^{1/3}$

Summaries of results by time point described below will be presented for the double-blind and OLE phases by the Placebo/Nipocalimab, Nipocalimab/Nipocalimab, and Nipocalimab (OL) groups based on the safety analysis set.

Baseline for randomized participants is always defined as the double-blind phase Day 1 visit. Baseline for participants who entered the OLE phase directly is the OLE phase Day 1 visit.

For the frequency of shifts to maximum or minimum values, summaries based on the safety (DB) analysis set will involve only double-blind phase time points; summaries based on the safety (OL) analysis set will involve only OLE phase time points; and summaries based on the "all nipocalimab" analysis set will involve all time points when nipocalimab was an assigned intervention in either the double-blind or OLE phases.

The number and percentage of participants with abnormal QTc interval will be summarized at each scheduled time point. The number and percentage of participants with QTc interval increases from baseline to the maximum postbaseline value will be summarized. Refer to the following table for summary categories.

Criteria for Abnormal QTc Values and Changes from Baseline	
QTc value	<=450
	>450 – 480
	>480 – 500
	>500
QTc change from baseline	<=30
	>30 – <=60
	> 60

A shift table will be provided summarizing the shift from baseline to maximum QTc interval classification.

Descriptive statistics of ECG parameters and change from baseline will be summarized at each scheduled time point.

Abnormality criteria (based on criteria defined below) will be applied to baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- Treatment-emergent will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (e.g., Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (e.g., Normal or High).

- If the baseline value is missing, a postbaseline abnormality will always be considered as treatment-emergent.

The number and percentage of participants with treatment-emergent ECG values outside predefined limits (relative to baseline) will be presented by intervention group:

- Heart rate (bpm): <50 and >100
- PR interval (msec): <120 and >200
- RR interval (msec): <600 and >1200
- QRS interval (msec): >120
- QTc (msec): >500

The interpretation of the ECGs as determined by the central ECG service will be displayed by the number and percentage of participants meeting the abnormality criteria. The interpretation will be summarized over time. Findings from the ECGs as determined by the central ECG service will be displayed by the number and percentage of participants with at least one occurrence of each finding separately for each phase (double-blind or OLE) and for findings that were treatment-emergent after any nipocalimab exposure in either phase (using the "all nipocalimab" analysis set).

A listing of participants with QTc >450 msec or QTc change from baseline >30 msec will also be provided.

5.6.3.4. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a semi-structured clinician-administered questionnaire designed to solicit the occurrence, severity, and frequency of suicide-related ideation and behaviors during the assessment period.

The following are C-SSRS categories and have binary responses (yes/no). Each category is based on a direct question in the C-SSRS. The categories are ordered by increasing seriousness.

Suicidal Ideation (1-5)

- Category 1: Wish to be dead
- Category 2: Non-specific active suicidal thoughts
- Category 3: Active suicidal ideation with any methods (not plan) without intent to act
- Category 4: Active suicidal ideation with some intent to act, without specific plan
- Category 5: Active suicidal ideation with specific plan and intent

Suicidal Behavior (6-10)

- Category 6: Preparatory acts or behavior
- Category 7: Aborted attempt
- Category 8: Interrupted attempt

- Category 9: Non-fatal suicide attempt
- Category 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).

The shift from baseline category to worst post-baseline category will be summarized with categories defined as 'no suicidal ideation or behavior', 'suicidal ideation', and 'suicidal behavior'. Summaries based on the safety (DB) analysis set will involve only double-blind phase time points; summaries based on the safety (OL) analysis set will involve only OLE phase time points; and summaries based on the "all nipocalimab" analysis set will involve all time points when nipocalimab was an assigned intervention in either the double-blind or OLE phases.

A listing of participants with suicidal ideation or suicidal behavior will be provided.

5.6.3.5. Infusion site reaction assessment

The frequency distribution of the type of reaction (No reaction, Erythema/Redness, Induration, Tenderness, Induration or Swelling, or Other) will be summarized at each scheduled time point and post-infusion time (30 minutes, 1 hour) by intervention group. Summaries will be presented for the double-blind and OLE phases by the Placebo/Nipocalimab, Nipocalimab/Nipocalimab, and Nipocalimab (OL) groups based on the safety analysis set.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Blood samples for measuring serum nipocalimab concentrations are to be collected from all participants at scheduled visits as indicated in the Schedule of Activities in the protocol.

PK analyses will be performed on the pharmacokinetics analysis set, defined as participants who have received at least 1 complete dose of nipocalimab in either the double-blind or OLE phase and have at least 1 valid post-dose blood sample drawn for serum nipocalimab concentration. Summaries will be presented by the Placebo/Nipocalimab, Nipocalimab/Nipocalimab, and Nipocalimab (OL) groups and will include only time points when nipocalimab was an assigned intervention (that is, post-baseline time points in the double-blind phase will not be included for the Placebo/Nipocalimab group).

Descriptive statistics (N, arithmetic mean, SD, median, range, coefficient of variation [CV%] and IQ range) will be used to summarize serum nipocalimab concentrations at each scheduled sampling time point. The PK concentration data may be displayed graphically, such as mean (±SD) and/or median (±IQ range) serum nipocalimab concentrations over time by intervention group.

Additional summaries of serum nipocalimab concentrations will include:

- Summary of serum nipocalimab concentrations at each specified sampling time point by baseline weight (<80 kg, ≥80 kg).

- Summary of serum nipocalimab concentrations at each specified sampling time point by age group (e.g., <65 years and ≥65 years).
- Summary of serum nipocalimab concentrations at each specified sampling time point by autoantibody status at baseline (positive and negative) and by specific autoantibody status at baseline (anti-AChR positive, anti-MuSK positive, anti-LRP4 positive, and negative).
- Summary of serum nipocalimab concentrations at each specified sampling time point by sex.
- Median (±IQ range) serum nipocalimab concentrations over time by baseline weight
- Median (±IQ range) serum nipocalimab concentrations over time by age
- Median (±IQ range) serum nipocalimab concentrations over time by autoantibody status at baseline (positive and negative) and by specific autoantibody status at baseline (anti-AChR positive, anti-MuSK positive, anti-LRP4 positive, and negative)
- Median (±IQ range) serum nipocalimab concentrations over time by sex

In addition, serum nipocalimab concentrations will be summarized by anti-drug antibody (ADA) status (positive and negative) (see Section 5.7.2.1).

Serum nipocalimab concentrations may also be summarized by other baseline characteristics, such as MG-ADL score at baseline (e.g., ≤9 and >9), region (East Asia, United States [US], rest of world), concomitant use of immunosuppressants, or by MG-ADL response status (e.g., ≥2-point improvement and <2-point improvement) at Week 24.

A population PK analysis using a nonlinear mixed-effects modeling approach will be used to characterize the disposition characteristics of nipocalimab in the current study. Data may be combined with those of other selected studies to support a relevant structural model. The clearance (CL) and volume of distribution (V) values will be estimated. The influence of important variables (such as body weight, age, and antibodies to nipocalimab) on the population PK parameter estimates will be evaluated. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate technical report.

Data handling guidelines

Unless otherwise specified, the following data handling guidelines will be applied to PK analyses:

- All serum nipocalimab concentration summaries for a particular sampling time point will include data obtained from treated participants at the time point of interest without imputing any missing concentration data, i.e, data summaries will be based on observed data.
- All serum nipocalimab concentrations below the lower limit of quantification (<LLOQ) or missing data will be labelled as such in the concentration data listings and SDTM data.
- All serum nipocalimab concentrations below the LLOQ will be imputed as zero in the summary statistics.
- The concentration data from a participant who meets one of the following dosing deviation criteria will be excluded from the by-time point data analyses from that time point onwards (note that serum nipocalimab concentrations prior to the first of the below events will be included in the summaries):

- Discontinued nipocalimab administrations
- Skipped a nipocalimab administration
- Received incomplete/incorrect dose
- Received incorrect study agent
- Received additional dose (i.e., received more than 1 nipocalimab infusion within the scheduled nipocalimab dosing window)

In addition, if a participant has an administration outside the ±3 days dosing window, the concentration data collected at and after that event will be excluded from the by-timepoint analyses. A concentration will be excluded if: (1) a pre-infusion sample was actually taken after nipocalimab administration (based on date/time) or (2) a concentration fell outside the pre-defined statistical range of mean ±10*SD of the concentration values obtained at the same protocol-specified sampling time point (SOP-07946-GXP). Additional exclusions of concentration data are to be implemented based on TV-GDL-00362. All participants and samples excluded from analysis will be document in the Clinical Study Report.

If there were multiple samples collected prior to an infusion, the closest sample before the infusion will be used. If a sample time or an infusion time was missing, the date will not be used. If the sampling time was the same as the infusion time, the sample will be included in the statistical summary.

5.7.2. Immunogenicity

Blood samples are to be collected for the detection of antibodies to nipocalimab at specified visits as indicated in the Schedule of Activities in the protocol.

“Sample ADA status” and sample titer as well as the cumulative “participant ADA status” and peak titer through the visit will be coded and provided by the bioanalytical group.

5.7.2.1. Participant ADA Classification

Participants evaluable for immunogenicity are defined as participants who received at least 1 dose of nipocalimab and had at least 1 post-treatment serum sample evaluable for antibodies to nipocalimab.

Results from the analysis of anti-drug antibodies (ADA) to nipocalimab will be classified as positive or negative for treatment-emergent ADA.

Participants who were positive for treatment-emergent antibodies to nipocalimab will include participants with treatment-boosted or treatment-induced antibodies to nipocalimab at any time after their first nipocalimab administration in the study (Shankar 2014):

- Participants with treatment-induced antibodies to nipocalimab have a negative ADA sample prior to nipocalimab administration and at least one post-treatment sample positive for ADA. For participants randomized to placebo in the double-blind phase, the reference sample is the last sample collected prior to the first nipocalimab administration in the OLE phase.

- Participants with treatment-boosted antibodies to nipocalimab have a positive ADA sample prior to nipocalimab administration and at least one post-treatment sample positive for ADA with titer at least 2-fold higher than the titer of the baseline sample. For participants randomized to placebo in the double-blind phase, the reference sample is the last sample collected prior to the first nipocalimab administration in the OLE phase.

Participants who were negative for treatment-emergent ADA will include participants with no post-treatment samples positive for ADA, participants with post-treatment samples positive for ADA with titers remaining the same as the baseline titers, or participants with post-treatment samples positive for ADA with reduced or disappeared titers. Participants who had a positive ADA sample prior to nipocalimab administration but had no appropriate samples available for immunogenicity assessment after study intervention will be classified as "participants with baseline ADA samples only".

5.7.2.2. Immunogenicity Analyses

The summary and analysis of antibodies to nipocalimab will be based on the observed data; therefore, no imputation of missing data will be performed.

Note, participant status is through each visit, thus, participant status and peak titers may change as the study progresses over time. Therefore, the "subject ADA status" at a visit represents the cumulative ADA status through that visit. A participant who has a negative ADA status through the last visit included in the database lock after the last participant, last visit of the double-blind phase, may have a positive ADA status through the last visit included in the final database lock after the last participant, last visit of the open-label phase. Peak titers can also change (increase) if a higher titer occurs after the initial database lock.

The summary of participants with baseline positive ADA samples will be based on the sample ADA status (positive or negative) at baseline. There will be no participant level ADA status at baseline.

Incidence of antibodies to nipocalimab (evaluable, treatment-emergent ADA positive, treatment-emergent ADA negative) and peak titers of ADA will be summarized using the Immunogenicity analysis set. Summaries will be presented by the Placebo/Nipocalimab, Nipocalimab/Nipocalimab, and Nipocalimab (OL) groups, and overall, and will involve all visits in either the double-blind or OLE phases, including follow-up safety visits, except visits in the double-blind phase for participants randomized to placebo.

Incidence of antibodies to nipocalimab and peak titers of ADA may also be summarized by baseline weight (e.g., <70 kg and ≥70 kg), age group (e.g., <65 years and ≥65 years), autoantibody status at baseline (positive and negative), specific autoantibody status (anti-AChR positive, anti-MuSK positive, anti-LRP4 positive, and negative), MG-ADL score at baseline (e.g., ≤9 and >9), region (East Asia, United States [US], rest of world), concomitant use of immunosuppressants, or by MG-ADL response status (e.g., ≥2-point improvement and <2-point improvement) at Week 24.

A listing of participants who are positive for antibodies to nipocalimab (treatment-emergent or treatment-boosted) will be provided with individual IgG, MG-ADL, and infusion-site reactions (if any).

The incidence of neutralizing antibodies (NAbs) to nipocalimab will be summarized for participants who are positive for antibodies to nipocalimab and have samples evaluable for NAbs.

Descriptive statistics (N, arithmetic mean, SD, median, range, and IQ range) of PK serum nipocalimab concentrations (value), MG-ADL total score (value and change from baseline), total IgG (value, change from baseline, and percent change from baseline), and serum anti-AChR autoantibody levels (value, change from baseline, and percent change from baseline) over time by treatment-emergent antibodies to nipocalimab status (positive or negative) will be assessed.

The number and percentage of participants with infusion-related reactions or infusion site reactions will be summarized by treatment-emergent antibodies to nipocalimab status (positive or negative). For each type of reaction, the number and percentage of participants with any reaction, a severe reaction, a serious reaction, and a reaction leading to discontinuation of study intervention will be summarized by treatment-emergent antibodies to nipocalimab status (positive or negative). In addition, the percentage of all nipocalimab infusions with an infusion-related reaction and with an infusion site reaction will be summarized by treatment-emergent antibodies to nipocalimab status.

The number and percentage of participants with ≥2-point improvement on the MG-ADL total score at Week 24 will also be summarized by treatment-emergent antibodies to nipocalimab status.

In addition, listings of participants with baseline positive ADA samples, participants who are classified as positive for treatment-emergent antibodies to nipocalimab and participants who discontinue the study by antibodies to nipocalimab status as well as graphical representation of median PK concentration by antibody status may be presented.

5.7.2.3. Other Immunogenicity Analyses

The following analyses will be conducted if there is a sufficient number (e.g., ≥20) of participants who are treatment-emergent ADA positive.

The Peak Titer for participants positive for antibodies to nipocalimab will be grouped by Peak Titer categories. Example: <10, 10 to <100, 100 to <1000, ≥1000.

Incidence of antibodies to nipocalimab across Peak Titer categories will be summarized.

Treatment-induced Onset (data summarized will be exclusive to baseline negative participants)

Days from first administration of study intervention to the date of first instance of treatment-induced ADA (positive for treatment-induced antibodies to nipocalimab) will be summarized.

Number of days until first instance of treatment-induced ADA = (Date of first instance of treatment-induced positive antibody- Date of first administration of nipocalimab + 1).

Participants with no treatment-induced ADA (negative for treatment-induced antibodies to nipocalimab) will be censored on the last date the participant was known to have blood samples to assess immunogenicity.

Survival techniques will be used to estimate the median time to treatment-induced ADA. The Kaplan-Meier plot of onset of treatment-induced ADA will be presented.

Treatment-boosted Onset (data summarized will be exclusive to baseline positive participants)

Days from first administration of study intervention to the date of first instance of treatment-boosted ADA (titer is ≥2-fold higher than predose titer, positive for treatment-boosted antibodies to nipocalimab) will be summarized.

Number of days until first instance of treatment-boosted ADA = (Date of first instance of treatment-boosted positive antibody - Date of first administration of nipocalimab + 1).

Participants with no treatment-boosted ADA (negative for treatment-boosted antibodies to nipocalimab) will be censored on the last date the participant was known to have blood samples to assess immunogenicity.

Survival techniques will be used to estimate the median time to treatment-boosted ADA. The Kaplan-Meier plot of onset of treatment-boosted ADA will be presented.

Duration of Treatment-induced ADA (data summarized is exclusive to baseline negative participants).

The duration of treatment-induced ADA refers to the longevity of treatment-induced ADA.

Duration of treatment-induced ADA (weeks) = (Date of first instance of negative antibody – Date of first instance of treatment-induced positive antibody +1)/7.

Date of first instance of negative for antibody should be after the date of first instance of treatment-induced positive antibody. Participants continuing with treatment-induced ADA will be censored on the last date the participant was known to have blood samples to assess immunogenicity.

Survival techniques will be used to estimate the median duration of treatment-induced ADA.

When the study duration is greater than 1 year and the number of positive participants is greater than 20, Persistent vs Transient response should also be categorized.

Persistent ADA response:

- Treatment-induced ADA detected at two or more sampling time points during the study intervention or follow-up period, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer.

- Treatment-induced ADA incidence only in the last sampling time point of the study intervention period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

Transient ADA response:

- Treatment-induced ADA detected only at one sampling time point during the study intervention or follow-up observation period (excluding the last sampling time point, which ought to be considered persistent unless shown to be undetectable at a later time).
- Treatment-induced ADA detected at two or more sampling time points during the study intervention (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the participant's last sampling time point is ADA-negative.

5.7.3. Pharmacodynamics

The following data handling guidelines apply to all pharmacodynamics parameters described in this section:

- If a participant misses a planned dose of study intervention at any visit, their data is excluded from all subsequent visits after the first occurrence of a missed dose.
- All summaries for a particular time point will include data obtained from treated participants at the time point without imputing any missing data, i.e, data summaries will be based on observed data.

5.7.3.1. Immunoglobulin G (IgG) and Subtypes (IgG1, IgG2, IgG3, IgG4)

Descriptive statistics of the value, change from baseline, and percent change from baseline will be presented at each scheduled sampling time point for total IgG and each IgG subtype. Descriptive statistics will include N, arithmetic mean, SD, geometric mean, median, range, and IQ range. Plots of median (±IQR) change from baseline and percent change from baseline at each scheduled sampling time point will be provided for total IgG and each IgG subtype. These summaries will be presented for the double-blind and OLE phases by the Placebo/Nipocalimab, Nipocalimab/Nipocalimab, and Nipocalimab (OL) groups based on the pharmacodynamics analysis set.

Baseline for randomized participants is always defined as the double-blind phase Day 1 visit. Baseline for participants who entered the OLE phase directly is the OLE phase Day 1 visit.

Similar to PK analyses (Section 5.7.1), descriptive statistics of the value, change from baseline, and percent change from baseline for total IgG may also be summarized by baseline weight, age group, autoantibody status at baseline, MG-ADL score at baseline, region, and concomitant use of immunosuppressants, or by MG-ADL response status at Week 24.

The number and percentage of participants with IgG ≤1 g/L will be summarized based on the occurrence in the double-blind phase only with an additional summary based on incidence during

any nipocalimab exposure in either the double-blind or OLE phase. A listing of participants with IgG ≤1 g/L will be provided.

A listing of IgG levels will be provided for participants who had an infection adverse event of special interest (see Section 6.8 [Appendix 8]).

To assess the relationship between IgG lowering and MG-ADL total score, the following may be performed:

- Scatterplots of MG-ADL change from baseline versus total IgG percent of baseline value at Weeks 22, 23, and 24 will be provided with a simple linear regression fit and sample Pearson correlation coefficient.
- Boxplots of MG-ADL change from baseline by quartiles of total IgG percent of baseline value at Weeks 22, 23, and 24.
- Proportion of treatment effect (Li 2001) on change from baseline in MG-ADL total score at Week 24 explained by percent change from baseline in total IgG at Week 24. See Section 6.17 (Appendix 17) for details.

5.7.3.2. Immunoglobulin A, M, and E

Descriptive statistics of value, change from baseline, and percent change from baseline value will be presented at each scheduled sampling time point in a similar manner as for IgG. Descriptive statistics will include N, arithmetic mean, SD, geometric mean, median, range, and IQ range.

5.7.3.3. Anti-AChR, Anti-MuSK, and Anti-LRP4 Autoantibodies

Descriptive statistics of value, change from baseline, and percent change from baseline will be presented at each scheduled sampling time point for anti-AChR autoantibodies (binding, blocking, and modulating) in a similar manner as described above for IgG. Descriptive statistics will include N, arithmetic mean, SD, geometric mean, median, range, and IQ range. A plot of median (±IQR) percent change from baseline at each scheduled time point will also be provided.

The same analyses will be performed for anti-MuSK autoantibodies and/or anti-LRP4 autoantibodies if at least 10 participants are positive for the given autoantibody at baseline. Otherwise, plots of individual participant values over time will be provided.

Summaries for an autoantibody will include those participants in the Pharmacodynamics analysis set who were positive for that autoantibody at baseline.

To assess the relationship between anti-AChR binding autoantibody lowering and MG-ADL total score, the following will be performed:

- Scatterplots of MG-ADL change from baseline versus anti-AChR binding autoantibody percent of baseline value at Weeks 22, 23, and 24 will be provided with a simple linear regression fit and sample Pearson correlation coefficient.

- Boxplots of MG-ADL change from baseline by quartiles of anti-AChR binding autoantibody percent of baseline value at Weeks 22, 23, and 24.
- Proportion of treatment effect (Li 2001) on change from baseline in MG-ADL total score at Week 24 explained by percent change from baseline in anti-AChR binding autoantibody at Week 24. See Section 6.17 (Appendix 17) for details.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

The relationships between serum nipocalimab concentration and efficacy will be analyzed graphically. A suitable pharmacokinetic/pharmacodynamic (PK/PD) model will be developed to describe the exposure-response relationship. Data may be combined with those of other selected studies to support a relevant structural PK/PD model. The results of the population PK/PD analysis may be presented in a separate technical report.

5.7.5. Biomarkers

Analyses of other exploratory biomarkers, if conducted, will be described in a separate statistical analysis plan.

5.7.6. Health Economics

5.7.6.1. Health Resource Utilization Questionnaire (HRUQ)

Each emergency room visit without hospitalization and each hospitalization that occurs during the study is recorded on the eCRF with an indication of whether the ER visit or hospitalization was because of myasthenia gravis worsening, myasthenia gravis crisis, or because of other reasons not associated with myasthenia gravis or, for hospitalizations only, other reasons in addition to myasthenia gravis.

Admission and discharge dates are collected for hospitalizations. Length of stay of a hospitalization is calculated as (the discharge date – the admission date + 1). If the participant is in hospital at the time of the last study visit, the date of the last study visit will be used for discharge date. For each participant, “total days in hospital for MG” for each phase will be calculated as the sum of the lengths of stay of all hospitalizations related to MG with admission in the phase. “Average length of stay for MG” will be calculated as “total days in hospital for MG” divided by the number of hospitalizations. Similar calculations will be performed for hospitalizations not related to MG.

The frequency distribution of the number of ER visits without hospitalization and the number of hospitalizations (e.g., 0, 1, 2, 3, 4, 5, >5) in a phase will be summarized by intervention group and whether the ER visit/hospitalization was related to myasthenia gravis or not. Separate summaries will be provided for the double-blind phase (using the primary efficacy analysis set) and the OLE phase (using the seropositive efficacy analysis set (OL)).

If ≥10 participants in either intervention group in the double-blind phase have at least 1 admission to hospital for an MG-related reason in the double-blind phase, descriptive statistics (N, mean, SD, median, minimum, maximum) of total days in hospital and average length of stay will be provided

for the subset of participants with hospitalizations by intervention group using the primary efficacy analysis set. Similar summaries will be performed for hospitalizations in the double-blind phase for non-MG-related reasons and for hospitalizations in the OLE phase if the 10 participant criterion for the respective phase and event is met.

5.7.6.2. Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The TSQM-9 is a 9-item generic participant reported outcome instrument to assess participants' satisfaction with medication (Atkinson 2004). It is derived from the longer TSQM Version 1.4 and covers 3 domains: effectiveness (3 items), convenience (3 items), and global satisfaction (3 items). Items are scored on a 7- or 5-point scale (ranging from 1 to 7 or 5) with higher scores indicating greater satisfaction. Domain scores are derived by adding the items within a domain and scaling to a value between 0 and 100, with higher scale scores indicating greater satisfaction. See Section 6.15 for details of the derivation.

The TSQM-9 is collected at Week 24 (or end of phase) in the double-blind phase and every 24 weeks in the OLE phase.

Descriptive statistics (N, mean, SD, median, minimum, maximum) for each TSQM-9 domain score will be provided for each scheduled time point in the double-blind phase (using the primary efficacy analysis set) and in the OLE phase (using the seropositive efficacy analysis set (OL)).

5.7.7. Actigraphy

Actigraphy will be performed at selected sites globally. The raw data sampled by the actigraphy watch sensors will be transformed into derived digital health endpoints, assessing the changes in physical activity, mobility, and sleep parameters during the 24-week double-blind, placebo-controlled phase. Endpoints include, but are not limited to, step count, activity count, sleep time, sleep efficiency and percent mobile time.

Details will be provided in a separate analysis plan and results will be summarized in a separate report.

5.7.8. Definition of Subgroups

Analyses of MG-ADL total score in the double-blind phase will be performed for each primary estimand by each of the subgroups listed below.

Summaries of TEAEs in the double-blind phase will be performed by region, age group, sex, race, body mass index, autoantibody positive/negative, and type of stable gMG therapy.

Subgroup	**Definition**
Region	• US • East Asia: Japan, China, South Korea, Taiwan • ROW: other countries/territories
Country/Territory	• Australia • France • Spain

Subgroup	Definition
	• Belgium • Germany • South Korea • Canada • Italy • Sweden • China • Japan • Taiwan • Czech Republic • Mexico • US • Denmark • Poland
Age Group	• 18 to <45 years • ≥45 to <65 years • ≥65 years
Sex	• Female • Male
Race	• White • Non-white
Body mass index (BMI)	• Normal (<25 kg/m^2) • Overweight (≥25 kg/m^2 to <30 kg/m^2) • Obese (≥30 kg/m^2)
Autoantibody positive/negative	• Seronegative • Seropositive
Autoantibody status	• Seronegative • Anti-AChR+ (positive for any of binding, blocking, or modulating anti-AChR autoantibodies and regardless of anti-MuSK or anti-LRP4 autoantibody status) • Anti-MuSK+ (anti-MuSK+, anti-AChR-, and either anti-LRP4+ or -) • Anti-LRP4+ (anti-LRP4+, anti-AChR-, and anti-MuSK-)
Baseline MG-ADL total score	• ≤9 • >9
Type of stable gMG therapy	• With immunosuppressant • Without immunosuppressant
Duration of gMG	• ≤5 years • >5 years
Age (years) at onset of MG	• ≤50 years • >50 years

5.8. Interim Analyses

No interim analyses are planned for this study.

5.8.1. Data Monitoring Committee (DMC) or Other Review Board

A DMC is employed for the review of safety data of this study and other nipocalimab studies in other indications (DMC Charter).

6. SUPPORTING DOCUENTATION

6.1. Appendix 1 List of Abbreviations

AChR	acetylcholine receptor
ADA	anti-drug antibody
AE	adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphokinase
ALT/SGPT	alanine aminotransferase
AR	Autoregressive
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
CDF	Cumulative distribution function
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computerized tomography
CV	coefficient of variation
DB	Double-blind
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ER	Emergency room
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
gMG	Generalized myasthenia gravis
HIS	Health status index
HLT	High level term
ICE	Intercurrent event
ICU	Intensive care unit
IgG/M/A/E	Immunoglobulin G/M/A/E
INR	International normalized ratio
IQ	interquartile
IV	Intravenous
IVIG	Intravenous immunoglobulin G
IWRS	interactive web response system
LLOQ	lower limit of quantification
LOS	Length of stay
LRP4	Low density lipoprotein receptor-related protein 4
MACE	Major adverse cardiovascular event
MAR	Missing at random
MCID	Minimum clinically important difference
MCMC	Markov chain Monte Carlo
MCT	Meaningful change threshold
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis – Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MI	Multiple imputation
MMRM	Mixed effects model for repeated measures
MNAR	Missing not at random
MuSK	Muscle-specific kinase
NAb	neutralizing antibodies

OL	Open-label
OLE	Open-label extension
PD	pharmacodynamic(s)
PGI-C/S	Patient global impression of change/severity
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PTE	Proportion of treatment effect
QMG	Quantitative Myasthenia Gravis
QoL	Quality of life
ROW	Rest of world
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	Standard error
SMQs	standardized MedDRA queries
SOC	System-organ class
TE	Treatment-emergent
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Not applicable.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group and overall. In addition, the distribution of participants by region (US, East Asia, ROW), country/territory, and site ID will be presented.

Table 5 presents a list of the demographic variables that will be summarized by intervention group and overall for the full, primary efficacy, and safety (OL) analysis sets. Demographics will also be summarized by region using the primary efficacy analysis set.

Table 5: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (18 to <45 years, ≥45 to <65 years, ≥65 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 6 presents a list of baseline characteristics that will be summarized by intervention group and overall for the full and primary efficacy analysis sets. Baseline characteristics will also be summarized by region using the primary efficacy analysis set.

Table 6: Baseline Characteristics

Continuous Variables:	**Summary Type**
Baseline MG-ADL total score	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Baseline QMG total score	
Duration of myasthenia gravis (years)	
Age (years) at onset of MG	
Categorical Variables	
Day 1 MGFA Classification (IIa, IIb, IIIa, IIIb, IVa, IVb)	Frequency distribution with the number and percentage of participants in each category.
Baseline MG-ADL total score (≤9, >9)	
Autoantibody status at screening (Anti-AChR+; Anti-MuSK+; Anti-LRP4+; Seronegative)	

Duration of myasthenia gravis (MG) in years will be calculated as: (informed consent date – start date of MG from medical history + 1)/365.25. Age (years) at onset of MG will be calculated as age at baseline minus duration of MG.

Table 7 presents the randomization stratification according to the IWRS that will be summarized by intervention group and overall for the full and primary efficacy analysis sets.

Table 7: Randomization Stratification per IWRS

Categorical Variables	
Baseline MG-ADL total score (≤9, >9)	Frequency distribution with the number and percentage of participants in each category.
Autoantibody status at screening (Anti-AChR positive and/or anti-MuSK positive; Anti-AChR negative and anti-MuSK negative)	

Table 8 presents a list of the gMG medical history variables that will be summarized by intervention group and overall for the full and primary efficacy analysis sets.

Table 8: Generalized Myasthenia Gravis Medical History Variables

Categorical Variables	
How was diagnosis of gMG confirmed (Autoantibodies; Clinical history and exam; Single fiber EMG; Repetitive nerve stimulation study; Historical information; Other methods)	Frequency distribution with the number and percentage of participants in each category.
CT scan for thymoma (Yes, No)	
MG flare/exacerbation/worsening weakness in the past year (Yes, No)	
Any MG crisis requiring hospitalization (Yes, No)	
Any prolonged ICU stay of more than 6 weeks (Yes, No)	
Why is participant enrolling in this study (Myasthenia gravis is not well-controlled on current medications; Myasthenia gravis is sub-optimally controlled on current medications; Not tolerating current myasthenia gravis medications; Other reasons)	

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category using the full and primary efficacy analysis sets.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

6.5. Appendix 5 Prior and Concomitant Medications

The Myasthenia Gravis Medical History eCRF collects information about various gMG medications the participant has taken, including information about dose, duration, and whether treatment was not tried or stopped due to side effects. The items collected for each gMG medication are listed below. Responses are Yes or No for all items, except for number of sessions tried for plasma exchange/immunoadsorption and IVIG. The frequency distribution of responses will be summarized for each medication using the full and primary efficacy analysis sets.

Corticosteroids
- Prescribed?
- Highest tolerable dose reached?
- Tried for at least 2 months?
- Not tried for that period due to side effects?

Plasma exchange or immunoadsorption therapies
- Prescribed?
- Tried for at least 5 sessions?
- Trial stopped due to side effects?
- Number of sessions

IVIG
- Prescribed?
- Tried for at least 5 sessions?
- Trial stopped due to side effects?
- Number of sessions

Azathioprine
- Prescribed?
- Highest tolerable dose reached?
- Tried for at least 12 months?
- Not tried for that period due to side effects?

Mycophenolate
- Prescribed?
- Highest tolerable dose reached?
- Tried for at least 12 months?
- Not tried for that period due to side effects?

Rituximab
- Prescribed?
- Highest tolerable dose reached?
- Treatment dose not reached due to side effects?

Eculizumab/Soliris
- Prescribed?
- Highest tolerable dose reached?
- Treatment dose not reached due to side effects?

Other immunosuppressant
- Prescribed?
- Highest tolerable dose reached?
- Treatment dose not reached due to side effects?
-

Prior and Concomitant medications collected on the Concomitant Medications eCRF will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the day of the first dose of study intervention, including those that started before and continued after the first dose of study intervention.

Separate summaries will be presented for the following categories of prior and concomitant medications:

- Prior gMG medications (gMG medications started and stopped before the first dose of study intervention)
- Prior medications, other than gMG medications (medications, other than gMG medications, used before the day of first dose of study intervention and which may or may not have been continued after the day of first dose of study intervention)
- Stable gMG therapy (gMG medications started before the first dose of study intervention and continued after the first dose of study intervention)

- Concomitant medications, other than stable gMG therapy
  - Medications, other than stable gMG therapy, started between the first and last doses of study intervention in the phase.
  - Medications, other than stable gMG therapy, used on or after the day of the first dose of study intervention, including those that started before and continued after the first dose of study intervention.
  - Rescue medication (IVIg, plasmapheresis) started between the first and last doses of study intervention in the phase. Rescue medications are defined as concomitant medications with a WHO Drug Dictionary (WHO-DD) coded term containing "IMMUNOGLOBULIN" (for IVIg) or a WHO-DD coded term of "BLOOD PLASMA" (for plasmapheresis).

Summaries of concomitant medications will be presented by ATC Level 2 term, intervention group, and study phase: double-blind (using the full and primary efficacy analysis set) and OLE (using the safety (OL) analysis set). The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

Prior medications will be summarized by intervention group and ATC Level 2 term using the full analysis set and the safety (OL) analysis set.

Stable gMG therapy in the double-blind phase will also be summarized using the primary efficacy analysis set. In addition, each participant's stable gMG therapy will be classified as a combination of the following categories of gMG therapy (e.g., "anticholinesterase", "anticholinesterase + corticosteroids" or "anticholinesterase + >1 immunosuppressant"):

- Anticholinesterase
- Corticosteroid
- 1 Immunosuppressant
- >1 Immunosuppressant

The number and percentage of participants in each combination will be summarized by intervention group using the primary efficacy analysis set.

Changes to the stable gMG therapy during the OLE phase will be categorized as:

- Discontinued a stable gMG therapy
- Decreased dose of a stable gMG therapy
- Increased dose of a stable gMG therapy
- Started a new gMG therapy

The number and percentage of participants with at least one occurrence in the OLE phase will be summarized by event and intervention group using the safety (OL) analysis set. A similar summary

based on changes to a corticosteroid therapy will also be provided. In the corticosteroid summary, the occurrence of dose decreases of ≥50% will also be summarized.

A listing of gMG medications will be provided for participants with a treatment-emergent adverse event of "Myasthenia gravis" or "Myasthenia gravis crisis" in either the double-blind or OLE phase.

6.6. Appendix 6 Medical History

General medical history will be summarized with the number and percentage of participants with at least one current or past finding (relative to the screening visit) for each body system by intervention group and overall using the full and safety (OL) analysis sets.

6.7. Appendix 7 Intervention Compliance

Compliance calculation is not applicable for this study.

6.8. Appendix 8 Adverse Events of Interest

Adverse events of special interest are defined as follows:

AE Special Interest Category	SOC	Additional condition
Infections	Infection and Infestations	Checkbox for AESI that indicates it was severe or required IV anti-infective or operative/invasive intervention

AE Special Interest Category	Preferred term	Additional condition
Hypoalbuminaemia	Hypoalbuminaemia	Checkbox for AESI that indicates albumin <20 g/L

Other adverse event of clinical interest are defined as follows:

AE of Clinical Interest Category	Preferred term	Additional condition
Infusion reaction	Any	Indicated as infusion reaction by investigator on eCRF and relationship to study intervention = "Related". Exclude infusion site reactions
Infusion site reaction	HLT of "Infusion site reaction"	
Serum sickness reaction	Serum sickness, serum sickness-like reaction	Requires clinical review
Anaphylactic reaction	Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Type I hypersensitivity, Kounis syndrome	Determined through SMQ algorithmic approach/Sampson's criteria
Potentially associated with glucocorticoid toxicity	**Cardiovascular:** Acute myocardial infarction*, angina pectoris, arteriosclerosis, blood cholesterol increased, blood pressure increased; cardiac failure, cardiovascular insufficiency, congestive cardiomyopathy, dyslipidaemia, fluid retention, hypercholesterolaemia, hyperlipidaemia, hypertension, hypertensive emergency, hypertriglyceridaemia, hypervolaemia, low density lipoprotein increased, myocardial infarction*, myocardial ischaemia, oedema, oedema peripheral, peripheral swelling	*Also a MACE preferred term
	Infections: all serious infections	
	Gastrointestinal: Duodenal ulcer, gastritis, gastritis erosive, gastrointestinal disorder, pancreatitis, pancreatitis acute	
	Psychological: affective disorder, agitation, anxiety, confusional state, depressed mood, depression, insomnia, irritability, libido decreased, major depression,	

AE of Clinical Interest Category	Preferred term	Additional condition
	mania, mental status changes, mood altered, nervousness, poor quality sleep	
	Endocrine/metabolic: adrenal insufficiency, blood glucose increased, blood potassium decreased, central obesity, Cushingoid, Cushing's syndrome, diabetes mellitus, diabetes mellitus inadequate control, glucose tolerance impaired, gynaecomastia, hyperglycaemia, hypokalaemia, influenza like illness, polymenorrhagia, menometrorrhagia, systemic inflammatory response syndrome, type 2 diabetes mellitus, waist circumference increased, weight increased	
	Dermatological: Acne, dermatitis acneiform, ecchymosis, hirsutism, increased tendency to bruise, skin atrophy, skin striae	
	Musculoskeletal: Hip fracture, humerus fracture, lower limb fracture, lumbar vertebral fracture, muscle atrophy, muscular weakness, myopathy, osteonecrosis, osteopenia, osteoporosis, spinal compression fracture, tendon rupture, wrist fracture	
	Ophthalmological: Cataract, cataract nuclear, glaucoma, intraocular pressure increased, open angle glaucoma, retinopathy hypertensive	
Potentially abuse-related	Aggression; Confusional state; Decreased activity; Dependence; Disorientation; Dissociation; Dissociative disorder; Dizziness; Drug abuse; Drug abuser; Drug dependence; Drug detoxification; Drug diversion; Drug rehabilitation; Drug tolerance; Drug tolerance increased; Drug use disorder; Drug withdrawal convulsions; Drug withdrawal headache; Drug withdrawal syndrome;, Euphoric mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Hallucination; Hallucination, auditory; Hallucination, gustatory; Hallucination, olfactory; Hallucination, synaesthetic;	

AE of Clinical Interest Category	Preferred term	Additional condition
	Hallucination, tactile; Hallucination, visual; Hallucinations, mixed; Inappropriate affect; Mental impairment; Product tampering; Psychomotor hyperactivity; Psychotic disorder; Rebound effect; Somatic hallucination; Somnolence; Substance abuser; Substance dependence; Substance use; Substance use disorder; Substance-induced mood disorder; Substance-induced psychotic disorder; Thinking abnormal; Withdrawal arrhythmia; Withdrawal syndrome	
Hyperlipidemia	Hyperlipidaemia; Lipids increased Lipids abnormal; Dyslipidaemia Hypertriglyceridaemia; Blood triglycerides increased; Blood triglycerides abnormal; Hypercholesterolaemia; Blood cholesterol increased; Blood cholesterol abnormal; Low density lipoprotein increased; Low density lipoprotein abnormal; Very low density lipoprotein abnormal; Very low density lipoprotein increased; Non-high-density lipoprotein cholesterol increased	
Activation of latent virus	Epstein-Barr Virus Infection reactivation; Epstein-Barr Virus Infection; Epstein-Barr Viraemia; Cytomegalovirus infection reactivation; Cytomegalovirus infection; Cytomegalovirus Viraemia; Herpes simplex reactivation; Herpes zoster reactivation; Herpes virus infection; Cytomegalovirus urinary tract infection; Cytomegalovirus gastrointestinal infection; Gastritis herpes; Genital herpes; Genital herpes simplex; Genital herpes zoster; Herpes dermatitis; Herpes oesophagitis; Herpes ophthalmic Herpes pharyngitis; Herpes sepsis Herpes simplex; Herpes simplex bronchitis; Herpes simplex cervicitis; Herpes simplex colitis; Herpes simplex encephalitis; Herpes simplex gastritis; Herpes simplex hepatitis; Herpes simplex meningitis; Herpes simplex meningoencephalitis; Herpes	

AE of Clinical Interest Category	Preferred term	Additional condition
	simplex meningomyelitis; Herpes simplex necrotising retinopathy; Herpes simplex oesophagitis; Herpes simplex otitis externa; Herpes simplex pharyngitis; Herpes simplex pneumonia; Herpes simplex sepsis; Herpes simplex viraemia; Herpes simplex virus urethritis; Herpes simplex visceral; Herpes zoster; Herpes zoster cutaneous disseminated; Herpes zoster disseminated; Herpes zoster infection neurological; Herpes zoster meningitis; Herpes zoster meningoencephalitis; Herpes zoster meningomyelitis; Herpes zoster meningoradiculitis; Herpes zoster necrotising retinopathy; Herpes zoster oticus; Herpes zoster pharyngitis; Herpetic radiculopathy; Lower respiratory tract herpes infection; Meningitis herpes; Meningoencephalitis herpetic; Meningomyelitis herpes; Nasal herpes; Necrotising herpetic retinopathy; Ophthalmic herpes simplex; Ophthalmic herpes zoster; Oral herpes; Oral herpes zoster; Pneumonia herpes viral; Proctitis herpes; Cytomegalovirus chorioretinitis; Cytomegalovirus colitis; Cytomegalovirus duodenitis; Cytomegalovirus enteritis; Cytomegalovirus enterocolitis; Cytomegalovirus gastritis; Cytomegalovirus gastroenteritis; Cytomegalovirus gastrointestinal ulcer; Cytomegalovirus hepatitis; Cytomegalovirus mononucleosis; Cytomegalovirus mucocutaneous ulcer; Cytomegalovirus myelomeningoradiculitis; Cytomegalovirus myocarditis; Cytomegalovirus nephritis; Cytomegalovirus oesophagitis; Cytomegalovirus pancreatitis; Cytomegalovirus pericarditis; Cytomegalovirus syndrome; Disseminated cytomegaloviral infection; Encephalitis cytomegalovirus; Pneumonia cytomegaloviral; Epstein Barr virus positive mucocutaneous ulcer	

AE of Clinical Interest Category	Preferred term	Additional condition
Myasthenia gravis	Myasthenia gravis Myasthenia gravis crisis	

AE of Clinical Interest Category	SMQ	Additional condition
Opportunistic infections	Opportunistic infections	Narrow scope
Hypersensitivity reaction	Hypersensitivity	Narrow scope
Suicidal ideation/behavior	Suicide/self-injury	Narrow and broad scope
MACE*	Conditions associated with central nervous system haemorrhages and cerebrovascular accidents	Narrow and broad scope
	Haemorrhagic central nervous system vascular conditions	Narrow scope
	Ischaemic central nervous system vascular conditions	Narrow scope
	Myocardial infarction	Narrow and broad scope
	Preferred terms of Troponin abnormal, Troponin I abnormal	
	Any AE with fatal outcome	

* All potential cases of MACE to be independently adjudicated.

6.9. Appendix 9 Medications of Special Interest

No concomitant medications of special interest are defined.

6.10. Appendix 10 Laboratory Toxicity Grading

Markedly abnormal criteria for selected laboratory tests are provided in the table below. Change and percent change are in reference to the baseline value as defined for each phase and intervention group in Section 5.6.3.1.

Category	Lab test	Sex	Unit	Markedly Abnormal Low*	Markedly Abnormal High*
CHEMISTRY	Albumin	BOTH	g/L	Decrease >10 and value <20	Increase >10 and value > 60
CHEMISTRY	Alkaline phosphatase	BOTH	U/L	N/A	Increase >100 and value >250
CHEMISTRY	Alanine transaminase (ALT)(SGPT)	BOTH	U/L	N/A	≥3xULN
CHEMISTRY	Aspartate transaminase (AST) (SGOT)	BOTH	U/L	N/A	≥3xULN
CHEMISTRY	Bicarbonate	BOTH	mmol/L	Decrease >20% and value <15.1	Increase >20% and value >34.9
CHEMISTRY	Blood urea nitrogen	BOTH	mmol/L	N/A	Increase >20% and value >17.9
CHEMISTRY	Calcium	BOTH	mmol/L	Decrease >20% and value <1.5	Increase >20% and value >3
CHEMISTRY	Chloride	BOTH	mmol/L	Decrease >5 and value <85	Increase >5 and value >120
CHEMISTRY	Creatinine	BOTH	umol/L	N/A	Increase >20% and value >250
CHEMISTRY	Gamma glutamyl transferase	BOTH	U/L	N/A	Increase >100 and value >300
CHEMISTRY	Glucose	BOTH	mmol/L	Decrease >20% and value <2.2	Increase >30% and value >16.7
CHEMISTRY	Phosphate	BOTH	mmol/L	Decrease >10% and value <0.6	Increase >10% and value >2.6

Category	Lab test	Sex	Unit	Markedly Abnormal Low*	Markedly Abnormal High*
CHEMISTRY	Potassium	BOTH	mmol/L	Decrease >10% and value <3	Increase >20% and value >6.0
CHEMISTRY	Sodium	BOTH	mmol/L	Decrease >10% and value <125	Increase >10% and value >155
CHEMISTRY	Total bilirubin	BOTH	umol/L	N/A	Increase >20% and value >45
CHEMISTRY	Total protein	BOTH	g/L	Decrease >20% and value <50	N/A
CHEMISTRY	Creatine Kinase	BOTH	U/L	N/A	Increase >20% and value >960
CHEMISTRY	Total Cholesterol	BOTH	mmol./L	N/A	≥6.2
CHEMISTRY	HDL	BOTH	mmol./L	<1.0	≥2.1
CHEMISTRY	LDL	BOTH	mmol./L	N/A	≥4.1
CHEMISTRY	Triglycerides	BOTH	mmol./L	N/A	>5.6
HEMATOLOGY	Hematocrit female	F	fraction	Decrease >15% and value <0.28	Increase >15% and value >0.50
HEMATOLOGY	Hematocrit male	M	fraction	Decrease >15% and value <0.28	Increase >15% and value >0.55
HEMATOLOGY	Hemoglobin	BOTH	g/L	Decrease >10% and value <80	Increase >10% and value >190
HEMATOLOGY	Neutrophils/Leukocytes	BOTH	fraction	Decrease> 30% and value <0.30	Increase >30% and value >0.90

Category	**Lab test**	**Sex**	**Unit**	**Markedly Abnormal Low***	**Markedly Abnormal High***
HEMATOLOGY	Monocytes/Leukocytes	BOTH	fraction	N/A	Increase >20% and value >0.20
HEMATOLOGY	Eosinophils/Leukocytes	BOTH	fraction	N/A	Increase >20% and value >0.10
HEMATOLOGY	Basophils/Leukocytes	BOTH	fraction	N/A	Increase >20% and value >0.06
HEMATOLOGY	Lymphocytes/Leukocytes	BOTH	fraction	Decrease > 20% and value <0.08	Increase >20% and value >0.60
HEMATOLOGY	Platelet count	BOTH	x10E9/L	Decrease >20% and value <100	Increase >20% and value >600
HEMATOLOGY	Red blood cell count Female	F	x10E12/L	Decrease >20% and value <3	Increase >20% and value >6.1
HEMATOLOGY	Red blood cell count Male	M	x10E12/L	Decrease >20% and value <3	Increase >20% and value >6.4
HEMATOLOGY	White blood cell count	BOTH	x10E9/L	Decrease >10% and value <2.5	Increase >20% and value >15

* Increases and decreases are calculated from baseline values

6.11. Appendix 11 Covid-19

COVID-19 medical history will be summarized including whether the participant received a COVID-19 vaccination prior to the study, whether the participant had a medical history of COVID-19 and the complications experienced and treatments taken, if any, during their COVID-19 disease.

Participant disposition as related to COVID-19 will be summarized by intervention group. This includes the following COVID-19 related disposition events:

- Termination of study due to COVID-19 and reason (COVID-19 adverse event, COVID-19 death, or other COVID-19 related reason)
- Discontinuation of double-blind study intervention due to COVID-19 and reason
- Discontinuation of open-label study intervention due to COVID-19 and reason
- Death related to COVID-19

Participants discontinuing treatment or terminating study participation due to COVID-19 and reason(s) will be listed.

Assessment of study compliance as related to COVID-19 will be summarized, including number of missed visits, and number of remote visits conducted. Participants whose visit compliance was impacted by COVID-19 will be listed.

Concomitant medications used for COVID-19 will be summarized. Participants receiving concomitant medications related to COVID-19, including vaccinations, will be listed. Medications used for COVID-19 are those indicated as taken for a COVID-19 adverse event. COVID-19 vaccinations include WHO-DD preferred terms Tozinameran, Elasomeran, and any other preferred term that begins with “COVID-19 VACCINE”.

Protocol deviations (major or minor) as related to COVID-19 will be summarized and listed.

Study intervention modifications due to COVID-19 will be summarized and listed.

Adverse events related to COVID-19 will be identified and coded using the MedDRA coding guidance for COVID-19, and summary tables will be provided for COVID-19 related TEAEs. COVID-19 related events include preferred terms in the narrow scope COVID-19 SMQ and any AE indicated as “Epi/pandemic Related” on the eCRF. The following will be listed by participant:

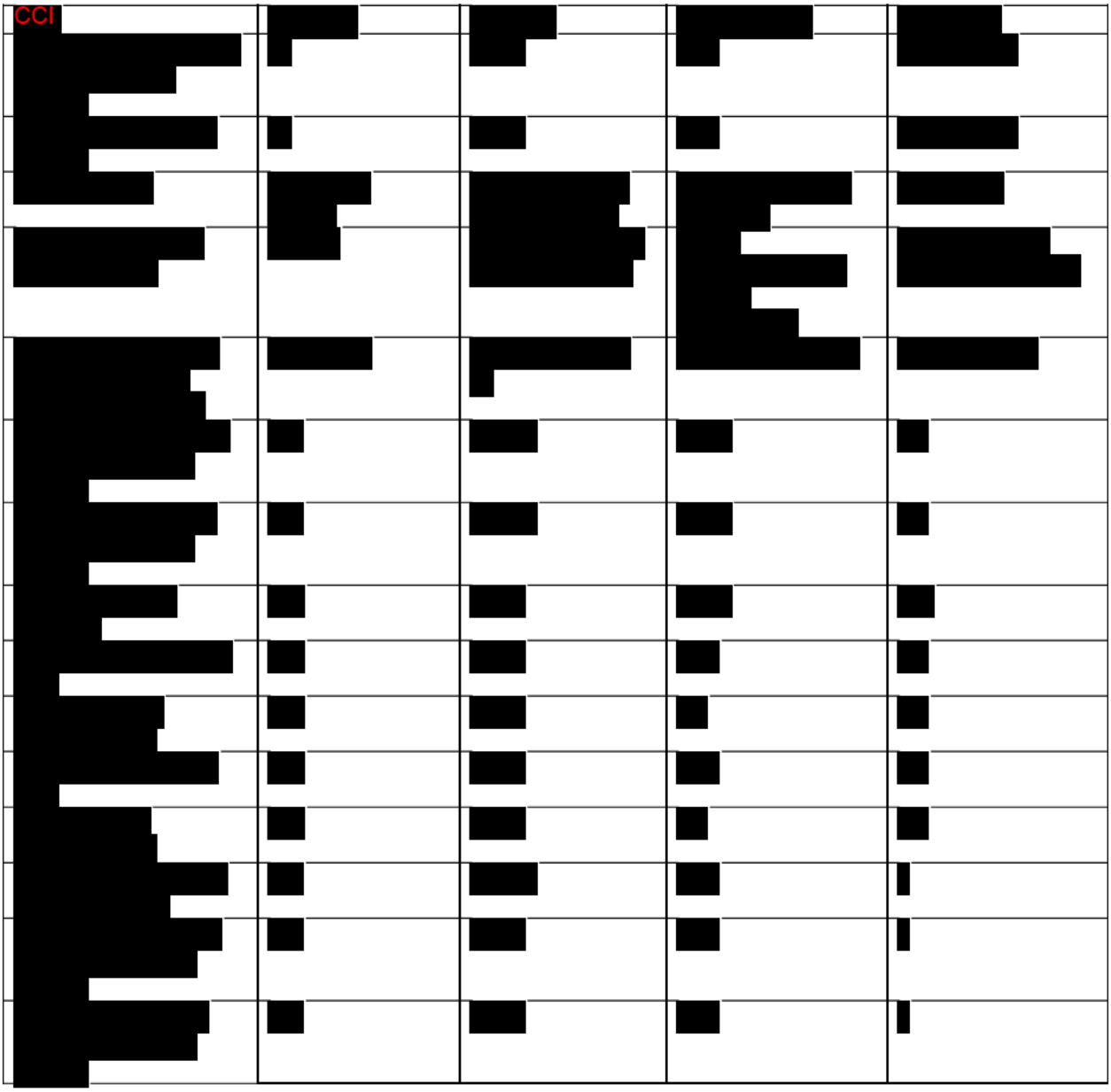
- TEAEs related to COVID-19
- Serious TEAEs related to COVID-19
- Deaths related to COVID-19

Results of SARS-CoV-2 antibody or viral testing done during the study will be listed.

6.12. Appendix 12 Myasthenia Gravis – Activities of Daily Living

Item	**None = 0**	**Mild = 1**	**Moderate = 2**	**Severe = 3**
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal speech, but can be understood	Difficult-to-understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do these functions
Impairment of ability to rise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant

6.13. Appendix 13 Quantitative Myasthenia Gravis



6.14. Appendix 14 Revised Myasthenia Gravis Quality of Life

Responses to each item below are rated by the patient, using a reflection period of "over the past few weeks" on a 3-point scale (0 = not at all, 1 = somewhat, and 2 = very much).

- I am frustrated by my MG
- I have trouble with my eyes because of my MG (e.g., double vision)
- I have trouble eating because of my MG
- I have limited my social activity because of my MG
- My MG limits my ability to enjoy hobbies and fun activities
- I have trouble meeting the needs of my family because of my MG
- I have to make plans around my MG
- I am bothered by limitations in performing my work (including work at home) because of my MG
- I have difficulty speaking due to my MG
- I have lost some personal independence because of my MG (e.g. Driving, shopping, running errands)
- I am depressed about my MG
- I have trouble walking due to my MG
- I have trouble getting around public places because of my MG
- I feel overwhelmed by my MG
- I have trouble performing my personal grooming needs due to my MG

6.15. Appendix 15 TSQM-9 Scoring

CCI

6.16. Appendix 16 Myasthenia Gravis Foundation of America Classification

Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

6.17. Appendix 17 Proportion of Treatment Effect Analysis

Based on observed data at Week 24 of the double-blind phase an ANCOVA model will be performed using the primary efficacy analysis set with change from baseline in MG-ADL total score ($\Delta MGADL$) as the dependent variable, study intervention as a factor ($Treat$), and percent change in total IgG ($\%\Delta IGG$) as a covariate:

$$\Delta MGADL = \beta_0 + \beta_1 Treat + \beta_2 \%\Delta IGG$$

Let D_{IgG} be the difference in the mean percent change from baseline in total IgG between nipocalimab and placebo at Week 24. The proportion of treatment effect on the change from baseline in MG-ADL total score at Week 24 that is explained by percent change from baseline in total IgG at Week 24 is estimated as (Li 2001):

$$PTE = (\hat{\beta}_2 * D_{IgG})/(\hat{\beta}_1 + (\hat{\beta}_2 * D_{IgG}))$$

The bootstrap method will be used to estimate the standard error of PTE and a 95% confidence interval of PTE will be constructed.

The same methodology may also be performed using percent change in anti-AChR binding autoantibody in place of percent change in total IgG and using the anti-AChR positive efficacy analysis set.

6.18. Appendix 18 Sample SAS Code for MMRM

Below is sample SAS MIXED procedure code for implementing the MMRM described in Section 5.3.3. The study intervention variable is `trt` with 1 = Placebo and 2 = Nipocalimab. `Abstatus` is the autoantibody status as randomized and `chg` is the change from baseline at each `week`. `Week` has 12 levels representing the 12 post-baseline timepoints at which the MG-ADL is collected with the last 3 levels representing Weeks 22, 23, and 24.

The linear contrast to estimate and test the between-group difference (nipocalimab minus placebo) for the average change from baseline over Weeks 22, 23, and 24 is specified in the `estimate` statement.

```
proc mixed data = mgadl method = reml;
class trt abstatus region week subject;
model chg = trt abstatus region week trt*week base / ddfm = kr;
repeated week / sub = subject type = un;

/** Estimate and test average between-group difference over   **/
/** weeks 22, 23, and 24                                      **/
estimate 'betw-grp diff over weeks 22, 23, 24'
    trt -3 3 trt*week 0 0 0 0 0 0 0 0 0 -1 -1 -1
                      0 0 0 0 0 0 0 0 0  1  1  1 / divisor = 3 cl;

/** Estimate average change over weeks 22, 23, and 24             **/
/**  in each group                                                **/
lsmestimate trt*week 'Placebo: avg chg over weeks 22, 23, 24'
                     0 0 0 0 0 0 0 0 0 1 1 1 divisor = 3,
                     'Nipocalimab: avg chg over weeks 22, 23, 24'
                     0 0 0 0 0 0 0 0 0 0 0 0
                     0 0 0 0 0 0 0 0 0 1 1 1 divisor = 3 / cl;

/** LS means over time and between group differences at each week **/
lsmeans trt*week / diff cl;

run;
```

6.19. Appendix 19 Intercurrent Event and Intercurrent Event Date Definitions

When the **hypothetical strategy** is applied to an ICE, observations of the endpoint collected after the participant ICE date are deemed missing.

When the **treatment policy strategy** is applied to an ICE, observations of the endpoint collected after the participant ICE date are included in the analysis.

Details of the imputation methods and sensitivity analyses associated with these strategies for the analysis of change from baseline of MG-ADL total score are described in Section 5.3.3.

When the **composite strategy** is applied to an ICE (for responder-type variables), observations of the endpoint collected after the participant ICE date are deemed to be "non-response" (e.g., a change from baseline > -2 for MG-ADL total score or change from baseline > -3 for QMG total score).

Details for how to determine if a participant had an ICE (ICE Definitions) and how to determine the participant ICE date are provided below.

ICE Definitions

- Discontinuation of study intervention: Double-blind study treatment not recorded as "Completed" in the eCRF.
- Discontinuation of stable gMG therapy: End date of every component of the stable gMG therapy is before the first infusion in the OLE or within 14 days after the last double-blind infusion for participants who did not enter the OLE.
- Change in stable gMG therapy: A change of dose in a stable gMG therapy is recorded as two observations, one for the original dose with an end date indicating the last date that dose was taken and one indicating when the changed dose started. A participant has this ICE if the end date of any component of the stable gMG therapy is before the first infusion in the OLE or within 14 days after the last double-blind infusion for participants who did not enter the OLE. Per protocol, dose changes of anticholinesterases are allowed. Only dose changes of corticosteroids and immunosuppressants will be considered for this ICE.
- Initiation of rescue therapy: Use of any concomitant medication with a WHO Drug Dictionary (WHO-DD) coded term containing "IMMUNOGLOBULIN" (for IVIg) or a WHO-DD coded term of "BLOOD PLASMA" (for plasmapheresis) with a start date after the first infusion in the double-blind phase and before the first infusion in the OLE or within 14 days after the last double-blind infusion for participants who did not enter the OLE.

Intercurrent event	Intercurrent event date
Discontinuation of study intervention not due to initiation rescue medication	Date of last infusion in the double-blind phase + 14 days[a]

Intercurrent event	**Intercurrent event date**
Discontinuation of study intervention due to initiation rescue medication	Earlier of: • Date of last infusion in the double-blind phase + 14 days[a] • Earliest start date across all rescue medications – 1 day[b]
Discontinuation of stable gMG therapy not due to initiation of rescue medication	Latest end date across all components of the stable gMG therapy
Discontinuation of stable gMG therapy due to initiation of rescue medication	Latest end date across all components of the stable gMG therapy
Change in stable gMG therapy	Earliest end date across all components of the stable gMG therapy.

[a] 14 days are added to account for the q2w dosing interval
[b] If rescue medication is started within 14 days of the last infusion in the double-blind phase, use the day before the start of rescue medication as the ICE date.

For participants with multiple ICEs, the participant ICE date is the earliest of the ICE dates as defined above.

6.20. Appendix 20 Additional Details for Multiple Imputation

Create monotone missing data pattern

Sample SAS MI procedure code for creating monotone missing data is below. Five hundred (500) imputed datasets are created for each combination of randomization group (TRT01P) and baseline MG-ADL randomization stratification level (STRATA02 [<9, ≥9]). Subsequent imputation steps will be performed for each imputed dataset (1 to 500).

```
proc mi data=<input dataset> nimpute=500 seed=<seed number>
        out=<output dataset>;
by trt01p strata02;
var base <list of visits>;
mcmc chain=single nbiter=200 niter=100 impute=monotone;
run;
```

Multiple imputation by MAR regression

Sample SAS MI procedure code for implementing the MAR regression multiple imputation method is below. The imputation model includes randomization group (TRT01P), the baseline MG-ADL and region randomization stratification variables (STRATA02 and STRATA03), and the baseline score. For analyses using the full analysis set (including both seropositive and seronegative participants) the autoantibody status (seropositive, seronegative) randomization stratification variable (STRATA01) will also be included.

```
proc mi data=<input dataset> out=<input dataset> nimpute=1
        seed=<seed number>;
by _imputation_;
var trt01p <strata01> strata02 strata03 base <list of visits>;
class trt01p <strata01> strata02 strata03;
monotone regression (<list of visits> = trt01p <strata01> strata02
                                        strata03 base);
run;
```

Multiple imputation by Copy Reference method

Sample SAS MI procedure code for implementing the stepwise Copy Reference multiple imputation method is below. Missing observations are imputed based on observed values in the placebo group. The imputation model includes randomization group (TRT01P), the baseline MG-ADL and region randomization stratification variables (STRATA02 and STRATA03), and the baseline score. For analyses using the full analysis set (including both seropositive and seronegative participants) the autoantibody status (seropositive, seronegative) randomization stratification variable (STRATA01) will also be included.

```
proc mi data=<input dataset> nimpute=1 seed=<seed number>
         out=<output dataset> _mcmc_seqcr;
by _imputation_;
class trt01p <strata01> strata02 strata03 ;
var <strata01> strata02 strata03 base <list of visits> ;
monotone regression;
```

```
mnar model(<list of visits>/modelobs=(trt01p="Placebo"));
run;
```

Multiple imputation by Jump to Reference method

Sample code for implementing the stepwise Jump to Reference multiple imputation method is below. The `mistep` SAS macro is used (Roger 2018). Missing observations are imputed based on observed values in the placebo group by setting the `trtx` variable to Placebo when there is a missing observation at visit `x`. The imputation model includes randomization group (TRT01P), the baseline MG-ADL and region randomization stratification variables (STRATA02 and STRATA03), and the baseline score. For analyses using the full analysis set (including both seropositive and seronegative participants) the autoantibody status (seropositive, seronegative) randomization stratification variable (STRATA01) will also be included.

```
%mistep(data=<input dataset>, out=mistep2,
        response=<visit 1>,
        class=trt1 <strata01> strata02 strata03,
        model=trt1 <strata01> strata02 strata03 base,
        seed=<seed number>);
%mistep(data=mistep2, out=mistep3,
        response=<visit 2>,
        class=trt2 <strata01> strata02 strata03,
        model=residual1 trt2 <strata01> strata02 strata03 base,
        seed=<seed number);
%mistep(data=mistep3, out=mistep4,
        response=<visit 3>,
        class=trt3 <strata01> strata02 strata03,
        model=residual1 residual2 trt3 <strata01> strata02 strata03 base,
        seed=<seed number>);
.
.
.
%mistep(data=mistep12, out=mistep13,
        response=<visit 12>,
        class=trt12 <strata01> strata02 strata03,
        model=residual1 residual2 residual3<…>residual11
              trt4 <strata01> strata02 strata03 base,
        seed=<seed number>);
```

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