Janssen Research & Development

Clinical Protocol

Protocol Title

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

Short Title

Efficacy and Safety Study of Nipocalimab IV Infusions for Adults With Generalized Myasthenia Gravis

Protocol MOM-M281-011; Phase 3
AMENDMENT 3

M281/ JNJ-80202135 (nipocalimab)

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

Regulatory Agency Identifier Number(s):
IND: 138975
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Status: Approved
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Country/Territory Affected**	**Date**
Amendment 3	All	15 AUGUST 2024
Amendment 2	All	11 JANUARY 2023
Amendment 1	All	21 JULY 2022
Original Protocol	All	19 MARCH 2021

Amendment 3 (15 August 2024)

Overall Rationale for the Amendment: To update the Study Intervention(s) Administered section of the protocol to align with the other studies in the nipocalimab program, to extend the maximum duration of the OLE in the EU region, and to align with standard language across the nipocalimab program. Additionally, clarifying edits from the latest sponsor protocol template were made throughout the protocol.

The changes made to the clinical protocol MOM-M281-011 as part of Protocol Amendment 3 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.11 Appendix 11: Protocol Amendment History.

Section Number and Name	**Description of Change**	**Brief Rationale**
Title page; 1.1 Synopsis	Added EU Trial number.	To align with EU CTR requirements.
1.3 SoA, Table 3	Updated to clarify visits.	Changes were made to clarify the counting of weeks. No changes were made to the frequency or scope of visit assessments.
1.3 SoA, Table 3; 10.10.1 Requirements for EU Region (EUR)	OLE extended from 192 to 240 weeks.	In the EUR, the maximum duration of the OLE period has been extended to Week 240. In non-EUR countries/territories, the OLE will be of variable duration as defined under Section 4.4 End of Study Definition.
2.3.1 Risks for Study Participation	Updated risk language in Table 5.	No changes to risks were identified; text was streamlined to better align with the latest IB.
4.2.1 Study-Specific Ethical Design Considerations	Blood volumes removed.	Blood volume information is not required in this section and is included in Section 8.
5.3.2 Activity	Removed “participants should not begin any new exercise program during the study.”	To clarify study expectations given the duration of the OLE period.
6.1 Study Intervention(s) Administered; 6.2 Preparation/Handling/Storage/ Accountability	Removed table describing study interventions administered and revised text describing study interventions to align with other protocols across the nipocalimab program.	To align across the nipocalimab program. The most current formulation information is maintained within the IB.
6.3 Measures to Minimize Bias	Modified text to allow unblinding of sites after completion of the primary analysis CSR.	Blind linked to operational aspects of the study no longer needs to be maintained for sites during the OLE period.
6.8.2 Rescue Medication/Therapy/Clinical Deterioration	For participants who undergo rescue treatment, text was revised from ‘must’ to ‘may’ complete an	In some circumstances it is not possible to have this unscheduled visit.

Section Number and Name	Description of Change	Brief Rationale
	unscheduled visit prior to continuing in the OLE.	
8 STUDY ASSESSMENTS AND PROCEDURES	Blood volumes updated.	To account for the extended duration of the OLE period.
8.1.3 Revised Myasthenia Gravis Quality of Life – 15	Repeated text removed.	To remove repeated information.
8.6 Biomarkers	Added "Sample collection and testing will comply with local regulations."	To align with current sponsor template.
9.5 Interim Analysis	Added text regarding interim analyses.	To allow periodic analysis of OLE data.
10.4.3 Informed Consent Process	Removed language informing participants who have received previous treatment with rituximab that they may be at an increased risk of infection during the study.	To provide consistency for all nipocalimab protocols. The risk remains as stated in the ICF.
	Removed standard protocol template language allowing an impartial witness to sign the ICF if the participant is unable to read or write.	Administrative correction to remove template text as participants are required to be able to read and write per Inclusion Criterion 16.
10.4.13 Record Retention	Added text regarding record retention under EU regulation.	To align with EU CTR requirements.
10.5.2 Attribution Definitions	Listed factors to be considered in causality assessment and specified that a causal relationship to study intervention should be documented in the participant's medical records.	To align with current sponsor template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

1. PROTOCOL SUMMARY

1.1. Synopsis

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

EU Trial Number: 2023-504152-97

Short Title: Efficacy and Safety Study of Nipocalimab IV Infusions for Adults With Generalized Myasthenia Gravis

DESCRIPTION OF COMPOUND

Nipocalimab is a fully human, aglycosylated, effectorless immunoglobulin G (IgG) 1 monoclonal antibody that targets the neonatal Fc receptor (FcRn) IgG binding site with high affinity at both neutral and acidic pH, thereby interfering with the binding, and hence recycling of native IgG. In endothelial cells, monocytes, and granulocytes, FcRn binding of IgG protects it from degradation and contributes to its long half-life. Interference with FcRn function results in a decrease in serum IgG concentrations. By blocking FcRn-mediated recycling of IgG, nipocalimab is expected to reduce circulating levels of IgG antibodies, including the pathogenic autoantibodies that cause generalized myasthenia gravis (gMG), thus improving disease manifestations.

BENEFIT-RISK ASSESSMENT

A Phase 2 study (MOM-M281-004) of nipocalimab in gMG has shown that the majority of, but not all, participants responded to nipocalimab. The potential risks of exposure to nipocalimab based on its mechanism of action include the potential for increased risk for infection, reduced effectiveness of routine vaccines, activation of latent virus, clinical manifestations of hypoalbuminemia, infusion reaction, drug-drug interactions, and increased lipids. Mitigation strategies include the exclusion of participants at high risk of serious complications, close monitoring of participant safety, and guidelines for participants' management (including monitoring of clinical laboratory tests and treatment interruption/discontinuation criteria), detailed review of permitted and prohibited concomitant medications, and comprehensive medical monitoring of safety data by the sponsor during the conduct of the studies. Comprehensive medical monitoring of safety data includes regular reviews and assessment of adverse events (AEs), adverse events of special interest (AESIs) and serious adverse events (SAEs), and the evaluations of vital signs, physical examination, and laboratory tests' results.

OBJECTIVES AND ENDPOINTS

Objective	Outcome Measures
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)	• Average change in QMG score over Weeks 22 and 24 of the double-blind placebo-controlled phase.

Objective	Outcome Measures
scale, in seropositive gMG participants when treatment is taken as directed.	
To evaluate the 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, 23, 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: 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	• 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.

Objective	Outcome Measures
participants when treatment is taken as directed.	
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-AChR, anti-MuSK, anti-LRP4[a]) 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.

[a] In China, anti-LRP4 autoantibody collection will only be tested at screening.

Objective	Outcome Measures
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[b] (including but not limited to IgG subtypes, IgM, IgA, IgE, MG-associated RNAs, complement proteins. Analyses could use proteomic, glycoprotein, and metabolomic markers).
To explore the changes in physical activity, mobility, and sleep, as measured by accelerometry, in nipocalimab compared to placebo in seropositive gMG participants when treatment is taken as directed (at selected sites).	• Change in Actigraphy watch-collected continuous data on physical activity, mobility, and sleep (including but 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.

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

Objective	Outcome Measures
	• 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.

Hypothesis

The primary hypothesis of this study is that IV nipocalimab is superior to placebo as measured by average change from baseline in the MG-ADL score over Weeks 22, 23 and 24 for seropositive participants (consisting of anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive).

OVERALL DESIGN

This 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. 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 open-label extension (OLE) phase. The OLE will be of variable duration per participating country/territory depending on the timing of market authorization and commercial availability of nipocalimab. For EU region (EUR)-specific information, please refer to Appendix 10. Efficacy, safety, PK, PD, and immunogenicity will be assessed according to the Schedule of Activities. 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. Rollover into the OLE of such participants will not be permitted unless the 24 weeks of study procedures have been completed. 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.

An independent Data Monitoring Committee (DMC) and Major Adverse Cardiovascular Events (MACE) Event Adjudication Committee (EAC) will be commissioned for this study. The responsibilities, authorities, and procedures of each committee will be documented in separate DMC and EAC charters.

Double-blind Placebo-controlled Phase

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[c]. 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

[c] Seronegative participants are no longer being recruited; all participants must have a positive serologic test for a gMG related pathogenic autoantibody (anti-AChR, anti-MuSK and/or anti-LRP4 autoantibodies), confirmed prior to randomization.

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).

Open-label Extension Phase

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/territory or until nipocalimab becomes available commercially or via other continued access program, whichever comes first. For EUR-specific information, please refer to Appendix 10. All participants entering the OLE phase will receive open label nipocalimab treatment of 15 mg/kg q2w. CCI [redacted]

Due to the COVID-19 pandemic, the MOM-M281-005 study, an open-label extension study to evaluate the safety, tolerability, and efficacy of nipocalimab administered to participants with gMG, was placed on hold and subsequently terminated. As a result, some participants from the MOM-281-004 study, a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of nipocalimab administered to adults with gMG, 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 the present study (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.

NUMBER OF PARTICIPANTS

Approximately 190 participants will be enrolled in the double-blind placebo-controlled phase of this study with approximately 95 participants planned in each treatment group. At least 150 eligible seropositive participants will be enrolled. Seronegative participants will also be enrolled.[d]

It is expected that approximately 30 participants who previously participated in the Phase 2 MOM-M281-004 study may directly enter the OLE phase of the MOM-M281-011 study.

INTERVENTION GROUPS AND DURATION

Double-blind Placebo-controlled Phase

Participants will be randomized to 1 of 2 treatment groups as described below:

- Nipocalimab: participants will receive infusion once every 2 weeks (30 mg/kg at first infusion and 15 mg/kg thereafter) for 24 weeks.
- Placebo: participants will receive infusion once every 2 weeks for 24 weeks.

Recalculation of dose during the double-blind placebo-controlled phase for weight gained or lost will be based on the weight measured for each participant every 4 weeks.

Open-label Extension Phase

Participants who completed the Phase 3 double-blind placebo-controlled phase or participants impacted by the study hold and subsequent termination of the MOM-M281-005 study will receive open label treatment

[d] Seronegative participants are no longer being recruited; all participants must have a positive serologic test for a gMG related pathogenic autoantibody (anti-AChR, anti-MuSK and/or anti-LRP4 autoantibodies), confirmed prior to randomization.

of nipocalimab 15 mg/kg administered by IV infusion q2w. CCI [redacted]

Recalculation of dose during the OLE phase for weight gained or lost will be based on the weight measured for each participant every 4 weeks through Extension Week 24 and every 12 weeks thereafter.

EFFICACY EVALUATIONS

Efficacy will be assessed in the following order: the patient-reported assessments of Neuro-QoL Fatigue, PGI-S, PGI-C, MG-QoL15r, EQ-5D-5L questionnaire, followed by the rater administered MG-ADL and then the QMG. Exploratory efficacy assessments will include Clinical Deterioration requiring hospitalization or rescue therapy, Myasthenia Gravis Foundation of America (MGFA) classification, and assessment of physical activity using an actigraphy watch (in selected countries/territories and sites).

PHARMACOKINETIC EVALUATIONS

Blood samples will be taken as described in the Schedule of Activities for measurement of serum nipocalimab concentrations to assess nipocalimab PK.

IMMUNOGENICITY EVALUATIONS

Serum samples will be evaluated for the presence and titers of ADA to nipocalimab. Serum samples that test positive for ADA will be further evaluated to determine the presence of NAb to nipocalimab.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Blood samples will be obtained as outlined in the Schedule of Activities for measurement of total IgG, IgG subtypes, IgM, IgA, IgE, MG-associated RNAs, complement proteins, proteomic, glycoprotein, and metabolomic markers.

SAFETY EVALUATIONS

Safety assessments include collection of AEs and SAEs, use of concomitant medications, clinical laboratory testing (including chemistry, hematology, lipid profiles, and urinalysis), ECGs, vital signs, and physical examinations. A serum or urine pregnancy tests will be performed only for women of childbearing potential (WOCBP). In addition, the emergence of suicidal ideation will be assessed using the C-SSRS. Severe or serious infections and events of hypoalbuminemia (<20 g/L) will be considered adverse events of special interest (AESI).

For participants affected by interruption of the MOM-M281-005 study due to the COVID-19 pandemic: Adverse events that occurred during the COVID-19 pandemic treatment interruption will be recorded as medical history. Recording of new AEs (ie, any new clinically relevant finding or worsening of a pre-existing condition) will start at the time of the ICF is signed for the OLE phase.

STATISTICAL METHODS

Double-blind Placebo-controlled Phase

Participant Information

The primary efficacy analysis set for the double-blind placebo-controlled phase will include all seropositive participants (anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive) who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase.

The full analysis set for the double-blind placebo-controlled phase will include all randomized participants who received at least 1 dose (partial or complete) of any study intervention in the double-blind phase.

Sample Size Determination

A sample size of 75 seropositive participants per group are 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. At least 150 eligible seropositive participants will be enrolled. Seronegative participants will also be enrolled[e].

Primary Estimand (applicable to regions outside of the European Union [EU])

- Population: Seropositive participants (anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive) with gMG who are on a stable MG therapy (or who discontinued MG therapy due to intolerance or lack of efficacy as defined in Inclusion Criterion #4).
- Endpoint: Average change from baseline (screening and Day 1) in MG-ADL total score over Weeks 22, 23 and 24 of the double-blind placebo-controlled phase.
- Intercurrent events and corresponding strategies:
  - Treatment discontinuation of study intervention only due to reasons other than initiation of rescue medication (Hypothetical strategy: as if the intercurrent event had not occurred)
  - Treatment discontinuation of both background MG medication and study intervention due to reasons other than initiation of rescue medication (Hypothetical strategy: see above)
  - Treatment discontinuation of study intervention due to initiation of rescue medication (Hypothetical strategy: see above)
  - Treatment discontinuation of both background MG medication and study intervention due to initiation of rescue medication (Hypothetical strategy: see above)
  - Change in background MG medication, (Hypothetical strategy: see above)
- Summary measure: Difference between treatment means.
- Treatment: 30 mg/kg loading dose followed by 15 mg/kg q2w of nipocalimab versus placebo.

Primary Estimand (applicable to the EU)

- Population: Seropositive participants (anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive) with gMG who are on a stable MG therapy (or who discontinued MG therapy due to intolerance or lack of efficacy as defined in Inclusion Criterion #4).
- Endpoint: Average change from baseline (screening and Day 1) in MG-ADL total score over Weeks 22, 23 and 24 of the double-blind placebo-controlled phase.
- Intercurrent events and corresponding strategies:
  - Treatment discontinuation of study intervention only due to reasons other than initiation of rescue medication (Treatment policy; irrespective of the occurrence of an intercurrent event)
  - Treatment discontinuation of both background MG medication and study intervention due to reasons other than initiation of rescue medication (Treatment policy: see above)

[e] Seronegative participants are no longer being recruited; all participants must have a positive serologic test for a gMG related pathogenic autoantibody (anti-AChR, anti-MuSK and/or anti-LRP4 autoantibodies), confirmed prior to randomization.

  - Treatment discontinuation of study intervention due to initiation of rescue medication (Hypothetical strategy: as if the intercurrent event had not occurred)
  - Treatment discontinuation of both background MG medication and study intervention due to initiation of rescue medication (Hypothetical strategy: see above)
  - Change in background MG medication, (Treatment policy: see above)
- Summary measure: Difference between treatment means.
- Treatment: 30 mg/kg loading dose followed by 15 mg/kg q2w of nipocalimab versus placebo.

Analysis Under the Primary Estimands

Regions outside of the EU

The primary efficacy endpoint, the average change from baseline in MG-ADL total score over Weeks 22, 23, and 24 of the double-blind placebo-controlled phase, will be analyzed using an MMRM with weekly change from baseline as the dependent variable; factors for treatment, autoantibody status, region, week, and treatment-by-week interaction; baseline MG-ADL total score as a covariate and participant as a random effect. Baseline is defined as the arithmetic mean of the screening and Day 1 assessments. An unstructured variance-covariance matrix will be used first. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1). The between-group difference of the average change over Weeks 22, 23, and 24 of the double-blind placebo-controlled phase 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. Observations after the occurrence of an intercurrent event will not be included in the primary analysis, consistent with the hypothetical strategy for handling intercurrent events. Missing data will be handled through the MMRM, assuming missing data are Missing at Random (MAR).

Sensitivity analyses will include a tipping point analysis using multiple imputation with delta adjustment.

EU

The analysis will proceed in the same manner as described above for regions outside of the EU, except for how observations collected after intercurrent events are handled. For intercurrent events addressed with the treatment policy strategy, observations collected after the intercurrent event will be included in the analysis. For intercurrent events addressed with the hypothetical strategy, observations collected after the intercurrent event will not be included in the analysis. Missing data that may result after an intercurrent event will be handled with a Copy Reference multiple imputation approach.

Sensitivity analyses will include a Jump to Reference multiple imputation approach.

Key Secondary Efficacy Endpoints

A fixed sequence approach will be applied to adjust for multiplicity and to control Type 1 error across the primary and the 5 key secondary efficacy endpoints. 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 endpoint. If the primary endpoint is statistically significant, the selected secondary endpoints will be assessed in the following order:

1. The average change in the QMG score over Weeks 22 and 24. Analyzed using a similar method (appropriate for the region) as for the primary efficacy endpoint, but since the QMG is not assessed at Week 23, the contrast will average the change from baseline over Weeks 22 and 24 of the double-blind placebo-controlled phase.

2. 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. 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 Week 22 or 23 in order to have a non-missing average score. A participant with a missing average score will be considered a nonresponder. Analyzed by Cochran-Mantel-Haenszel test controlling for the baseline MG-ADL total score randomization strata (≤9, >9), autoantibody status, and region.
3. Loading dose response, defined for each participant as improvement in the MG-ADL total ≥2 points at Week 1 and/or Week 2. A participant with a missing assessment at either time point will be considered a nonresponder at that time point. Analyzed by Cochran-Mantel-Haenszel test controlling for the baseline MG-ADL total score randomization strata (≤9, >9), autoantibody status, and region.
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 between Week 6 through Week 23 (excursions defined as loss of improvement in MG-ADL score of ≥ 2 points from baseline). A participant with a missing assessment at a time point will be considered a nonresponder at that time point. Analyzed by Cochran-Mantel-Haenszel test controlling for the baseline MG-ADL total score randomization strata (≤9, >9), autoantibody status, and region.
5. 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 50% 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 Week 22 or 23 in order to have a non-missing average score. A participant with a missing average score will be considered a nonresponder. Analyzed by Cochran-Mantel-Haenszel test controlling for the baseline MG-ADL total score randomization strata (≤9, >9), autoantibody status, and region.

Other Efficacy Endpoints

Between-group differences and 95% confidence intervals of the change from baseline in MG-ADL score at each timepoint will be estimated from the same MMRM described above (as appropriate for the region). The percentage of MG-ADL responders, defined as improvement in the MG-ADL total score of ≥2 points, will be summarized at each time point. Similar analyses will be performed for QMG, including sustainability of response as defined for MG-ADL above, where QMG response is defined as improvement of ≥3 points.

Time to first MG-ADL response in the double-blind placebo-controlled period will be summarized with Kaplan-Meier estimates.

The percentage of participants with minimum symptom expression, defined as a MG-ADL total score of 0 or 1, will be summarized at each time point. The percent 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 24-week double-blind placebo-controlled phase will also be summarized.

Change from baseline in the Neuro-QoL Fatigue total score, MG-QoL15r total score, and PGI-S will each be analyzed using a similar MMRM described above for the primary efficacy endpoint. The frequency distributions of PGI-S and PGI-C scores will also be summarized at each time point. Descriptive statistics of the change from baseline in EQ-5D-5L visual analog scale and health status index will be summarized at each time point. The distribution of the level of responses (level 1, 2, 3, 4, and 5) for each of the EQ-5D-5L health dimensions of mobility, self-care, usual activity, pain and discomfort, and anxiety and depression will be summarized at each time point.

Analyses of the MG-ADL described above, and for selected secondary efficacy endpoints, will be repeated for the full analysis set (both seropositive and seronegative participants) and for the seronegative subgroup.

Additional descriptive summaries of MG-ADL will be performed for each type of anti-autobody (anti-AChR, anti-MuSK, anti-LRP4) as the sample size in each subgroup allows.

The raw data sampled by the actigraphy watch sensors will be transformed into derived digital health endpoints, assessing the changes on 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.

Open-label Extension Phase

All efficacy data will be summarized using descriptive statistics.

Other Analyses

Serum nipocalimab concentrations will be summarized over time to assess the PK of nipocalimab.

The incidence and titers of antibodies to nipocalimab will be summarized by treatment group over time.

Selected circulating biomarkers will be assayed and their potential relationship to clinical status may be explored.

A pharmacometrics model-based assessment will be conducted to describe the relationships of PK, PD (IgG lowering), and efficacy (MG-ADL and QMG). Details will be provided in a model-based PK/IgG/efficacy analysis plan, and results of the model-based PK/IgG/efficacy analysis will be presented in a separate technical report.

Safety Analyses

Safety data will be analyzed for both study phases using the full analysis set.

The verbatim terms used in the electronic case report form (eCRF) by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group. Separate summaries will be provided for each phase of the study. Participants who die, who discontinue treatment due to an AE, or who experience an SAE will be summarized separately. Listings of all participants with MACE (non-fatal myocardial infarction, stroke, and cardiovascular death) will be provided.

The treatment-emergent AEs (TEAEs) of special interest (AESI) will be examined separately grouped in the following categories: Severe or serious infections and hypoalbuminemia (<20 g/L). The AESIs will be further listed in the SAP.

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

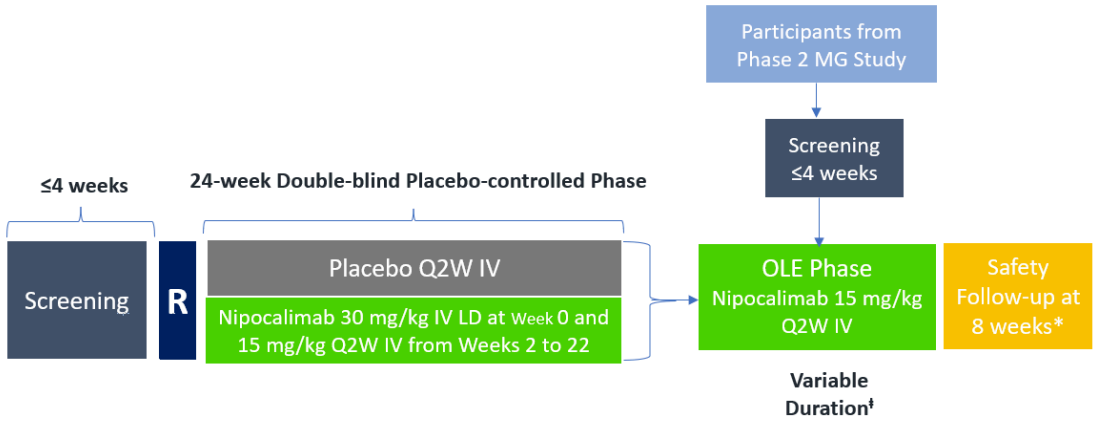
The ECG data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made. All clinically relevant abnormalities in ECG waveforms that are changes from the baseline readings will be reported.

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, body weight measurements, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

The percentage of participants with suicidal ideation or suicidal behavior based on the C-SSRS will be summarized.

1.2. Schema

Figure 1: Schematic Overview of the Study



R: Randomization into double-blind phase (1:1). LD: Loading Dose OLE: Open-label extension

* Participants who withdraw or discontinue after receiving any amount of study intervention will be required to complete a safety follow-up visit 8 weeks after their last dose.

‡ For EUR-specific information refer to Appendix 10.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities - Double-Blind Placebo-controlled Phase

	Screening Phase Days[a] -28 to -1	Double-Blind Placebo-controlled Phase[b]															
		Day 1	W1	W2	W3	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W23	W24/ EOP/ET[b]
Visit Window (days)			±1	±2	± 2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Type of Visit	**Site**	**Site**	**Phone[c]**	**Site**	**Phone[c]**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Phone[c]**	**Site**
Study Procedure																	
Screening/Administrative																	
Informed consent[d]	X																
Inclusion/exclusion criteria[e]	X																
Demographics	X																
Medical history	X																
Weight	X	X				X		X		X		X		X			X[f]
Height	X																
Study Intervention Administration																	
Randomization		X															
Study intervention infusion		X		X		X	X	X	X	X	X	X	X	X	X		X[g]
Efficacy Assessments[h]																	
Neuro-QoL-Fatigue		Pre		Pre		Pre		Pre		Pre		Pre		Pre	Pre		X[f]
PGI-S		Pre		Pre		Pre		Pre		Pre		Pre		Pre	Pre		X[f]
PGI-C				Pre		Pre		Pre		Pre		Pre		Pre	Pre		X[f]
MG-QoL15r		Pre		Pre		Pre	Pre	Pre		Pre		Pre		Pre	Pre		X[f]
EQ-5D-5L		Pre		Pre		Pre		Pre		Pre		Pre		Pre	Pre		X[f]
MG-ADL	X	Pre	X	Pre	X	Pre	Pre	Pre		Pre		Pre		Pre	Pre	X	X[f]
QMG	X	Pre		Pre		Pre		Pre		Pre		Pre		Pre	Pre		X[f]
MGFA classification	X	Pre								Pre							X[f]
Actigraphy data collection (at selected sites)[t]	← Continuous assessment through study visits in the double-blind phase →																

Table 1: Schedule of Activities - Double-Blind Placebo-controlled Phase

	Screening Phase Days[a] -28 to -1	Double-Blind Placebo-controlled Phase[b]															
		Day 1	W1	W2	W3	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W23	W24/ EOP/ET[b]
Visit Window (days)			±1	±2	± 2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Type of Visit	**Site**	**Site**	**Phone[c]**	**Site**	**Phone[c]**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Phone[c]**	**Site**
Study Procedure																	
Safety Assessments																	
Physical examination	X[i]	Pre[j]		Pre[j]		Pre[j]		Pre[j]		Pre[j]		Pre[j]		Pre[j]			X[f,i]
C-SSRS[h]	X	Pre		Pre		Pre		Pre		Pre		Pre		Pre			X[f]
Vital signs[k]	X	Pre, Post		Pre, Post		Pre, Post	Pre, Post	Pre, Post	Pre Post	Pre, Post	Pre, Post	Pre, Post	Pre, Post	Pre, Post	Pre, Post		X[f]
12-lead ECG	X									Pre							X[f]
Infusion reaction evaluation[k,l]		X		X		X	X	X	X	X	X	X	X	X	X		X[g]
Clinical Laboratory Tests																	
Blood for clinical laboratory assessments	X	Pre		Pre		Pre		Pre		Pre		Pre		Pre			Pre[f]
Lipid panel	X[m]	Pre[m]				Pre[m]		Pre[m]		Pre[m]							X[f,m]
Urinalysis (dipstick)	X	Pre		Pre		Pre		Pre		Pre		Pre		Pre			X[f]
Urine drug screen	X																
Pregnancy test (S serum, U urine)[n,o]	S	U, Pre				U, Pre		U, Pre		U, Pre		U, Pre		U, Pre			U[f]
FSH (for menopausal women)[u]	X																
HIV-1 & 2, hepatitis B & C	X																
Clinical Pharmacology Assessments																	
Serum for nipocalimab concentrations[o]		Pre, Post		Pre, Post		Pre, Post		Pre, Post		Pre, Post		Pre, Post		Pre, Post			X[f]
Serum for ADA and NAb to nipocalimab[o]		Pre		Pre		Pre		Pre		Pre		Pre		Pre			X[f]

Table 1: Schedule of Activities - Double-Blind Placebo-controlled Phase

	Screening Phase Days[a] -28 to -1	Double-Blind Placebo-controlled Phase[b]															
		Day 1	W1	W2	W3	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W23	W24/ EOP/ET[b]
Visit Window (days)			±1	±2	± 2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Type of Visit	**Site**	**Site**	**Phone[c]**	**Site**	**Phone[c]**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Phone[c]**	**Site**
Study Procedure																	
Medical Resource Utilization																	
HRUQ[s]		X								X							X[f]
TSQM-9																	X[f]
Pharmacodynamics and Biomarkers																	
Serum for autoantibody levels[o,q]	X	Pre		Pre		Pre	Pre	Pre		Pre		Pre		Pre	Pre		X[f]
Blood for exploratory[r] biomarkers		Pre		Pre		Pre		Pre		Pre		Pre		Pre			X[f]
Serum for Ig types[r]	X	Pre		Pre		Pre	Pre	Pre		Pre		Pre		Pre	Pre		X[f]
Ongoing Participant Review																	
Adverse events		← Monitored throughout the study →															
Prior and concomitant medications	X	← Monitored throughout the study →															

Abbreviations: ADA anti-drug antibody; AE adverse event; C-SSRS Columbia-Suicide Severity Rating Scale; ECG electrocardiogram; EOP end of phase; EQ-5D-5L EuroQol 5-dimension 5-level quality of life questionnaire; ET early termination; FSH follicle-stimulating hormone; HIV human immunodeficiency virus; HRUQ Healthcare Resource Use Questionnaire; Ig immunoglobulin; IV intravenous; MG-ADL Myasthenia Gravis-Activities of Daily Living; MGFA Myasthenia Gravis Foundation of America; MG-QoL 15r Revised Myasthenia Gravis Quality of Life – 15 Scale; NAb neutralizing antibodies; Neuro-Qol-Fatigue Fatigue items of the Quality of Life in Neurological Disorders scale; OLE open-label extension; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; PK pharmacokinetic; pre pre-infusion; PRO patient-reported outcome; post post-infusion; QMG Quantitative Myasthenia Gravis; S serum; TSQM-9 Treatment Satisfaction Questionnaire for Medication; U urine; W week

Note: Pre and post refer to the timing of the assessment relative to the study intervention infusion.

Footnotes:

[a] The screening period may be extended by up to 2 weeks to accommodate delays in obtaining screening autoantibody results.

[b] Participants who discontinue study intervention during the double-blind placebo-controlled phase for any reason other than Clinical Deterioration requiring hospitalization or rescue therapy should continue study procedures according to the Schedule of Activities until the 24-week phase is completed. Rollover into the OLE of such participants will not be permitted unless the 24 weeks of study procedures have been completed. Participants who permanently discontinue or withdraw from the study either due to a clinical deterioration or for any other reason during the double-blind placebo-controlled phase should complete the ET visit assessments. These participants should also return for a safety follow-up visit 8 weeks after the last infusion.

[c] Phone visits are to be performed by telephone call only (**not** video call).

[d] Must be signed before first study-related activity.

[e] Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Appendix 4, Regulatory, Ethical, and Study Oversight Considerations. Check clinical status again before first dose of study intervention.

[f] These assessments should be performed for all participants. For participants who continue to the OLE phase, these assessments must be completed prior to the first infusion of the OLE phase.

[g] Participants who continue to OLE phase only.

[h] **The participant's acetylcholinesterase inhibitor dose must be withheld for approximately 12 hours or longer prior to performing MG-ADL and QMG at all visits, and attempts will be made to reschedule the visit within the per protocol visit window if the dose was taken <12 hours prior**. Participants may take their dose of acetylcholinesterase inhibitor once the MG-ADL and QMG are completed. **All the efficacy assessments must be done starting at approximately the same time of day (± 2 hours) as performed at screening**, and prior to study intervention administration on infusion days. The following PROs must be completed first: Neuro-QoL-Fatigue, PGI-S, PGI-C, MG-QoL15r, EQ-5D-5L followed by the MG-ADL and then the QMG (in that order). The C-SSRS should be performed after completion of the efficacy assessments.

[i] Complete physical examination, including assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, extremities.

[j] Focused physical examination for changes in neurologic function, upper respiratory tract (ears, nose, throat, and sinuses), eyes, and lungs, abdomen, or skin.

[k] Vital signs (temperature, recumbent systolic blood pressure and diastolic blood pressure, respiratory rate, and pulse rate) will be measured prior to the start of each infusion, 30 minutes post-infusion (all infusions), and 1-hour post-infusion (first 3 infusions).

[l] Participants will be observed for safety 1-hour post-infusion after the first 3 infusions; if no clinically relevant AEs related to the infusion are observed in these first 3 infusions, participants will be observed for 30 minutes after subsequent infusions. Refer to Section 8.2.7 and Section 8.2.8 for details for infusion reaction evaluation.

[m] A full lipid panel will be collected at this visit. Lipid labs at Screening visit can be non-fasting, while all other lipid draws in the double-blind placebo-controlled phase will be fasting. Fasting is recommended for at least 6 hours. Fasting lipid panel includes total cholesterol, HDL, LDL (calculated), and triglycerides. If sites/participants cannot accommodate fasting for the duration of the double-blind placebo-controlled phase due to scheduling or medical issues, non-fasting may be permitted following discussion with the sponsor's medical monitor.

[n] Women of childbearing potential only, including premenopausal or perimenopausal (ie, not postmenopausal where postmenopausal is defined as amenorrhea 12 months or greater), and also including those with a screening FSH ≤40 IU/L or 40 mIU/mL. Additional serum pregnancy testing may be performed at the discretion of the investigator or if required by local regulations.

[o] Test results must be read prior to dosing.

[p] All blood samples for assessing predose serum nipocalimab concentration and antibodies to nipocalimab MUST be collected BEFORE the administration of the study intervention. One blood sample (instead of 2) will be collected for PK/ADA and the obtained serum sample will be split for each assay. Postdose samples will be collected 45 minutes (±15 minutes) after the end of infusion. The blood sample should be drawn from the opposite arm than the IV line.

[q] In China, anti-LRP4 autoantibody collection will only be tested at Screening.

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

[s] Medical resource utilization (MRU) data, associated with medical encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ) and will be reviewed at the scheduled visits and on an ongoing basis whenever an encounter occurs.

[t] Only applicable to participants randomized at select sites post-Amendment 1. The actigraphy watch will be provided to the participant at the screening visit and worn continuously on the non-dominant wrist from the screening visit until Week 24/ET/EOP of the double-blind placebo-controlled phase. Participants who will not prove eligible will return their actigraphy watch to the study site. Participants will bring the watch to each visit, during which the data from the watch may be downloaded, as necessary. At the Week 24/ET/EOP visit, participants will return the actigraphy watch to the study site.

[u] FSH at screening is required for female participants exhibiting amenorrhea for approximately 12 months (ie, perimenopausal). If the FSH is not elevated (i,. if FSH is ≤40 IU/Lor 40 mIU/mL), they must follow contraception guidance for WOCBP. Women exhibiting amenorrhea for 12 months or greater are classified as post-menopausal and do not need FSH testing.

Table 2: Schedule of Activities - Open-label Extension Phase (Extension Week 1 through Extension Week 24)

	Nipocalimab Treatment Period													
	Q2W Regimen													
	Screening[a] (-28 to -1)	Open-label Entry Day 1[b] (ED1)	EW 2	EW 4	EW 6	EW 8	EW 10	EW 12	EW 14	EW 16	EW 18	EW 20	EW 22	EW 24
Visit Window (Days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Study Procedure														
Screening/Administrative														
Informed consent (ICF)[c]	X													
Inclusion/exclusion criteria[d]	X													
Demographics	X													
Medical history	X													
Study Intervention Administration														
Study intervention infusion		X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments[e]														
Neuro-QoL Fatigue Assessment		Pre		Pre		Pre		Pre		Pre		Pre		Pre
PGI-S		Pre		Pre		Pre		Pre		Pre		Pre		Pre
PGI-C				Pre		Pre		Pre		Pre		Pre		Pre
MG-QoL15r		Pre		Pre		Pre		Pre		Pre		Pre		Pre
EQ-5D-5L		Pre		Pre		Pre		Pre		Pre		Pre		Pre
MG-ADL	X	Pre	Pre	Pre	Pre	Pre		Pre		Pre		Pre		Pre
QMG	X	Pre		Pre		Pre		Pre		Pre		Pre		Pre
MGFA Clinical Classification	X	Pre						Pre						Pre
Safety Assessments														
Physical examination[f]	X	X						X						X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X		X		X		X		X		X		X
Height	X													
12-lead ECG	X	X						X						X

Table 2: Schedule of Activities - Open-label Extension Phase (Extension Week 1 through Extension Week 24)

	Nipocalimab Treatment Period													
	Q2W Regimen													
	Screening[a] (-28 to -1)	Open-label Entry Day 1[b] (ED1)	EW 2	EW 4	EW 6	EW 8	EW 10	EW 12	EW 14	EW 16	EW 18	EW 20	EW 22	EW 24
Visit Window (Days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Study Procedure														
C-SSRS[e]	X	X		X				X						X
Infusion reaction evaluation[h]		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests														
Blood for clinical laboratory assessments	X	Pre	Pre	Pre		Pre		Pre		Pre		Pre		Pre
Lipid panel (non-fasting)	X			Pre				Pre						Pre
Urinalysis	X	Pre	Pre	Pre		Pre		Pre		Pre		Pre		X
Urine drug screen	X													
Serology for HIV, Hepatitis B, Hepatitis C	X													
Pregnancy Test (S serum, U urine)[i,j]	S	U, Pre		U, Pre		U, Pre		U, Pre		U, Pre		U, Pre		U, Pre
FSH (for menopausal women)[q]	X													
Clinical Pharmacology Assessments														
Serum for, nipocalimab concentrations, ADA and NAb[k,l,m]		X				X				X				X
Medical Resource Utilization														
HRUQ[p]		X						X						X
TSQM-9														X
Pharmacodynamics and Biomarkers														
Blood sample for exploratory biomarkers[k, n]		X		X		X		X						X

Table 2: Schedule of Activities - Open-label Extension Phase (Extension Week 1 through Extension Week 24)

	Nipocalimab Treatment Period													
	Q2W Regimen													
	Screening[a] (-28 to -1)	Open-label Entry Day 1[b] (ED1)	EW 2	EW 4	EW 6	EW 8	EW 10	EW 12	EW 14	EW 16	EW 18	EW 20	EW 22	EW 24
Visit Window (Days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Study Procedure														
Serum for Ig types[k,n]	X	X		X		X		X						X
Serum for autoantibodies[k,o]		X		X		X		X						X
Ongoing Participant Review														
Concomitant therapy/Rescue Therapy	← Monitored throughout the study →													
Adverse events	← Monitored throughout the study →													

Abbreviations: ADA anti-drug antibodies; AE adverse event; COVID-19 coronavirus disease 2019; C-SSRS Columbia-Suicide Severity Rating Scale; ED extension day; EQ-5D-5L EuroQol 5-Dimension 5-Level questionnaire; EW OLE extension Week; ET early termination; HIV human immunodeficiency virus; HRUQ Healthcare Resource Use Questionnaire Ig immunoglobulin; IV intravenous; MG myasthenia gravis; MG-ADL Myasthenia Gravis – Activities of Daily Living; MGFA Myasthenia Gravis Foundation of America; MG-QoL15r revised Myasthenia Gravis Quality of Life 15 Scale; NA not applicable; NAb neutralizing antibodies; Neuro-QoL Quality of Life in Neurological Disorders; OLE open-label extension; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; PK pharmacokinetic; pre pre-infusion; PRO patient-reported outcome; QMG Quantitative Myasthenia Gravis; . TSQM-9 Treatment Satisfaction Questionnaire for Medication.

Footnotes:

[a] No screening is required for participants who directly transition from the double-blind placebo-controlled phase. Screening must be performed for return participants affected by the interruption of study MOM-M281-005 due to the COVID-19 pandemic.

[b] For participants who directly transition into the OLE from the double-blind placebo-controlled phase, the EOP/ET visit will be the same as the Day 1 visit of the OLE. The assessments from the last visit in the double-blind placebo-controlled phase can suffice for the Day 1 OLE assessments.

[c] Must be signed before first study-related activity (return participants affected by the interruption of study MOM-M281-005 due to the COVID-19 pandemic only).

[d] Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Appendix 4, Regulatory, Ethical, and Study Oversight Considerations. Check clinical status again before first dose of study intervention.

[e] **The participant's acetylcholinesterase inhibitor dose must be withheld for approximately 12 hours or longer prior to performing MG-ADL and QMG at all visits, and attempts will be made to reschedule the visit within the per protocol visit window if the dose was taken <12 hours prior.** Participants may take their dose of acetylcholinesterase inhibitor once the MG-ADL and QMG are completed. **All the efficacy assessments must be done starting at approximately the same time of day (± 2 hours) as performed at screening**, and prior to study intervention administration on infusion days. The following PROs must be completed

first: Neuro-QoL-Fatigue, PGI-S, PGI-C, MG-QoL15r, EQ-5D-5L followed by the MG-ADL and then the QMG (in that order). The C-SSRS should be performed after completion of the efficacy assessments.

[f] Full physical examinations to be performed at OLE enrollment and end of treatment/early termination, and a focused physical examination at all other site visits. Focused physical examinations should determine if there has been any change in neurologic function, upper respiratory tract (ears, nose, throat, and sinuses), eyes and lungs, abdomen, or skin.

[g] Vital signs (temperature, recumbent systolic blood pressure and diastolic blood pressure, respiratory rate, and pulse rate) will be measured prior to the start of each infusion, 30 minutes post-infusion (all infusions), and 1-hour post-infusion (first 3 infusions).

[h] Participants will be observed for safety 1-hour post-infusion after the first 3 infusions; if no clinically relevant AEs related to the infusion are observed in these first 3 infusions, participants will be observed for 30 minutes after subsequent infusions. Refer to Section 8.2.7 and Section 8.2.8 for details for infusion reaction evaluation.

[i] Women of childbearing potential only, including premenopausal or perimenopausal (ie, not postmenopausal where postmenopausal is defined as amenorrhea 12 months or greater), and also including those with a screening FSH ≤40 IU/L or 40 mIU/mL. Additional serum pregnancy testing may be performed at the discretion of the investigator or if required by local regulations.

[j] Test results must be read prior to dosing.

[k] Blood samples must be collected before the start of the nipocalimab infusion.

[l] The serum from this blood sample will be split into aliquots and may be tested for nipocalimab concentrations, ADA, and NAb.

[m] All blood samples for assessing predose serum nipocalimab concentration and antibodies to nipocalimab MUST be collected BEFORE the administration of the study intervention. One blood sample (instead of 2) will be collected for PK/ADA and the obtained serum sample will be split for each assay. The blood sample should be drawn from the opposite arm than the IV line.

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

[o] In China, anti-LRP4 will only be tested at screening.

[p] Medical resource utilization (MRU) data, associated with medical encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ) and will be reviewed at the scheduled visits and on an ongoing basis whenever an encounter occurs.

[q] FSH at screening is required for female participants exhibiting amenorrhea for approximately 12 months (ie, perimenopausal). If the FSH is not elevated (ie, if FSH is ≤40 IU/L or 40 mIU/mL), they must follow contraception guidance for WOCBP. Women exhibiting amenorrhea for 12 months or greater are classified as post-menopausal and do not need FSH testing.

Table 3: Schedule of Activities - Open-label Extension Phase (Extension Week 26 through Extension Week 240)

	Nipocalimab Treatment Period	
	Q2W Regimen	
	Continue visits Q2W (to receive nipocalimab infusions)	End of Treatment/ET (2W after last nipocalimab dose)
Visit Window (Days)	±3	±3
Study Procedure		
Study Intervention Administration		
Study intervention infusion	Q2W (from W24)	
Efficacy Assessments[a]		
Neuro-QoL Fatigue Assessment	Pre Q12W (from W24)	X
PGI-S	Pre Q12W (from W24)	X
PGI-C	Pre Q12W (from W24)	X
MG-QoL15r	Pre Q12W (from W24)	X
EQ-5D-5L	Pre Q12W (from W24)	X
MG-ADL	Pre Q12W (from W24)	X
QMG	Pre Q12W (from W24)	X
MGFA Clinical Classification	Pre Q12W (from W24)	X
Safety Assessments		
Physical examination[b]	Q12W (from W24)	X
Vital signs[c]	Q2W (from W24)	X
Weight	Q12W (from W24)	X
12-lead ECG	Q24W (from W24)	X
C-SSRS[a]	Q12W (from W24)	X
Infusion reaction evaluation[d]	Q2W (from W24)	
Clinical Laboratory Tests		
Blood for clinical laboratory assessments	Q12W (from W24) through Week 96, then Q24W (ie, W120, etc)	X

Table 3: Schedule of Activities - Open-label Extension Phase (Extension Week 26 through Extension Week 240)

	Nipocalimab Treatment Period	
	Q2W Regimen	
	Continue visits Q2W (to receive nipocalimab infusions)	End of Treatment/ET (2W after last nipocalimab dose)
Visit Window (Days)	±3	±3
Study Procedure		
Lipid panel (non-fasting)	Q12W (from W24) through Week 96, then Q24W (ie, W120, etc)	X
Urinalysis	Q12W (from W24) through Week 96, then Q24W (ie, W120, etc)	X
Pregnancy Test (S serum, U urine)[e,f]	Q4W U, Pre	
Clinical Pharmacology Assessments		
Serum for, nipocalimab concentrations, ADA and NAb[g,h,i]	Q12W (from W24) through Week 96, then Q24W (ie, W120, etc)	X
Medical Resource Utilization		
HRUQ	Q12W (from W24)	X
TSQM-9	Q24W (from W24)	X
Pharmacodynamics and Biomarkers		
Blood sample for exploratory biomarkers[g,j]	Q12W (from W24) through Week 96, then Q24W (ie, W120, etc)	X
Serum for Ig types[g,j]	Q12W (from W24) through Week 96, then Q24W (ie, W120, etc)	X
Serum for autoantibodies[g,k]	Q12W (from W24) through Week 96, then Q24W (ie, W120, etc)	X
Ongoing Participant Review		
Concomitant therapy/Rescue Therapy	← Monitored throughout the study →	
Adverse events	← Monitored throughout the study →	

Abbreviations: ADA anti-drug antibodies; AE adverse event; COVID-19 coronavirus disease 2019; C-SSRS Columbia-Suicide Severity Rating Scale; EQ-5D-5L EuroQol 5-Dimension 5-Level questionnaire; ET early termination; HIV human immunodeficiency virus; HRUQ Healthcare Resource Use Questionnaire; Ig immunoglobulin; IV intravenous; MG myasthenia gravis; MG-ADL Myasthenia Gravis – Activities of Daily Living; MGFA Myasthenia Gravis Foundation of America; MG-QoL15r revised Myasthenia Gravis Quality of Life 15 Scale; NA not applicable; NAb neutralizing antibodies; Neuro-QoL Quality of Life in Neurological Disorders; OLE open-label extension;; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; PK pharmacokinetic; pre pre-infusion; PRO patient-reported outcome; Q2W every 2 weeks; Q4W every 4 weeks; Q12W every 12 weeks; Q24W every 24 weeks; QMG Quantitative Myasthenia Gravis; TSQM-9 Treatment Satisfaction Questionnaire for Medication; W week.

Note: CCI [redacted]

Footnotes:

[a] **The participant's acetylcholinesterase inhibitor dose must be withheld for approximately 12 hours or longer prior to performing MG-ADL and QMG at all visits, and attempts will be made to reschedule the visit within the per protocol visit window if the dose was taken <12 hours prior.** Participants may take their dose of acetylcholinesterase inhibitor once the MG-ADL and QMG are completed. **All the efficacy assessments must be done starting at approximately the same time of day (± 2 hours) as performed at screening**, and prior to study intervention administration on infusion days. The following PROs must be completed first: Neuro-QoL-Fatigue, PGI-S, PGI-C, MG-QoL15r, EQ-5D-5L followed by the MG-ADL and then the QMG (in that order). The C-SSRS should be performed after completion of the efficacy assessments.

[b] Full physical examinations to be performed at study enrollment and end of treatment/early termination, and a focused physical examination at all other site visits. Focused physical examinations should determine if there has been any change in neurologic function, upper respiratory tract (ears, nose, throat, and sinuses), eyes and lungs, abdomen, or skin.

[c] Vital signs (temperature, recumbent systolic blood pressure and diastolic blood pressure, respiratory rate, and pulse rate) will be measured prior to the start of each infusion and 30 minutes post-infusion.

[d] Participants will be observed for safety 1-hour post-infusion after the first 3 infusions; if no clinically relevant AEs related to the infusion are observed in these first 3 infusions, participants will be observed for 30 minutes after subsequent infusions. Refer to Section 8.2.7 and Section 8.2.8 for infusion reaction evaluation.

[e] Women of childbearing potential only. Additional serum pregnancy testing may be performed at the discretion of the investigator or if required by local regulations.

[f] Test results must be read prior to dosing.

[g] Blood samples must be collected before the start of the nipocalimab infusion.

[h] The serum from this blood sample will be split into aliquots and may be tested for ADA, nipocalimab concentrations, and NAb.

[i] All blood samples for assessing predose serum nipocalimab concentration and antibodies to nipocalimab MUST be collected BEFORE the administration of the study intervention. One blood sample (instead of 2) will be collected for PK/ADA and the obtained serum sample will be split for each assay. The blood sample should be drawn from the opposite arm than the IV line.

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

[k] In China, anti-LRP4 will only be tested at screening.

Table 4: Safety Follow-up Phase

Phase	Safety Follow-up Visit
Study Week	**Varies Per Participant**
Visit	**8 Weeks after the participants last infusion of study intervention**
Visit Window, ±Days	**±7**
Study Procedure	
Weight	X
Chemistry, hematology, non-fasting lipid panel, and urinalysis	X
Urine pregnancy test[a]	X
Physical examination	X
C-SSRS	X
Vital signs	X
12-lead ECG	X
Serum for, nipocalimab concentrations, ADA, and NAb[b]	X
Serum for Ig types[c]	X
Adverse events	X
Concomitant medications	X

Participants who permanently discontinue or withdraw from any phase of the study will be requested to return to the study site 8 weeks from last infusion to complete follow-up assessments

[a] Women of childbearing potential only.

[b] The serum from this blood sample will be split into aliquots and may be tested for ADA, nipocalimab concentrations, and NAb.

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

2. INTRODUCTION

With a prevalence of 15 to 25 cases per 100,000 individuals and an annual incidence of 0.8 to 1 case per 100,000 individuals (Carr 2010; Gilhus 2019), myasthenia gravis (MG) is a rare, heterogeneous, neuromuscular disease characterized by fluctuating, fatigable muscle weakness. Weakness most often affects ocular, bulbar, proximal extremity, neck, and respiratory muscles, fluctuates during the day, and worsens with fatigue, repetitive activities, heat, infection, and stress (Grob 2008). In most cases, initial symptoms are ocular and include ptosis and diplopia, but within 2 to 3 years of onset, the disease usually worsens and other muscles become affected; this is referred to as generalized MG (gMG). Additional symptoms typically include difficulty chewing, dysphagia, dysarthria, hypophonia, dyspnea, an inability to hold the mouth closed, a "snarling" expression when attempting to smile, an appearance of sadness or sleepiness, difficulty holding the head upright, and weakness in the hands and feet (Grob 2008; Scherer 2005). Disease progression is associated with considerable morbidity due to aspiration, an increased incidence of respiratory infections and of falls, and side effects of immunosuppressant therapies (Gilhus 2016a). In addition, respiratory muscle weakness can lead to myasthenic crisis, which can be life threatening and require hospitalization, mechanical ventilation, tube feeding, fast-acting immunosuppressive agents, and intensive care (Gilhus 2016a; Sanders 2016).

Myasthenia gravis is caused by pathogenic autoantibodies that impair cholinergic transmission in the postsynaptic membrane at the neuromuscular junction and impair or prevent muscle contraction (Gilhus 2015; Gilhus 2016a; Gilhus 2016b). In approximately 85% of cases, circulating antibodies target the acetylcholine receptor (AChR) itself. Up to half of the remaining 15% of patients have antibodies against muscle-specific tyrosine kinase (MuSK), an enzyme critical for neuromuscular junction formation and agrin induced AChR clustering, while approximately 7% to 8% of patients have neither anti-AChR nor anti-MuSK antibodies and have historically been considered "seronegative" (Meriggioli 2012). In this latter group, approximately 10% have pathogenic autoantibodies against lipoprotein-related protein receptor 4, an end plate protein that, along with MuSK, serves as an agrin receptor and is required for AChR clustering and normal neuromuscular junction formation (Meriggioli, 2012; Zhang 2012).

There is no cure for MG and most patients require lifelong treatment (recently reviewed in Barnett 2019; Dalakas 2019; Farmakidis 2018; Gilhus 2019; Mantegazza 2018; Morren 2020). Preferred symptomatic treatment of gMG is with acetylcholinesterase inhibitors, such as pyridostigmine (Sanders 2016). However, to meet the treatment goals of full or nearly full physical function and a high quality of life, most patients with gMG also require thymectomy and/or treatment with corticosteroids and/or immunosuppressive medications, such as azathioprine, mycophenolate, mofetil/mycophenolic acid, cyclosporine, and tacrolimus (Barnett 2019). More recently, targeted immunosuppressants have been used, such as rituximab, a B-cell depleting monoclonal antibody and eculizumab, an inhibitor of C5 activation, which is a key step in complement activation (Barnett 2019). Several new agents, including rozanolixizumab, efgartigimod, and RVT-1401, are under investigation (Gable 2020). For acute severe episodes, fast-acting therapeutic modalities aimed at removing autoantibodies, such as plasma exchange and immunoadsorption, or producing immunomodulatory effects, such as intravenous

immunoglobulin (IVIg), are often used. While many patients with gMG can be managed with existing therapies, most of these treatments are associated with sometimes serious side effects, pregnancy contraindication, accessibility issues, patient inconvenience, and overall time and cost implications. Despite availability of treatment options, significant unmet need persists, as 10% to 20% of patients may not respond to treatment and are currently left with no viable therapeutic options (Schneider-Gold 2019; Silvestri 2014); this significant unmet need was also reflected by the 7% self-reported refractory cases in a recent survey of US MGFA registry participants (Boscoe 2019). These patients either fail to respond adequately or cannot tolerate multiple therapies for MG and continue to suffer profound muscle weakness and severe disease symptoms that limit function and can be life threatening (Howard 2013; Mantegazza 2018; Sanders 2016; Sathasivam 2014; Silvestri 2014). Thus, there is a clear unmet medical need for new safe and effective treatments for gMG.

Nipocalimab (also referred to as JNJ-80202135 or M281) is a fully human aglycosylated immunoglobulin (Ig)G1 monoclonal antibody (mAb) designed to selectively bind, saturate, and block the IgG binding site on the endogenous neonatal Fc receptor (FcRn). The primary role of FcRn in humans is to bind, salvage, and recycle IgG into circulation or transport IgG across the placenta, following nonspecific pinocytosis into endothelial cells and cells of the reticuloendothelial system. At homeostasis, FcRn recycles IgG to maintain serum IgG levels and extend IgG half-life and also regulates immune cell inflammatory responses to IgG complexes. By targeting the IgG binding site on FcRn, nipocalimab is expected to block the binding and, hence, recycling of IgG, resulting in a decrease in circulating IgG antibody levels, including pathogenic IgG autoantibodies and alloantibodies. FcRn has been shown also to contribute to the protection of circulating immune complexes (CICs), and the inhibition of FcRn results in more rapid elimination of CICs (Blumberg 2019). Clinical studies with other anti-FcRn mAbs or Fc fragments confirm that blockade of IgG binding to FcRn rapidly decreases IgG to low but predictable steady-state levels while also effectively decreasing circulating levels of pathogenic autoantibodies by increasing IgG catabolism (Peter 2020). In addition, it has been shown that induction of inflammatory pathways is dependent on FcRn and can be blocked by an FcRn inhibitor. Furthermore, this blockade of FcRn-IgG binding may also directly inhibit inflammatory immune cell responses to IgG that recruit and stimulate lymphocytes (Blumberg 2019; Hubbard 2020).

Administration of nipocalimab has not been observed to reduce levels of other immunoglobulins, including immunoglobulin IgA, IgM, or IgE, or impact other aspects of immune system response to infection, considering FcRn blockage only affects IgG half-life and does not prevent IgG production.

To date, nipocalimab has not been approved in any therapeutic indication. Because of its mechanism of action, nipocalimab is being evaluated for the treatment of patients with diseases mediated by pathogenic IgG antibodies, including gMG and warm autoimmune hemolytic anemia (wAIHA), as well as diseases of the fetus and newborn caused by maternofetal transfer of pathogenic IgG antibodies, such as early onset severe hemolytic disease of the fetus and newborn (EOS-HDFN).

For the most comprehensive nonclinical and clinical information regarding nipocalimab, refer to the latest version of the Investigator's Brochure (IB).

The term “study intervention” throughout the protocol, refers to the biologic product as defined in Section 6.1, Study Interventions Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Results of clinical studies support nipocalimab’s safety and potential efficacy. As discussed in Section 2.2, nipocalimab was well tolerated by healthy adults in 3 completed Phase 1 studies and by adult patients with gMG in a completed Phase 2 study. In all studies, treatment with nipocalimab produced marked and sustained reductions in IgG concentrations, confirming its intended mechanism of action. In the Phase 2 gMG study, nipocalimab produced rapid, dose-dependent, sustained IgG and anti-AchR autoantibody reduction. Correspondingly, clinically meaningful improvement in disease manifestations as measured by the Myasthenia -Gravis-Activities of Daily Living (MG-ADL) scale and other efficacy endpoints were observed. These data support continued development of nipocalimab for gMG. The present study is a Phase 3 pivotal study to confirm efficacy of nipocalimab in gMG.

2.2. Background

Nonclinical Studies

The nonclinical pharmacology, pharmacokinetics (PK), and toxicity of nipocalimab have been adequately characterized in appropriately designed nonclinical studies that support the potential efficacy, safety, and mechanism of action. Pharmacological studies showed that nipocalimab binds with high affinity to the IgG binding site of FcRn preventing FcRn-mediated IgG recycling and promoting IgG catabolism in vitro. In vivo, nipocalimab administered intravenously (IV) induced serum IgG decreases in rodents or nonhuman primates and ameliorated disease pathology in animal models of pathogenic IgG-driven autoimmune disease. Pharmacokinetic and pharmacodynamic (PD) evaluation of IV nipocalimab in cynomolgus monkeys and mice established consistent dose-, exposure-, and time-dependent relationships between PK, the PD effect on FcRn receptor occupancy (RO) and the lowering of serum IgG concentrations.

In repeat-dose toxicity studies of IV nipocalimab in the cynomolgus monkey, nipocalimab was administered once-weekly at doses up to the maximum feasible dose of 300 mg/kg for up to 6 months in duration. Pharmacokinetic and PD assessment indicated target effects of dose-dependent receptor occupancy and reductions in serum IgG concentration occurred in a dose-dependent manner. Chronic administration of nipocalimab was well tolerated without adverse effects, including those associated with infection. Importantly, no immunotoxic effects were observed in a comprehensive evaluation of innate and humoral immunity. In a reproductive toxicology study in which pregnant cynomolgus monkeys received IV nipocalimab at doses of up to 300 mg/kg

from the early second trimester (ie, gestational day 45) through parturition, serum IgG in dams, fetuses, and newborns was decreased with no evidence of nipocalimab-related developmental toxicity or impact on fetal or infant survival.

These nonclinical pharmacology and toxicology results support the potential safety and efficacy of nipocalimab and its clinical investigation in diseases caused by pathogenic IgG including gMG.

For the most comprehensive nonclinical information regarding nipocalimab, refer to the latest version of the IB for nipocalimab.

Clinical Studies

Phase 1 Studies of IV Nipocalimab

Safety, PK, and PD data are available from 3 completed Phase 1 studies in healthy adult participants: a first-in-human (FIH) study of single ascending doses (SAD; n=34) up to 60 mg/kg and multiple ascending doses (MAD; n=16) up to 30 mg/kg weekly for 4 weeks (MOM-M281-001), a single-dose escalating infusion rate study (MOM-M281-007; n=40), and a single escalating dose study conducted in Japanese adults (MOM-M281-010; n=24).

Pharmacokinetic parameters for IV nipocalimab showed dose dependency and likely target-mediated disposition. Across the SAD dose groups (0.3 to 60 mg/kg), maximum serum nipocalimab concentration (C_{max}) increased in a dose-proportional manner, whereas area under the concentration-time curve (AUC) increased in a greater than dose-proportional manner. Serum clearance (CL) decreased nearly 50% from 10 to 60 mg/kg, while half-life ($t_{1/2}$) increased with increasing dose, from 7.36 hours at 3 mg/kg to 32.2 hours at 60 mg/kg. Pharmacokinetic parameters of nipocalimab were not estimated for the MAD dose groups (15 or 30 mg/kg weekly x 4) due to sparse PK sampling design on the MAD part of the study.

A close PK/PD relationship was observed, with the onset of PD effects (FcRn RO, IgG, and albumin mean decreases) occurring rapidly following all dose levels of nipocalimab. Recovery of IgG and albumin toward baseline values following the last dose of nipocalimab was observed to occur later at higher dose levels.

In healthy participants, IV nipocalimab was well tolerated with no deaths or serious adverse events (SAEs) reported. The majority of the treatment-emergent adverse events (TEAEs) were transient, mild, or moderate in severity, resolved without intervention, and were assessed as unrelated to treatment. Infusions of IV nipocalimab were also well tolerated over infusion times from 15 minutes to 2 hours.

In SAD and MAD in healthy participants, there was no clear relationship between nipocalimab dose and the presence of neutralizing antibodies (NAbs), anti-drug antibodies (ADA), or ADA titers.

Phase 2 Studies of IV Nipocalimab

In the Phase 2 study of nipocalimab in adults with gMG (Study MOM-M281-004), IV nipocalimab was administered for 8 weeks in 4 nipocalimab groups (5 mg/kg every 4 weeks [q4w; n=14], 30 mg/kg q4w [n=13], 60 mg/kg every 2 weeks [q2w; n=14], and 60 mg/kg single dose [n=13]) and the IV placebo group (n=14). Study conduct has been completed and the final report is in preparation.

Consistent with its mechanism of action, nipocalimab produced dose-dependent, transient decreases in mean serum IgG concentrations. Infusions of IV nipocalimab were generally safe and well tolerated in this study with no deaths, discontinuations due to TEAEs, TEAEs of Common Terminology Criteria for Adverse Events ≥Grade 3, or adverse events of special interest (AESIs, infection or hypoalbuminemia ≥Grade 3). The overall incidence of TEAEs was similar between the combined nipocalimab group (83.3%) and placebo group (78.6%). Three SAEs were reported during the study; an SAE of musculoskeletal pain was reported for 1 nipocalimab-treated participant (30 mg/kg q4w) and 2 SAEs (ischaemic stroke, myasthenia gravis) were reported in placebo-treated participants; none of the SAEs were considered by the investigator as related to study intervention.

Preliminary safety data on a limited number of patients with gMG in the recently terminated long-term extension study (MOM-M281-005) and in the wAIHA study have raised no safety concerns. A Phase 2 study which is evaluating IV nipocalimab administered to pregnant women at high risk for EOS-HDFN (MOM-M281-003) is ongoing. Refer to the IB for details.

While a dose-dependent increase in the number of nipocalimab-treated patients with NAb was observed in gMG participants, NAb titers were low throughout the studies. Overall, IV administration of nipocalimab did not lead to a detectable clinically relevant immune response against nipocalimab. No definitive conclusions can be made regarding the impact of immunogenicity on PK due to the low sample sizes.

For the most comprehensive information regarding nipocalimab, refer to the latest version of the IB.

2.3. Benefit-Risk Assessment

The potential risks of exposure to nipocalimab based on its mechanism of action are summarized in Table 5.

More detailed information about the known and expected benefits and risks of nipocalimab may be found in the IB.

2.3.1. Risks for Study Participation

Table 5: Potential Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Lack of improvement or clinical worsening of gMG	A Phase 2 study of nipocalimab in gMG has shown that the majority of, but not all, patients responded to nipocalimab.	• During the study, participants will be permitted to continue treatment of gMG with standard of care medications (Section 6.8). • Participants may discontinue study intervention if it is not in their best interest or if they need to initiate protocol-prohibited medications including certain biologics (Sections 6.8.1 and 7.1). • Participants will be allowed to use rescue medications as needed (Section 6.8.2).
Risks Due to Study Intervention(s)		
Potential Increased Risk for Infection due to Decreased Serum IgG Concentrations	As predicted based on its mechanism of action, nipocalimab was associated with dose-dependent reductions in IgG of up to 80% to 85% of baseline in cynomolgus monkey and human studies. However, nipocalimab did not increase either the incidence, severity, or duration of infection in any of the nonclinical and clinical studies conducted to date.	• Patients with severe acute or chronic infections requiring anti-infective therapies are excluded from participation in the study (Section 5.2). • Temporary and permanent study intervention stopping criteria for infections are included in Sections 7.1 and 7.2 respectively. • All infections will be monitored closely. Treatment-emergent infections meeting the AESI criteria must be reported to the sponsor within 24 hours (Section 8.3.6). • Participants who have had a live vaccine within 4 weeks prior to screening or have a known need to receive a live vaccine during the study, or within at least 8 weeks after the last dose of study intervention in this study are excluded from participation in the study.
Reduced Effectiveness of Routine Vaccines due to Decreased IgG	Due to the expected reduction in IgG as a result of the overall effect of nipocalimab on total IgG concentrations, a reduction in vaccine-specific IgG titers can be expected. While decreases in vaccine titers were observed in the FIH study, there has been no increase in the incidence, severity, or duration of infection in any of the nonclinical and clinical studies conducted to date.	• It is recommended that participants are up-to-date on all age-appropriate vaccinations prior to screening as per routine local medical guidelines. • Non-live vaccinations should be administered as per the assessment of the investigator.
Activation of Latent Virus due to Decreased IgG	Due to the expected reduction in IgG as a result of the overall effect of nipocalimab on IgG concentrations, activation of latent virus	• Serology testing is done at screening to exclude participants with HIV, or

Table 5: Potential Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	is a potential risk. To date, there has been no observed increase in the frequency of latent virus activation in clinical studies with nipocalimab.	hepatitis B or C infection (Section 5.2). • Temporary and permanent study intervention stopping criteria for infections are included in Sections 7.1 and 7.2, respectively. • Infections will be monitored closely and treatment-emergent infections meeting the AESI criteria must be reported to the sponsor within 24 hours (Section 8.3.6).
Clinical Manifestations of Hypoalbuminemia	Nipocalimab selectively targets the IgG binding site on FcRn and does not block the albumin binding site. Reasons for observed albumin modulations are under investigation. Nipocalimab was associated with modest, self-limited, recoverable and asymptomatic reductions in albumin, in both the nonclinical and clinical studies conducted to date.	• Participants will be monitored for albumin abnormalities by regular safety laboratory assessments. • Hypoalbuminemia <20 g/L should be reported as AESI within 24 hours (Section 8.3.6). • Study intervention interruption rules for 3+ pedal edema, ascites, or pleural or pericardial effusions are included in the protocol. (Section 7.1.2)
Infusion Reaction	Infusion reactions have been observed with the administration of biologics, and in particular with monoclonal antibodies. For the most up to date information, refer to the Infusion Reaction section of the nipocalimab IB.	• Participants will be monitored for infusion reactions.
Drug-drug interaction	Nipocalimab is expected to reduce exposure of therapeutic agents that contain the Fc region of IgG (eg, IVIg, Fc-based biologics like eculizumab, rituximab, infliximab, adalimumab, and Fc fusion proteins). The DDI observed in study MOM-M281-008 was consistent with the mechanism of action of nipocalimab and confirmed the hypothesis that nipocalimab could reduce the PK exposure of IgG-based mAbs via inhibition of FcRn mediated recycling. High doses of nipocalimab may reduce serum albumin up to 25%. The concomitant use of drugs with both high protein binding rate (>95%) and narrow therapeutic index may lead to higher free drug concentrations which could increase the risk for potential toxicities. For the most up to date information, please refer to Drug-drug Interactions section of the nipocalimab IB.	• Patients who are on IgG Fc-containing protein therapeutics are excluded from the study. • Patients treated with nipocalimab and who are on concomitant medications which have high protein binding rate (>95%) and narrow therapeutic index (such as but not limited to warfarin, sulfasalazine, mycophenolate mofetil, leflunomide) should be monitored for potential impacts of nipocalimab on efficacy and safety of those medications.

Table 5: Potential Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Increased lipids	Elevations in total cholesterol and LDL were reported recently with another experimental drug in the same pharmacological class of FcRn antagonists. In the MOM-M281-001 and MOM-M281-004 studies, asymptomatic, dose dependent, reversible elevations in non-fasting mean total cholesterol were observed up to 25% of baseline. In both studies, elevations in total cholesterol appear to mirror the kinetics of the decreases in albumin observed with nipocalimab. For the most up to date information, please refer to the Increased Lipids section of the nipocalimab IB.	• Participants with recent MI, stroke, or unstable angina, within 12 weeks of study entry will be excluded from participation in the study. • Routine laboratory investigations for lipid panel (Total cholesterol, LDL, HDL, Triglycerides) will be performed in the study. • Lipids are routinely monitored in participants throughout the study. • In participants with elevated lipids at any time during the study, it is recommended that investigators initiate or continue appropriate therapy for dyslipidemia as per local health guidelines. In participants with persistently elevated lipids (above LDL threshold of 190 mg/dL or the triglyceride threshold of 1,000 mg/dL), it is strongly recommended that investigators initiate appropriate therapy or modify current therapy for dyslipidemia per local health guidelines.
Placental infarction	Abnormal placental infarctions have been observed in non-clinical and clinical studies of nipocalimab. Placental infarction could lead to reduced placental function, and, as a result, inadequate fetal growth and development. For the most up to date information, please refer to the Placental Infarction section of the nipocalimab IB.	• Pregnant women are excluded from this study and patients must agree to use highly effective methods of contraception. • Pregnancy tests are conducted throughout. Participants who become pregnant will be withdrawn and followed up until delivery or termination of pregnancy.
Low IgG in infants born to mothers with EOS-HDFN receiving nipocalimab during pregnancy	Low IgG concentrations in infants born to mothers with EOS-HDFN receiving Nipocalimab during pregnancy (between Weeks 14 to 35) were observed. For the most up to date information, please refer to the Low IgG in Infants Born to Mothers With EOS-HDFN Having Received Nipocalimab During Pregnancy section of the nipocalimab IB.	• Pregnant women are excluded from this study and patients must agree to use highly effective methods of contraception. • Pregnancy tests are conducted throughout. Participants who become pregnant will be withdrawn and followed up until delivery or termination of pregnancy.

Abbreviations: AESI adverse event of special interest; DDI drug-drug interaction; EOS early onset severe; Fc fragment crystallizable; FcRn neonatal Fc receptor; FIH first in human; gMG generalized myasthenia gravis; HDFN hemolytic disease of the fetus and newborn; HDL high density lipoprotein; virus; HIV human immunodeficiency virus; IB investigator's brochure; IgG immunoglobulin G; IVIg intravenous immunoglobulin; LDL low density lipoprotein; mAb monoclonal antibody; MI myocardial infarction; PK pharmacokinetic(s).

2.3.2. Benefits for Study Participation

There is no established benefit to participants of receiving study intervention. There is evidence that inflammation through autoantibodies and IgG-antigen immune complexes plays an important role in the pathogenesis of gMG. Given the scientific rationale for FcRn blockade and that nipocalimab shows early signs of efficacy in an autoantibody-driven disease like gMG, nipocalimab may provide benefit in the treatment of gMG (Section 2.2). Participants in the study will help in evaluating this study intervention in the treatment of gMG and increasing understanding of gMG. Thus, the knowledge gained from this study has the potential to benefit many more patients suffering from gMG and thus offers potential public health benefits.

Participants may also experience some benefit from the participation in a clinical study irrespective of receiving study treatment, due to regular visits and assessments monitoring their overall health.

2.3.3. Benefit-Risk Assessment for Study Participation

The available results from nonclinical and clinical studies (Phase 1 and Phase 2 studies), the scientific and clinical rationale for the anti-IgG mechanism of action in gMG, and the measures taken to minimize the potential risks justify the potential benefits that may be provided to participants with gMG in this study.

3. OBJECTIVES AND ENDPOINTS

The study objectives and related outcome measures are shown in the table below.

Objective	Outcome Measures
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 the 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	• 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.

Objective	Outcome Measures
seropositive gMG participants when treatment is taken as directed.	
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, 23, 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: severe or serious infections and hypoalbuminemia < 20g/L). • Change in vital sign 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.

Objective	Outcome Measures
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-AChR, anti-MuSK, anti-LRP4) [f] 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	• Evaluate exploratory biomarkers[g] (including but not limited to IgG subtypes, IgM, IgA, IgE, MG-associated RNAs, complement

[f] In China, anti-LRP4 autoantibody collection will only be tested at screening.

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

Objective	Outcome Measures
in gMG participants when treatment is taken as directed.	proteins. Analyses could use proteomic, glycoprotein, and metabolomic markers).
To explore the changes in physical activity, mobility, and sleep, as measured by accelerometry, in nipocalimab compared to placebo in seropositive gMG participants when treatment is taken as directed (at selected sites).	• Change in Actigraphy watch-collected continuous data on physical activity, mobility, and sleep (including but 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.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis of this study is that IV nipocalimab is superior to placebo as measured by average change from baseline in the MG-ADL score over Weeks 22, 23 and 24 of the double-blind placebo-controlled phase for seropositive participants (consisting of anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive).

4. STUDY DESIGN

4.1. Overall Design

This 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. 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.

Approximately 190 participants will be enrolled into the double-blind placebo-controlled phase of this study with 95 in each treatment group. At least 150 eligible seropositive (anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive) participants will be enrolled. Seronegative participants will also be enrolled[h]. Participants in each of the seropositive and seronegative groups will be randomly assigned in a 1:1 ratio to receive either placebo or nipocalimab. The 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 score (≤9, >9) and region (East Asia, United States [US], rest of world).

The study will consist of: a screening period of up to 4 weeks, a 24-week double-blind placebo-controlled phase, and an open-label extension (OLE) phase that will be of variable duration per participating country/territory depending on the timing of market authorization and commercial availability of nipocalimab. For EU region (EUR)-specific information, see Section 10.10.1. Participants will continue to take their stable MG therapy(ies), if on any, throughout the screening phase and the double-blind placebo-controlled phase. Tapering one of the participant's concomitant MG medications every 4 weeks is allowed in the OLE phase if the disease has been stable in the past 4 weeks as reflected by MG-ADL scores and based on the investigator's discretion. Participants who discontinue 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. Participants who discontinue study intervention for a reason other than Clinical Deterioration requiring hospitalization or rescue therapy during the double-blind placebo-controlled phase, will be encouraged to complete study procedures per the Schedule of Activities (Table 1) for the 24-week period. Rollover into the OLE of such participants will not be permitted unless the 24 weeks of study procedures have been completed. Participants who permanently discontinue or withdraw from the study either due to a clinical deterioration or for any other reason

[h] Seronegative participants are no longer being recruited; all participants must have a positive serologic test for a gMG related pathogenic autoantibody (anti-AChR, anti-MuSK and/or anti-LRP4 autoantibodies), confirmed prior to randomization.

should complete the ET visit assessments. These participants should also return for a safety follow-up visit 8 weeks after the last infusion.

Screening Phase

After providing written informed consent and within 28 days prior to the double-blind placebo-controlled phase, participants will be screened to evaluate their eligibility for study participation. Participants must have a diagnosis of MG with generalized muscle weakness meeting the clinical criteria for gMG as defined by the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II a/b, III a/b, or IV a/b that is not well controlled with stable MG therapy (or, who discontinued MG therapy due to intolerance or lack of efficacy as specified in Inclusion Criterion # 4), and MG-ADL score ≥6.

Safety evaluations (eg, physical examination, vital signs, electrocardiogram (ECG), and clinical laboratory tests [including chemistry, hematology, lipid profiles, and urinalysis]) will be performed. Adverse events will be collected from the time a signed and dated informed consent form (ICF) is obtained until the completion of the last study procedure on the final follow-up visit.

Refer to Section 5.4, Screen Failures, for conditions under which the repeat of any screening procedures are allowed.

Double-blind Placebo-controlled Phase

Participants who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned in a 1:1 ratio to receive either placebo or nipocalimab (30 mg/kg for first infusion, 15 mg/kg thereafter) once every 2 weeks (q2w). On the q2w schedule (starting from Day 1), the participants will receive study intervention (placebo or nipocalimab) and undergo safety, efficacy, PK, PD, and immunogenicity assessments. As outlined in the Schedule of Activities (Section 1.3, Table 1), the participant will be contacted by phone for a remote assessment of MG-ADL, adverse events (AEs), and concomitant medications for some assessment visits. Participants who discontinue study intervention during the double-blind placebo-controlled phase for a reason other than Clinical Deterioration requiring hospitalization or rescue therapy will be required to complete study procedures per the Schedule of Activities (Table 1) for the 24-week phase. Rollover into OLE of such participants will not be permitted unless the 24 weeks of study procedures have been completed.

Participants will be observed for safety 1-hour post-infusion after the first 3 infusions; if no clinically relevant AEs related to the infusion are observed in these first 3 infusions, participants will be observed for 30 minutes after subsequent infusions.

Open-label Extension Phase

Participants who complete the double-blind placebo-controlled phase will continue in an OLE phase where treatment with nipocalimab will continue until 2 years after marketing authorization in a participant's local country/territory or until nipocalimab becomes available commercially or via other continued access program, whichever comes first. Details specific for sites in EU are presented in Section 10.10.1. Assessments done at the Week 24 visit of the double-blind placebo-

controlled phase will serve as baseline (first visit) of the OLE phase, and participants will receive their first infusion of open-label nipocalimab during the same visit after completion of the Week 24 visit assessments. Please refer to Section 5.1.2 for information on participants eligible to enroll in the OLE phase.

Due to the coronavirus disease 2019 (COVID-19) pandemic, the MOM-M281-005 study, an open-label extension study to evaluate the safety, tolerability, and efficacy of nipocalimab administered to participants with gMG, was placed on hold and subsequently terminated. As a result, some participants from the MOM-281-004 study, a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of M281 administered to adults with generalized myasthenia gravis, 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 the present study (bypassing the double-blind placebo-controlled treatment phase of the present study). These participants will undergo a screening assessment to confirm eligibility for entry into the OLE phase of the study. If eligible, the participant will start the OLE phase at Extension Day 1 of the Schedule of Activities (ED1; Table 2).

All participants enrolling in the OLE phase will receive nipocalimab 15 mg/kg q2w by IV infusion starting on OLE Day 1. Tapering one of the participant's concomitant MG medications every 4 weeks is allowed in the OLE phase if the disease has been stable in the past 4 weeks as reflected by MG-ADL scores and based on the investigator's discretion. CCI [redacted] No other nipocalimab dosing regimen should be used.

When considering tapering of concomitant MG medications, the investigator should adhere to the following:

- Taper 1 concomitant medication at a time, not 2 concomitant medications simultaneously;
- When the decision has been made to taper a corticosteroid concomitant medication, the following must be done:
  - For participants on a corticosteroid dose >30 mg per day, the dose should be decreased by no more than 10 mg every 4 weeks, until a dose of ≤30 mg per day is reached. For participants on a corticosteroid dose of ≤30 mg per day, the dose should be decreased by no more than 5 mg every 4 weeks. Once the investigator considers the corticosteroid taper completed, the participant should remain on the current dosing regimen for nipocalimab and the concomitant MG medications for at least 4 weeks before considering tapering another concomitant MG medication.
- The tapering of mycophenolate mofetil, azathioprine, or methotrexate should be performed no more frequently than every 6 months. The tapering of cyclosporine or tacrolimus should be performed no more frequently than every 3 months.

Recalculation of dose during the OLE phase for weight gained or lost will be based on the weight measured for each participant every 4 weeks through Extension Week 24 and every 12 weeks thereafter.

Participants will be observed for safety 1-hour post-infusion after the first 3 infusions; if no clinically relevant AEs related to the infusion are observed in these first 3 infusions, participants will be observed for 30 minutes after subsequent infusions.

Follow-Up/End of Study Visit

Participants who discontinue 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 (Table 4).

An independent Data Monitoring Committee (DMC) and Major Adverse Cardiovascular Events (MACE) Event Adjudication Committee (EAC) will be commissioned for this study. Refer to Committees Structure in Appendix 4 (Section 10.4), Regulatory, Ethical, and Study Oversight Considerations for details.

A diagram of the study design is provided in Section 1.2, Schema (Figure 1).

4.2. Scientific Rationale for Study Design

Participant Population

The study population will include adult participants (≥18 years of age) who meet MGFA Clinical Classification Class II a/b, III a/b, or IV a/b for gMG that is not well controlled with stable MG therapy (if on any). Published data show that approximately 85% patients with gMG are anti-AChR positive (Meriggioli 2012). The sponsor proposes to enroll approximately 150 of the total Phase 3 study population to be seropositive (anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive) and these participants will comprise the primary efficacy analysis set. To further evaluate the efficacy and safety in seronegative patients, the sponsor proposes to enroll approximately 40 participants who are seronegative[i]. Enrolling seronegative participants will help address the unmet medical need of these patients who are often excluded from clinical trials.

Study Phase/Periods, Intervention Groups

This is a multi-phase study to address several questions. The first phase is a double-blind, placebo-controlled phase to evaluate the efficacy and safety of nipocalimab compared to placebo in participants with gMG. Participants will be randomized to nipocalimab (15 mg/kg q2w following a loading dose of 30 mg/kg) or placebo for 24 weeks. Data collected in this phase address the primary objective of efficacy of nipocalimab in comparison to placebo.

The second phase is an OLE phase to evaluate long-term safety and efficacy of nipocalimab in participants with gMG. Participants who completed the double-blind placebo-controlled phase will

[i] Seronegative participants are no longer being recruited; all participants must have a positive serologic test for a gMG related pathogenic autoantibody (anti-AChR, anti-MuSK and/or anti-LRP4 autoantibodies), confirmed prior to randomization.

have the option to receive open-label treatment with nipocalimab. Tapering one of the participant's concomitant MG medications every 4 weeks is allowed in the OLE phase if the disease has been stable in the past 4 weeks as reflected by MG-ADL scores and based on the investigator's discretion.

A. Choice of Control Arm

The target population for the Phase 3 study is patients with moderate to severe gMG who are not well controlled by their current standard of care MG therapy; thus, all eligible participants must have MG-ADL scores ≥6 at screening and baseline and be on stable MG treatment (eg, glucocorticoids, or immunosuppressants, or must have discontinued corticosteroids and/or immunosuppressants ≥4 weeks prior to screening due to intolerance or lack of efficacy as specified in Inclusion Criterion #4). A placebo comparator arm (placebo + standard of care) was chosen for this study as it is an accepted approach for the conduct of pivotal trials in MG (Howard 2017), allows for evaluation of a placebo response (Frisaldi 2019), and therefore, provides the most valid comparison versus active treatment for the analyses of safety, tolerability, efficacy, PD, and immunogenicity in the selected target population.

B. Double-blind Treatment Duration

The duration of the double-blind placebo-controlled phase (24 weeks) is anticipated to be sufficient for assessment of efficacy and safety based on nipocalimab's mechanism of action and results of the Phase 2 study demonstrating efficacy on the MG-ADL as early as Week 2 and sustained up to Day 57 (the primary assessment time point in Phase 2).

The maintenance of nipocalimab's effect, as well as the long-term safety of nipocalimab will be further evaluated in the OLE phase.

C. Choice of Primary and Key Secondary Endpoints

The primary endpoint is average change from baseline on the MG-ADL score over Weeks 22, 23 and 24 of the 24-week double-blind placebo-controlled phase. The MG-ADL is a widely used and well validated patient-reported clinical outcome measure with a 1-week recall period. The MG-ADL is an 8-item scale, including 2 items on daily life activities which are negatively affected in most patients with gMG (ability to brush teeth or comb hair and limitations in the ability to rise from a chair) and 6 items reflecting other MG manifestations (including diplopia, ptosis, chewing, swallowing, voice/speech problems, and respiratory symptoms), and combines them into a single scale. Each item is scored between 0 and 3, with total scores ranging from 0 to 24 and higher scores indicating worse disease; a decrease of ≥2 points in total score for individual patients is considered a clinically meaningful response (Muppidi 2011; Wolfe 1999). Analysis of the Phase 2 data has shown that a maximum and stable decrease in MG-ADL is obtained at or before Week 8. Taking the average score over Weeks 22, 23 and 24 is intended to reduce the variability and enable an observation of stable response.

Key secondary efficacy endpoints (assessed in the 24-week double-blind placebo-controlled phase) include the following:

1. Average change from baseline in QMG score over weeks 22 and 24 of the double-blind, placebo-controlled phase (scale is not assessed at Week 23).
2. MG-ADL response, defined as 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. 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 one non-missing value at Week 22 or 23 in order to have a non-missing average score. A participant with a missing average score will be considered a nonresponder.
3. Loading dose response, defined as percentage of participants with improvement in MG-ADL total score of ≥2 points at Week 1 and/or Week 2. A participant with a missing assessment at either time point will be considered a nonresponder at that time point.
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 between Week 6 through Week 23 (excursions defined as loss of improvement in MG-ADL score of ≥ 2 points at baseline). A participant with a missing assessment at a time point will be considered a nonresponder at that time point.
5. 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 50% 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 Week 22 or 23 in order to have a non-missing average score. A participant with a missing average score will be considered a nonresponder.

Analysis of the percentage of responders on the MG-ADL (ie, key secondary efficacy endpoint 2) is considered a meaningful endpoint for physicians and patients alike. For measurement of MG-ADL response (key secondary efficacy endpoint 4), allowing 2 non-consecutive excursions is intended to account for variability of MG-ADL scores due to inherent disease fluctuation. Minimum symptom expression, ie, an MG-ADL of 0 or 1 (secondary efficacy endpoint), is a desired treatment goal. Since the final score achieved on the MG-ADL may vary depending on the baseline score, the study will also evaluate the relative symptom improvement defined as ≥50% improvement on MG-ADL score from the baseline score. This endpoint takes individual patient's baseline score into consideration and is a clinically meaningful endpoint for patients. A 50% improvement was chosen also due to clinical considerations: per protocol inclusion criteria, participants are required to have an MG-ADL score of ≥6 at screening/baseline, ie, moderate to severe disease; ≥50% improvement will result in an MG-ADL score of 3 or better, corresponding to mild disease (Petersson 2021). Conversely, the most severely affected participant with a maximal MG-ADL score of 24, would also expect to experience substantial clinical benefit with a score of 12 or lower.

The QMG is a widely used and well validated clinician administered quantitative measure of MG disease severity (Barnett 2018; Barohn 1998). It includes 13 items that measure endurance or fatigability, taking into account the fluctuating nature of the disease. These items include ptosis, diplopia, orbicularis oculi weakness, swallowing a cup of water, speech, percent predicted forced vital capacity, grip strength (2 items), arm endurance (2 items), leg endurance (2 items), and neck flexion endurance. All items are scored on a scale of 0 to 3, with total scores ranging from 0 to 39 and higher scores indicating greater disease severity. Demonstrating efficacy on QMG will provide

additional evidence of efficacy through a clinician administered scale and support the primary efficacy endpoint.

Biomarker Collection

Biomarker samples will be collected to help to explain interindividual variability in clinical outcomes, to better understand the disease, or to help identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the PD of nipocalimab to better understand the disease, and to aid in evaluating the intervention-clinical response relationship.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Both serum total IgG and pathogenic AChR+, MuSK+, or LRP4+ autoantibody levels will be measured throughout the study. The kinetic and maximal % reduction in IgG will be assessed as PD readout. Biomarker data collected in the present study will further solidify the PK-PD-efficacy model established from the Phase 2 study, to show drug response in MG processes or markers previously shown to be responsive to other treatments, and to stratify and characterize the patient population. Serum nipocalimab levels (PK), and incidences of ADA and NAb to nipocalimab will be measured as secondary endpoints.

Additional exploratory biomarker samples[j] will be collected to better understand the disease and to aid in evaluating the intervention-clinical response relationship.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study, and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the US Department of Health and Human Services Office for Human Research Protections, and US Food and Drug Administration (FDA) guidelines of 550 mL in any 8-week period,(US FDA 1998; US HHS 1998;) as well as the European Commission guidelines of 500 mL per donation and 3 L per consecutive 12 month period (EC 1998).

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

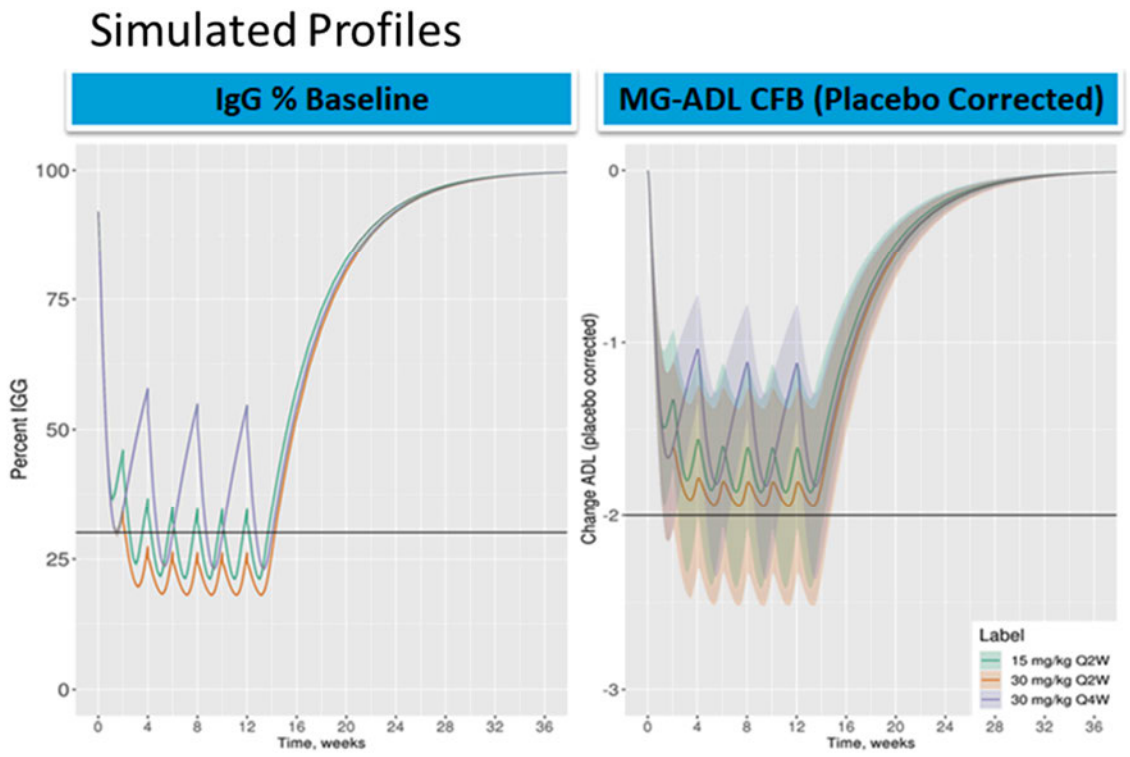
4.3. Justification for Dose

The proposed dose level and dosing regimen for the Phase 3 study in participants with gMG of 30 mg/kg IV loading dose on Day 1 followed by 15 mg/kg IV q2w maintenance doses from Week 2 was based on observed data from the Phase 2 study and extensive modeling and simulation of the dose response relationships for IgG and MG-ADL.

In the Phase 2 study, rapid, dose-dependent IgG lowering was observed one week after the initial dose in all dose groups, with maximal IgG lowering achieved at Week 2 in the 60 mg/kg single dose and 60 mg/kg q2w groups. Dose-dependent improvements in MG-ADL scores were also observed, suggesting a correlation between IgG lowering and MG-ADL scores. Importantly, nipocalimab was generally well tolerated across all dose groups.

Population PK/PD/efficacy modeling analyses were conducted using data obtained from nipocalimab Phase 1 and 2 studies to evaluate the relationship between PK, IgG lowering, and MG-ADL, in addition to other efficacy and safety endpoints (including serum albumin and total cholesterol). The results indicated that the q2w dosing interval would provide more sustained IgG lowering and MG-ADL reduction at all simulated dose levels when compared with the q4w dosing interval. While modeling and simulation suggested numerical differences in IgG lowering and MG-ADL reduction between the 15 and 30 mg/kg q2w dosing regimens (the model-predicted mean IgG lowering is 73.8% versus 79.4%, respectively), the additional 5.6% IgG reduction with 30 mg/kg q2w is expected to have minimal additional MG-ADL improvement at steady-state trough beyond the improvement expected with 15 mg/kg q2w (Figure 2). Therefore, the 15 mg/kg q2w dose regimen is selected as the single maintenance dose regimen to be studied for this Phase 3 study in gMG since this is a rare disease with high unmet need. Lower doses would likely result in suboptimal efficacy, while higher doses may not yield much difference in efficacy as predicted for gMG.

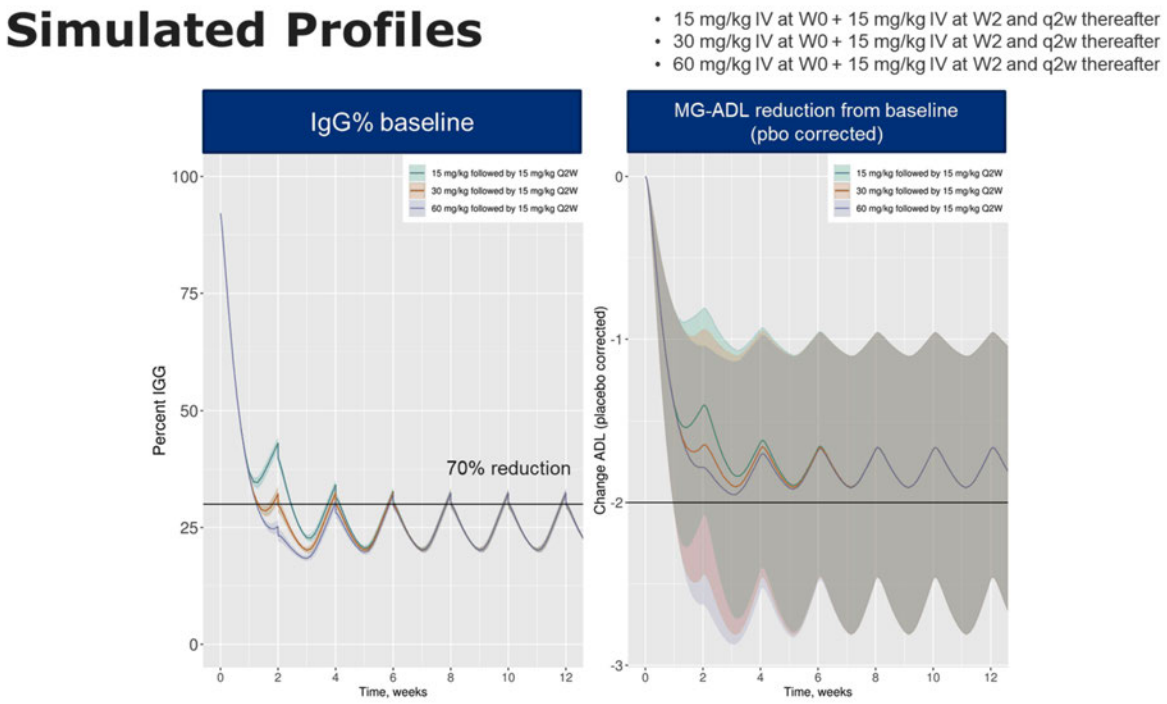
Figure 2: Model-Predicted IgG Reduction and MG-ADL Improvement with 15 mg/kg and 30 mg/kg Q2W Maintenance Dosing



Abbreviations: ADL Activities of Daily Living; CFB change from baseline; IgG immunoglobulin G; MG-ADL Myasthenia Gravis-Activities of Daily Living; Q2W every 2 weeks.
Colored lines and areas are the predicted mean and the associated 90% prediction interval.

To expedite the onset of an efficacy response, a loading dose of 30 mg/kg nipocalimab on Day 1 will be instituted prior to 15 mg/kg q2w maintenance dosing beginning at Week 2. It is anticipated that the 30 mg/kg loading dose will generate a rapid and deep IgG lowering during the first 2 weeks (model-predicted mean IgG lowering of 64% and 67%, respectively, at Weeks 1 and 2) with potential early MG-ADL response, better than the expected response with a 15 mg/kg dose on Day 1 (Figure 3).

Figure 3: Model-Predicted IgG Reduction and MG-ADL Improvement with a 30 mg/kg Loading Dose



Abbreviations: ADL Activities of Daily Living; CFB change from baseline; IgG immunoglobulin G; MG-ADL Myasthenia Gravis-Activities of Daily Living; Q2W every 2 weeks.

The predicted exposure with a 30 mg/kg IV loading dose on Day 1 followed by 15 mg/kg IV q2w maintenance doses is well below the observed PK exposure observed from 60 mg/kg q2w dosing regimen in the Phase 2 gMG study (MOM-M281-004), which was generally well-tolerated based on the currently available safety data. The dosing regimen planned for this study is expected to have an average of <20% albumin lowering and <20% total cholesterol increase at steady state. The magnitudes of albumin reduction and total cholesterol increase are not expected to be clinically significant and are less than those observed in prior studies with 30 mg/kg IV weekly or 60 mg/kg IV q2w dose regimens. Therefore, the proposed dose regimen in this Phase 3 study is expected to be safe and well-tolerated.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, within the timeframe specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if the participant has completed assessments at the last visit of the OLE phase.

Participants entering the OLE phase will continue until 2 years after marketing authorization in the participant's local country/territory or until nipocalimab becomes available commercially or via other continued access program, whichever comes first.

EUR-specific information is presented in Section 10.10.1.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in the double-blind placebo-controlled phase in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

Approximately 190 participants are planned to be randomized into the double-blind placebo-controlled phase (95 in each treatment group of which approximately 75 per group will be seropositive [anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive]). To be eligible, participants must have gMG that is not well controlled with stable MG therapy (or have discontinued corticosteroids and/or immunosuppressants ≥4 weeks prior to screening due to intolerance or lack of efficacy as specified in Inclusion Criterion #4) and must remain on their stable MG therapy (if on any) throughout the study.

Approximately 150 participants will be seropositive and these participants will comprise the primary efficacy analysis set. Approximately 40 participants will be seronegative[k]. Together with the seropositive participants, these participants will comprise the full analysis set.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

Enrollment of Participants from Phase 2

Due to the COVID 19 pandemic, the MOM-M281-005 OLE study an open-label extension study to evaluate the safety, tolerability, and efficacy of nipocalimab administered to participants with gMG, was placed on hold and subsequently terminated. As a result, some participants from the MOM-M281-004 study, a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of nipocalimab administered to adults with generalized myasthenia gravis, 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 the present

[k] Seronegative participants are no longer being recruited; all participants must have a positive serologic test for a gMG related pathogenic autoantibody (anti-AChR, anti-MuSK and/or anti-LRP4 autoantibodies), confirmed prior to randomization.

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

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria for Double-blind Placebo-Controlled Phase Entry

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. Criterion modified per Amendment 1.

   1.1 ≥18 years of age at the time of consent, and as applicable, must also meet the legal age of consent in the jurisdiction in which the study is taking place.

Type of Participant and Disease Characteristic

2. Criterion modified per Amendment 2

   2.1 Diagnosis of MG with generalized muscle weakness meeting the clinical criteria for gMG as defined by the MGFA Clinical Classification Class II a/b, III a/b, or IVa/b at screening.[1]

3. MG-ADL score of ≥6 at screening and baseline.

4. Criterion modified per Amendment 1.

   4.1 Has suboptimal response to current stable therapy for gMG according to the investigator. Stable therapy is defined as the following, as applicable to their specific therapy(ies):

   a. If taking an acetylcholinesterase inhibitor, the participant must have been on a stable dose and regimen for at least 2 weeks prior to screening. Changes to the dose of acetylcholinesterase inhibitors may be permitted if medically necessary during any phase of the trial.

   b. If taking a glucocorticosteroid, the participant must have been on a stable dose and regimen for at least 4 weeks prior to baseline.

   c. If currently receiving immunosuppressants, the participant must have been on the given immunosuppressant for ≥6 months and on a stable dose for ≥3 months prior to baseline. Allowed concomitant immunosuppressants are azathioprine,

[1] Seronegative participants are no longer being recruited; all participants must have a positive serologic test for a gMG-related pathogenic autoantibody (anti-AChR, anti-MuSK and/or anti-LRP4 autoantibodies), confirmed prior to randomization.

mycophenolate mofetil/mycophenolic acid, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide.

OR

Has discontinued corticosteroids and/or immunosuppressants/immunomodulators including eculizumab or other novel approved immune agents at least 4 weeks prior to screening due to intolerance or lack of efficacy.

Note: All above background medications must be optimized and unchanged for the duration specified in Criteria #4 prior to screening and/or baseline visits. Investigators are encouraged to consider all treatment escalation options, including thymectomy, prior to enrolling. Participants started on new treatments must meet the above stable dose duration rules, and cannot meet exclusion criterion #6 as defined in Section 5.2.

5. A participant using herbal, naturopathic, traditional Chinese remedies, ayurvedic or nutritional supplements, or medical marijuana (with a doctor's prescription) is eligible if the use of these medications is acceptable to the investigator. These remedies must remain at a stable dose and regimen from baseline through the double-blind placebo-controlled phase of the study.

6. Criterion modified per Amendment 1.

   6.1 Participants who have undergone splenectomy (if local regulatory authority has not requested exclusion of participants with splenectomy) must be at least 3 months post resection prior to screening and must be vaccinated as per the United States Center for Disease Control and Prevention annual Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States. (https://www.cdc.gov) OR must be vaccinated as per country- or territory-specific guidelines or local regulations.

   Note: This criterion is not applicable if splenectomy is excluded by the local authority.

7. Has sufficient venous access to allow drug administration by infusion and blood sampling as per the protocol.

8. Criterion modified per Amendment 1.
   8.1 Is recommended to be up to date on all age-appropriate vaccinations prior to screening as per routine local medical guidelines. It is strongly recommended that participants will have completed a locally-approved (or emergency use-authorized) COVID-19 vaccination regimen at least 2 weeks prior to study-related visits or procedures. Study participants should follow applicable local vaccine labeling, guidelines, and standards-of-care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment.

Sex and Contraceptive/Barrier Requirements

9. Criterion removed per Amendment 1.

10. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at Screening and a negative urine pregnancy test at Day 1 prior to administration of study intervention.

11. Criterion modified per Amendment 1.

    11.1 A woman must be (as defined in Section 10.6, Appendix 6, Contraceptive and Barrier Guidance)

    a. Not of childbearing potential
    b. Of childbearing potential and
        - Practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 30 days after last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Section 10.6, Appendix 6 Contraceptive and Barrier Guidance.

    Note: Labeling requirements of concomitant treatment a participant is currently receiving will supersede if more stringent.

12. A woman must agree not to donate eggs (ova, oocytes), or freeze for future use for the purposes of assisted reproduction, during the study and for a period of 30 days after the administration of study intervention.

13. Criterion modified per Amendment 1

    13.1 A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for at least 90 days after receiving the last administration of study intervention. In addition, male participants with partners who are a woman of childbearing potential are highly encouraged to inform their partner to use highly effective contraception methods that result in a low failure rate (less than 1% per year). See Section 10.6, Appendix 6, Contraceptive and Barrier Guidance.

14. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 90 days after receiving the last administration of study intervention.

Informed Consent

15. Criterion modified per Amendment 1.

    15.1 Must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to voluntarily participate in the study and comply with all study procedures. Participants who initially provide consent and subsequently withdraw it prior to randomization, will be deemed as having failed this inclusion criterion. Must be legal age of consent in the jurisdiction in which the study is taking place, at the time of consent.

16. Must be able to read and write.

5.1.2. Inclusion Criteria for Open-label Extension Phase Entry

The OLE phase is open to 2 groups of participants: participants who have completed the 24-week double-blind placebo-controlled phase and former participants in the nipocalimab MOM-M281-004 study or MOM-M281-005 study.

Participants who have completed the 24-week double-blind placebo-controlled phase will continue to the OLE phase. Participants who had study intervention discontinued for a reason other than a Clinical Deterioration requiring hospitalization or rescue therapy (IVIg, plasmapheresis), and who completed the scheduled of assessments for the full 24-week double-blind placebo-controlled phase, may enter the OLE based on the investigator's discretion. Participants who had study intervention discontinued because of rescue therapy during the double-blind phase are eligible to enter the OLE phase based on investigator's discretion after completion of an End of Phase (EOP) Visit. In these instances, the EOP visit assessments must not be combined with those of the OLE Day 1 assessments. Additionally, while there is no fixed duration limit between EOP and OLE Day 1, in instances where the interval is greater than 4 weeks, the investigator should assess if it is appropriate to continue treatment in the OLE phase in consultation with the sponsor's medical monitor. Participants who received IVIg as rescue treatment during the double-blind placebo-controlled phase would need to wait at least 4 weeks before receiving nipocalimab in the OLE.

Participants affected by interruption of the MOM-M281-005 study due to the COVID 19 pandemic must meet the following Inclusion Criteria:

1. The investigator has confirmed that the participant is not receiving, or has not received since the interruption of the Phase 2 study, any medication that might put the participant at risk when receiving nipocalimab or might interfere with the assessment of the safety of nipocalimab.

2. Criterion modified per Amendment 1

2.1 Participants who have undergone splenectomy (if local regulatory authority has not requested exclusion of participants with splenectomy) must be at least 3 months post resection prior to screening and must be vaccinated as per the United States Center for Disease Control and Prevention annual Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States. (https://www.cdc.gov) OR must be vaccinated as per country- or territory-specific guidelines or local regulations.

Note: This criterion is not applicable if splenectomy is excluded by the local authority.

3. Has sufficient venous access to allow drug administration by infusion and blood sampling as per the protocol.

4. Criterion modified per Amendment 1.

4.1 Is recommended to be up to date on all age-appropriate vaccinations prior to screening as per routine local medical guidelines. It is strongly recommended that participants will have completed a locally-approved (or emergency use-authorized) COVID-19 vaccination regimen at least 2 weeks prior to study-related visits or procedures. Study participants should follow applicable local vaccine labeling, guidelines, and standards-of-care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment.

5. Sex and Contraceptive/Barrier Requirements as outlined in Double-blind Placebo-Controlled Phase inclusion criteria # 9, #10, #11, #12, #13, and #14 above.

6. Criterion modified per Amendment 1.

6.1 Must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to voluntarily participate in the study and comply with all study procedures. Participants who initially provide consent and subsequently withdraw it prior to randomization, will be deemed as having failed this inclusion criterion. Must be legal age of consent in the jurisdiction in which the study is taking place, at the time of consent.

5.2. Exclusion Criteria for Double-blind Placebo-Controlled Phase Entry and Open-label Extension Phase Entry of Returning Phase 2 Participants

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Coexisting Medical Conditions or Past Medical History

1. Criterion modified per Amendment 1.

1.1 Has a history of severe and/or uncontrolled hepatic (eg, viral/alcoholic/autoimmune hepatitis/cirrhosis and/or metabolic liver disease),

gastrointestinal, renal, pulmonary, cardiovascular, psychiatric, neurological musculoskeletal disorder, hypertension, any other medical disorder(s) (eg, diabetes mellitus), or clinically significant abnormalities in screening laboratory, that might interfere with the patient's full participation in the study, and/or might jeopardize the safety of the participant or the validity of the study results.

Note: Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participants (eg, compromise well-being) or that could prevent, limit, or confound the protocol-specified assessments**.**

2. Has any confirmed or suspected clinical immunodeficiency syndrome not related to treatment of his/her gMG, or has a family history of congenital or hereditary immunodeficiency unless confirmed absent in the participant.

3. Criterion modified per Amendment 1.

   3.1 Has MGFA Class I disease or presence of MG crisis (MGFA Class V) at screening, history of MG crisis within 1 month of screening, or fixed weakness (and/or 'burnt out' MG). (Note: Participants should not be actively deteriorating at the screening or baseline visit such that they meet the criteria for Clinical Deterioration as defined in Section 6.8.2).

4. Is dependent on gastric tube for nutritional needs or is ventilator-dependent.

5. Is actively undergoing radiation or chemotherapy for an unresected thymoma/malignant thymoma. Participants with stable, benign thymoma (stage I or IIa, for example) for which no treatment has been undertaken in the past 3 years may be allowed following discussion with the sponsor's medical monitor.

6. Has had a thymectomy within 12 months prior to screening, or thymectomy is planned during the study.

7. Has current or a history of any neurologic disorder other than MG that might interfere with the accuracy of study assessments, including but not limited to any chronic neurodegenerative disease, altered level of consciousness, dementia, abnormal mental status, major congenital neurologic defect, Lambert-Eaton myasthenic syndrome, drug induced MG, or hereditary forms of myasthenic syndrome.

8. Currently has a malignancy or has a history of malignancy within 3 years before screening (with the exception of localized basal cell carcinoma and/or squamous cell carcinoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months [defined as a minimum of 12 weeks] before the first study intervention administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study intervention administration).

9. Has known allergies, hypersensitivity, or intolerance to nipocalimab or its excipients (refer to the IB).

10. Has shown a previous severe immediate hypersensitivity reaction, such as anaphylaxis to therapeutic proteins (eg, monoclonal antibodies).

11. Has experienced myocardial infarction, unstable ischemic heart disease, or stroke within 12 weeks of screening.

12. Is planning to father a child while enrolled in this study or donate sperm within 90 days after the last administration of study intervention.

13. Is currently breastfeeding, pregnant, intends to become pregnant during the study, or is planning egg donation during the study or within 30 days after the last dose of study intervention.

14. History of moderate or severe substance or alcohol use disorder according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) criteria, except nicotine or caffeine, within 1 year before screening.

Concomitant or Previous Medical Therapies Received

15. Criterion modified per Amendment 1.

    15.1 Is currently taking eculizumab or other novel immune agents, IgG Fc-related protein therapeutics, or Fc-conjugated therapeutic agents, including factor or enzyme replacement.

16. Has received, rituximab within 6 months prior to first administration of study intervention. **This criterion does not apply to returning Phase 2 participants.**

17. Criterion modified per Amendment 1.

    17.1 Has received, or is expected to receive, a live vaccine within 4 weeks prior to screening or has a known need to receive a live vaccine during the study, or within 8 weeks after the last administration of study intervention. **For the Bacille Calmette-Guerin (BCG) vaccine, see exclusion criterion 33.** Participants are allowed to receive a vaccine conditionally approved by their regional health advisory for emergency use for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), unless it is a live vaccine. Concomitant enrollment in an investigational trial for any SARS-CoV-2 (COVID-19) vaccine while participating in this study is not permitted.

18. Has received plasmapheresis, immunoadsorption therapy, or IVIg within 6 weeks prior to baseline.

19. Has another medical condition that requires oral or parenteral corticosteroids unless the dose has been stable for at least 4 weeks prior to baseline and is expected to remain stable during the study. Inhaled, intra-articular, topical or ocular corticosteroids are not exclusionary. **This criterion does not apply to returning Phase 2 participants.**

20. Has another medical condition that requires an immunosuppressive agent unless the medication has been used for at least 6 months, the dose has been stable for at least 3 months prior to baseline and the medication and the dose are expected to remain stable during the study. **This criterion does not apply to returning Phase 2 participants.**

21. Has previously received nipocalimab. **This criterion does not apply to returning Phase 2 participants.**

Prior/Concurrent Clinical Study Experience

22. Has received an investigational intervention (including investigational vaccines) within 3 months or 5 half-lives (whichever is longer) or used an invasive investigational medical device within 3 months before the planned first dose administration of study intervention [or is currently enrolled in an investigational study]. Participants are allowed to receive a vaccine conditionally approved by their regional health advisory for emergency use for SARS-CoV-2.

Infections or Predisposition to Infections

23. Has a severe infection including opportunistic infections (eg, pneumonia, biliary tract infection, diverticulitis, *Clostridium difficile* infection, cytomegalovirus, pneumocystosis, aspergillosis, etc.) requiring parenteral anti-infectives and/or hospitalization, and/or is assessed as serious/clinically significant by the investigator, within 8 weeks prior to screening. The participant may be rescreened after the 8-week exclusionary period has passed.

24. Has a chronic infection (eg, bronchiectasis, chronic osteomyelitis, chronic pyelonephritis) or requires chronic treatment with anti-infectives (eg, antibiotics, antivirals).

25. Tests positive for hepatitis B virus (HBV) infection (see Appendix 3, [Section 10.3]).

26. Is seropositive for antibodies to hepatitis C virus (HCV), unless they satisfy 1 of the following conditions:

    Has a history of successful treatment, defined as being negative for HCV RNA at least 24 weeks after completing antiviral treatment, and has a negative HCV RNA test result at screening,

OR

While seropositive, has a negative HCV RNA test result at least 24 weeks prior to screening and a negative HCV RNA test at screening.

27. History of being human immunodeficiency virus (HIV)1 or HIV2 antibody-positive, or tests positive for HIV at screening.

28. COVID-19 infection:

During the 6 weeks prior to screening, have had ANY of

(a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR

(b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR

(c) close contact with a person with known or suspected SARS-CoV-2 infection:

Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

- obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, e.g. fever, cough, dyspnea)

AND

- with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

NOTES on COVID-related exclusion:

- The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/standards of care.
- Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

Other Exclusions

29. Criterion modified per Amendment 1.

29.1 Has current suicidal ideation evidenced by a "yes" response to Questions 4 or 5 in the Suicidal Ideation section of the C-SSRS at screening or baseline, or a history of active suicidal ideation or suicidal behavior in the past year prior to screening.

NOTE: If a participant meets protocol exclusion criterion 29, then the results should be discussed with the sponsor's medical monitor, unless urgency of the participant's medical situation prevents this, and along with screen-failing the participant, appropriate medical interventions and measures should be undertaken by the investigator. Clinically significant findings based on C-SSRS should be reported as AEs/SAEs as applicable.

30. Had major surgery (eg, requiring general anesthesia) within 3 months before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

31. Criterion removed per Amendment 1.

32. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

Prior/Concurrent Clinical Study Experience

33. Has had a BCG vaccination within 1 year of first administration of study intervention.

Infections or Predisposition to Infections

34. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening.

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening and baseline where applicable. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 4, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Agree not to receive a live vaccine (including BCG) during the study and for 8 weeks after receiving the last dose of study intervention.

5.3.1. Meals and Dietary Restrictions

In the double-blind placebo-controlled phase, participants are required to fast for at least 6 hours prior to collection of blood for clinical laboratory assessments at baseline, Weeks 4, 8, 12, and 24. If sites/participants cannot accommodate fasting due to scheduling or medical issues for the duration of the double-blind placebo-controlled phase, non-fasting may be permitted following discussion with the sponsor's medical monitor. In both the double-blind placebo-controlled phase and the OLE phase, when not fasting, participants may only have room-temperature food/fluids during the 1 hour preceding the collection of efficacy assessments and until efficacy assessments are completed.

5.3.2. Activity

Participants may continue their usual activities, including exercise, during the study, but are recommended to not have excessive exertion on the day of or day before an infusion/assessment visit.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once with approval of the sponsor’s medical monitor. Rescreened participants must be assigned new participant numbers.

In some cases, participants who fail screening for reasons that are subsequently addressed may be considered for rescreening. Reasons to consider rescreening include any transient condition that resulted in screen failure and has since resolved.

Participants being rescreened must sign a new ICF and undergo appropriate screening evaluation according to the Schedule of Activities (Section 1.3). This will include interim medical history, safety assessments, clinical laboratory assessments, and ECG, as discussed with the sponsor's medical monitor. Follicle-stimulating hormone (FSH) tests do not need to be repeated if the results at screening indicated menopause status. If rescreening takes place less than 3 months after screening, the HIV and hepatitis B and C tests do not need to be repeated if their results at screening did not meet exclusion criterion #25, exclusion criterion #26, and exclusion criterion #27.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Appendix 8 (Section 10.8). Criteria for temporary discontinuation of study intervention are described in Section 7.1.2.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

The designation of Auxiliary Medicinal Product(s) (AxMP) is provided in compliance with the EU CTR in the table below and is applicable to countries within the EU/EEA.

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Product(s)</td><td>Authorization status in the EU:

<table><tr><td>Authorized</td><td>Placebo (saline)</td></tr><tr><td>Unauthorized</td><td>Nipocalimab</td></tr></table>Saline (placebo) is being used in accordance with the terms of its marketing authorization.</td></tr>
<tr><td>Auxiliary Medicinal Product(s) (AxMP)</td><td>Authorization status in the EU:

<table><tr><td>Authorized</td><td>IVIg, Standard of care background treatment (as defined in Inclusion Criterion #4)</td></tr><tr><td>Unauthorized</td><td>N/A</td></tr></table>IVIg and standard of care medications will be used in accordance with the terms of their marketing authorization.</td></tr>
</table>

Study intervention administration must be captured in the source documents and the case report form (CRF).

Nipocalimab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients. Placebo will be a commercially available saline solution.

For details on rescue medications, refer to Section 6.8.2, Rescue Medication. For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.8.

Description of Interventions

Double-blind Placebo-controlled Phase

Participants in the study will maintain their standard of care treatment (if any, see also Section 5.1.1, Inclusion Criterion #4) and will be randomized to 1 of 2 treatment groups described below:

- Nipocalimab: Participants will receive nipocalimab 30 mg/kg loading dose, followed by nipocalimab 15 mg/kg IV q2w.
- Placebo: Participants will receive placebo IV q2w.

Participants will remain on their assigned treatment through Week 24. All participants will receive a planned total of 12 IV infusions over a 24-week period.

Recalculation of dose during the double-blind placebo-controlled phase for weight gained or lost will based on the weight measured for each participant every 4 weeks.

Participants should continue their stable standard of care therapy for gMG (if on any, see also Section 5.1.1, Inclusion Criterion #4) and should maintain the same dose and regimen throughout the double-blind placebo-controlled phase. Tapering of prior MG medications may be performed during the OLE phase (see next section). An increase in dose of the stable standard of care therapy is not permitted at any point in the study, nor is the addition of new immunomodulatory therapies.

Open-label Extension Phase

All participants enrolling in the OLE phase will receive nipocalimab 15 mg/kg q2w by IV infusion starting on OLE Day 1. No other nipocalimab dosing regimen should be used. Recalculation of dose during the OLE phase for weight gained or lost will based on the weight measured for each participant every 4 weeks through Extension Week 24 and every 12 weeks thereafter.

Tapering one of the participant's concomitant MG medications every 4 weeks is allowed in the OLE phase if the disease has been stable in the past 4 weeks as reflected by MG-ADL scores and based on the investigator's discretion. When considering tapering of concomitant MG medications, the investigator should adhere to the following:

- Taper 1 concomitant medication at a time, not 2 or more concomitant medications simultaneously
- When the decision has been made to taper a corticosteroid concomitant medication, the following must be done:
  - For participants on a corticosteroid dose >30 mg per day, the dose should be decreased by no more than 10 mg every 4 weeks, until a dose of ≤30 mg per day is reached. For

participants on a corticosteroid dose of ≤30 mg per day, the dose should be decreased by no more than 5 mg every 4 weeks. Once the investigator considers the corticosteroid taper completed, the participant should remain on the current dosing regimen for nipocalimab and the concomitant MG medications for at least 4 weeks before considering tapering another concomitant MG medication.

- The tapering of mycophenolate mofetil, azathioprine, or methotrexate should be performed no more frequently than every 6 months. The tapering of cyclosporine or tacrolimus should be performed no more frequently than every 3 months.

Note: CCI [redacted]

6.2. Preparation/Handling/Storage/Accountability

For nipocalimab IV administrations, the study intervention will be supplied as a sterile solution in a single-use glass vial. Saline will be used as placebo. Study intervention will be prepared for IV administration based on the instructions provided to clinical sites in the investigational product and procedures instructions (IPPI) by an unblinded pharmacist.

The nipocalimab solution in the vial should be clear to slightly opalescent and colorless to slightly brown and may contain small translucent particles. Do not use nipocalimab if the liquid is cloudy or discolored or has large particles. Protection from light is not required during the preparation and administration of the study intervention material but avoid direct exposure to sunlight. Aseptic techniques must be used during the preparation and administration of the study intervention material for IV administration.

Placebo will be a commercially available saline infusion bag or bottle. Refer to the IPPI and study site investigational product procedures manual (SIPPM) for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form maintained by the unblinded pharmacist. All study intervention will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study

intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials, such as used needles and syringes, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention must be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will only be used for individuals participating in the study. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

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 by or 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 period. 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 primary analysis CSR is complete.

- The following measurements obtained after screening (during the double-blind period) will be masked to the investigator, study team members and participants 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 masked to the investigator, study team members, and participants during the double-blind placebo-controlled phase: serum lipid profiles, c-reactive protein, complement proteins (C3, C4, CH50, C5a), circulating immune complexes (CIC), and striational antibodies.

Given that albumin laboratory results are masked, the investigator and sponsor will be notified if their patient meets the laboratory criteria for hypoalbuminemia <20 g/L (<2.0 g/dL). These hypoalbuminemia AESI cases will be handled similarly to an SAE for reporting purposes and reviewed by the DMC as they occur. Similarly, the investigator and sponsor will be alerted if LDL and/or triglycerides are significantly elevated; the criteria for these alerts are defined within the Laboratory Manual. If there is sufficient safety concern such that the investigator draws local laboratory samples to check the level of any masked laboratory assessments, the medical monitor or sponsor should be notified immediately. The participant may be required to be discontinued from study intervention.

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 primary analysis CSR is complete. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. 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.

Additionally, a given participant's treatment assignment may be unblinded to the sponsor, the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and site personnel to fulfill regulatory reporting requirements for suspected unexpected serious adverse reactions (SUSARs). If a participant is unblinded by the site, the information must be entered in the appropriate section of the eCRF and in the participant's source documents.

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 placebo-controlled phase Week 24 evaluations (or the last participant completes their last visit in double-blind placebo-controlled phase) and the data are locked. Investigative sites and participants will remain blinded to initial intervention assignment until after the primary analysis CSR is completed.

6.4. Study Intervention Compliance

Study-site personnel will maintain a log of all study intervention administered. Study intervention supplies for each participant will be inventoried and accounted for.

Study intervention will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be conducted according to the IPPI.

Additional details may be provided in the site sIPPM that is provided separately. Compliance with the treatment schedule is required.

6.5. Dose Modification

No dose modification is permitted during the double-blind placebo-controlled phase of the study.

All participants in the OLE phase of the study will receive nipocalimab infusion q2w (15 mg/kg). No other dosing regimen should be used. Tapering one of the participant's concomitant MG medications every 4 weeks is allowed in the OLE phase if the disease has been stable in the past 4 weeks as reflected by MG-ADL scores and based on the investigator's discretion.

Note: CCI [redacted]

6.6. Continued Access to Study Intervention After the End of the Study

Local regulations on continued access will always take precedence. Plans for continued access stated in this protocol may change if new information on the benefit-risk profile of nipocalimab becomes available during the study or program.

Participants who complete the double-blind placebo-controlled phase will continue to the OLE phase. The duration of each participant's participation in the OLE phase will continue until 2 years

after marketing authorization in the participant's local country/territory or until nipocalimab becomes available commercially or via other continued access program, whichever comes first.

Details specific for sites in EUR are presented in Section 10.10.1.

6.7. Treatment of Overdose

For this study, any dose of study intervention greater than 10% of the intended dose at a single dosing visit specified in this protocol will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the sponsor's medical monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Discuss with the sponsor's medical monitor if 1 or more additional serum samples for PK analysis will be required and at what time points.

6.8. Concomitant Therapy

Concomitant therapies must be recorded throughout the study beginning from the time the participant signs the ICF to 8 weeks after the last dose of study intervention.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the CRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

In participants with elevated lipids at any time during the study, it is recommended that investigators initiate or continue appropriate therapy for dyslipidemia as per local health guidelines.

6.8.1. Prohibited Therapies

Use of additional immunosuppressants or immunomodulators (including mAbs) for MG or other background medical conditions, other than those explicitly allowed in the inclusion/exclusion criteria (Sections 5.1 and 5.2), are prohibited. Use of a mAb specifically approved for treatment of COVID-19 infections, including emergency use-authorized mAbs for COVID-19 per local regulations, may be permitted for participants who medically require it. Because concomitant exposure to nipocalimab may reduce the efficacy of anti-COVID-19 mAbs, study intervention must be withheld upon administration of anti-COVID-19 mAbs. It is unknown how long nipocalimab has to be stopped to minimize its effect on the efficacy of anti-COVID-19 mAbs. The resumption of the study intervention may be considered for participants who have recovered from

COVID-19 and must be discussed with the sponsor's medical monitor. Prohibited therapies include, but are not limited to, the following:

- IgG-Fc-related protein therapeutics (for example, mAbs, among others)
- rituximab
- eculizumab
- botulinum toxin

As these lists cannot be exhaustive, please consult the medical monitor and/or study sponsor to discuss prior to starting or continuing any biologic or other advanced therapies. In addition, other medications per label may interfere with the function of the neuromuscular junction and worsen the clinical symptoms of MG. Local health guidance, clinical judgement, and the risk-to-benefit ratio of the medication should be taken into consideration before prescribing or continuing such medications in this study.

For France-specific requirements see Section 10.10.2.

6.8.2. Rescue Medication/Therapy/Clinical Deterioration

Clinical Deterioration is defined as any of the following:

- An MG crisis, defined as MG-related weakness sufficiently severe to necessitate intubation, or requires noninvasive ventilation to avoid intubation, or would be severe enough to delay extubation following surgery (Sanders 2016), with the respiratory failure being due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness may accompany respiratory muscle weakness, or may be the predominant feature in some patients.
- An MG flare, exacerbation or deterioration reflected by worsening in MG strength or clinical assessment scores, warranting hospitalization or MG rescue therapy. Of note, an MG worsening in strength or clinical assessment scores that does not warrant hospitalization or rescue therapy would not be considered Clinical Deterioration.
- Any participant whom the investigator believes will jeopardize his/her health if MG rescue therapy is not given (eg, emergent situations).

In participants experiencing a Clinical Deterioration, the use of rescue therapy (IVIg, plasmapheresis) will be permitted, as per the clinical judgment of the investigator. The use of other medications as rescue therapy, such as increasing doses of background standard of care medications, or prescribing oral or IV corticosteroids, is not permitted.

If rescue therapy is needed during the double-blind placebo-controlled phase, the participant will be discontinued from the phase. Participants receiving IVIg or plasmapheresis rescue therapy should not receive study intervention (nipocalimab or placebo) concomitantly due to the potential for nipocalimab to reduce the efficacy of IVIg as rescue therapy and additional IgG reduction post plasmapheresis. (Section 1.3).

Participants who require rescue treatment during the double-blind phase must complete an EOP visit and are eligible to enter the OLE phase based on investigator's discretion. In these instances,

the EOP visit assessments must not be combined with those of the OLE Day 1 assessments. Additionally, while there is no fixed duration limit between EOP and OLE Day 1, in instances where the interval is greater than 4 weeks, the investigator should assess if it is appropriate to continue treatment in the OLE phase in consultation with the sponsor's medical monitor. Participants who received IVIg as rescue treatment during the double-blind placebo-controlled phase must wait at least 4 weeks before receiving a subsequent dose of nipocalimab in the OLE. For participants who require rescue treatment during the OLE phase, their continued participation in the study must be discussed with the sponsor's medical monitor. Participants who are confirmed that they can continue may complete an Unscheduled visit prior to continuing in the OLE phase. Participants who received IVIg as rescue treatment during the OLE phase must wait at least 4 weeks before receiving a subsequent dose of nipocalimab in the OLE. Participants who discontinue from the OLE phase must complete an ET visit. Every effort should be made to notify the sponsor within 24 hours should a participant require a rescue therapy. Routine use of Plasma Exchange or IVIg as maintenance therapy to control MG symptoms outside of rescue is not permitted.

The study site will supply rescue medication that will be obtained locally.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.8.3. Vaccinations (Including COVID-19)

When considering use of locally approved non-live vaccines (including emergency-use-authorized COVID-19 vaccines) in study participants, follow the applicable local vaccine labeling, guidelines, and standards-of-care for participants receiving immune-targeted therapy. For study participants receiving a locally approved (including emergency-use-authorized) COVID-19 vaccine, in order to help identify acute reactions potentially related to the COVID-19 vaccine, it is recommended that, where possible, vaccine and study intervention be administered on different days, separated by as large an interval as is practical within the protocol.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The participant becomes pregnant.
- A participant develops an infection with life-threatening consequences and requiring urgent interventions.
- A participant develops an infection that is unresponsive or worsening while on anti-infective therapy.
- A participant develops a Clinical Deterioration requiring hospitalization or rescue therapy. Please see Section 6.8.2 for next steps after discontinuation.

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant develops a severe allergic reaction and/or severe infusion reaction related to the study intervention (eg, anaphylaxis as per Sampson's (2006) criteria [Appendix 9, Section 10.9]).

The sponsor's medical monitor should be notified of discontinuation of study intervention for any of these reasons.

If a participant discontinues study intervention before the end of the double-blind placebo-controlled phase for a reason other than Clinical Deterioration requiring hospitalization or rescue therapy, the participant will continue all other assessments per the Schedule of Activities (Section 1.3; Table 1) until completion of the phase. Rollover into OLE of such participants will not be permitted unless the 24 weeks of study procedures have been completed. Participants who permanently discontinue or withdraw during the double-blind placebo-controlled phase should complete the ET visit assessments. These participants should also return for a safety follow-up visit 8 weeks after the last infusion (Table 4). Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Participants who discontinue will not be replaced.

7.1.1. Liver Chemistry Stopping Criteria

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met as outlined in Appendix 7 (Section 10.7) Liver Safety: Suggested Actions and Follow-Up Assessments or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant

7.1.2. Temporary Discontinuation

Study intervention administration may be interrupted, and the sponsor's medical monitor notified, for the following events:

- If a participant develops a severe or medically significant but not immediately life-threatening infection requiring IV anti-infective or operative/invasive intervention and requiring hospitalization or prolongation of existing hospitalization, the investigator should consider withholding study intervention until the clinical scenario clarifies whether the infection is improving or getting worse.
- If a participant develops 3+ pedal edema, ascites, or pleural or pericardial effusions.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document.

Withdrawal of Consent

A participant may withdraw consent to further study treatment while maintaining consent for further assessments in the double-blind placebo-controlled phase, Safety Follow-up Phase, and/or subsequent contact with site personnel to provide information about their health status. A Withdrawal of Consent Form may be used to confirm which study activities the participant is withdrawing consent. If the participant withdraws consent during the double-blind placebo-controlled phase and declines participation in the Safety Follow-up Phase, or enters the Safety Follow-up Phase and subsequently withdraws consent prior to completion of the Safety Follow-up Visit, the participant should be encouraged to consent to subsequent contact by site personnel 8 weeks from last infusion of study intervention. This could include telephone contact with the participant, caregiver, or treating physician to inquire about the participant's health status. During this contact, site personnel will collect information about concomitant medications, AEs, and SAEs that may have occurred within the 8 weeks since last infusion of study intervention. If the participant withdraws all consent, including withdrawal of consent from future contact by site personnel, no additional assessments or data collection will occur.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 4, Regulatory, Ethical, and Study Oversight Considerations; Section 10.4.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, and to ascertain whether the participant wishes to or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Table 1, Table 2, Table 3, and Table 4) summarizes the frequency and timing of efficacy, immunogenicity, PK, PD, and safety measurements applicable to this study.

All patient-reported outcome (PRO) assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses. Training will be provided for administration of PROs.

Blood Sample Collection

The total blood volume to be collected will be approximately 1,100 to 1,200 mL for participants in China and approximately 1,600 to 1,700 mL for all other participants. The total blood volume is inclusive of the full duration of the double-blind placebo-controlled phase and up to Week 240 of the OLE.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the Schedule of Activities (Section 1.3; Table 1, Table 2, Table 3, and Table 4) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and nipocalimab IB)
- Study site investigational product and procedures manual, laboratory manual(s), and laboratory supplies. Certain Clinical Outcome Assessments (COAs; includes both PROs and rater administered assessments) will be collected using an electronic device while others will be collected on paper worksheets. Therefore, the following materials will be provided:
- IWRS user guide and worksheets
- eCRF completion instructions
- Sample ICFs
- Any other manual or guideline that is deemed necessary for good execution of the study, including MACE Adjudication, if applicable

8.1. Efficacy Assessments

Investigator assessments and PROs of efficacy are included in this section.

For PRO measures:

- The PRO instrument will be provided in the local language in accordance with local guidelines.
- The PRO instrument must be available for regulators and for IRB/ERC submissions, therefore the PRO instrument or screen shots need to be attached to the protocol or provided in a companion manual with the instruments that will be submitted with the protocol.
- The PRO and AE data will not be reconciled with one another.

8.1.1. Myasthenia Gravis – Activities of Daily Living

The MG-ADL is administered by a trained qualified healthcare professional (eg, physician, physician assistant, nurse practitioner, nurse) and provides a rapid assessment of the patient's MG symptom severity. The MG-ADL should be administered by the same healthcare professional for a given participant throughout the study. In certain circumstances a change in rater may be permitted when it is unavoidable (eg, rater left the institution, rater unavailable for several weeks, etc). It is recommended that the reasons for an upcoming rater change be discussed in advance with the sponsor, if possible. The assessment should be performed at approximately the same time of day from Screening Visit, throughout the study. The participant's acetylcholinesterase inhibitor dose must be withheld for approximately 12 hours or longer prior to performing MG-ADL at all visits, and attempts made to reschedule the visit within the per protocol visit window if the dose was taken <12 hours prior. Eight functions (talking, chewing, swallowing, breathing, impairment of ability to brush teeth or comb hair, impairment of ability to arise from a chair, double vision, eyelid droop) are rated on a 4-point scale. The total score can range from 0 to 24. A higher score indicates greater symptom severity.

8.1.2. Quantitative Myasthenia Gravis

The QMG test is a standardized quantitative strength assessment comprising 13 components (and is administered by a trained qualified healthcare professional eg, physician, physician assistant,

nurse practitioner, nurse). The QMG should be administered by the same healthcare professional for a given participant throughout the study. In certain circumstances a change in rater may be permitted when it is unavoidable (eg, rater left the institution, rater unavailable for several weeks, etc). It is recommended that the reasons for an upcoming rater change be discussed in advance with the sponsor, if possible. The assessment should be performed at approximately the same time of day from Screening Visit throughout the study. The participant's acetylcholinesterase inhibitor dose must be withheld for approximately 12 hours or longer prior to performing QMG at all visits, and attempts made to reschedule the visit within the per protocol visit window if the dose was taken <12 hours prior. The quantitative results of each strength component are mapped to the following 4-point scale:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe

The total score can range from 0 to 39. A higher score indicates greater weakness.

8.1.3. Revised Myasthenia Gravis Quality of Life – 15

The MG-QoL15r is a patient-reported outcome instrument that measures MG-specific health-related quality of life (Burns 2016). The MG-QoL15r contains 15 items that evaluate patients' experience related to Myasthenia Gravis over the "past few weeks" on a 3-point Likert-type scale (0=Not at all; 1=Somewhat; 2=Very much). The total score can range from 0 to 30. A higher score indicates more limitation.

8.1.4. Neuro-QoL-Fatigue

The Neuro-QoL Fatigue version 1.0 is a 19-item questionnaire developed and validated for use in common neurological conditions which assesses patient-reported fatigue and associated impact on physical, mental, and social activities during the past 7 days (Health Measures n.d.). Each item included in the Neuro-QoL Fatigue questionnaire is graded on a 5-point Likert-type scale (1=Never; 2=Rarely; 3=Sometimes; 4=Often; 5=Always) with higher scores reflecting more fatigue. The total raw scores are calculated by summing 19 items and raw score is converted to a T-score.

8.1.5. Patient Global Impression of Severity

The PGI-S will be used to assess the severity of fatigue due to gMG. The PGI-S will be administered at the same timepoints as the Neuro-QoL Fatigue. The participant will answer the following question:

Please choose the response below that best describes the overall severity of your fatigue over the past 7 days.

1 = None

2 = Mild

3 = Moderate

4 = Severe

5 = Very Severe

8.1.6. Patient Global Impression of Change

The PGI-C, derived from the scale published by the National Institute of Mental Health, assesses if there has been an improvement or decline in patient-reported status since the beginning of the treatment. The participant will answer the following question:

Please choose the response below that best describes the overall change in your fatigue compared to your first study visit:

1 = Much better

2 = Moderately better

3 = A little better

4 = No change

5= A little worse

6 = Moderately worse

7 = Much worse

8.1.7. EuroQol 5-Dimension 5-Level

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises 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 participant selects an answer for each of the 5 dimensions considering the response that best matches his or her health "today." The descriptive system can be represented as a health state. The

EQ-VAS self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 to 100.

The time taken to complete the questionnaire varies with age, health status, and setting but is likely to be approximately 1 minute.

8.1.8. Treatment Satisfaction Questionnaire for Medication

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) (Atkinson 2004) is a 9-item generic patient reported outcome instrument to assess patients' satisfaction with medication. It is derived from the longer TSQM Version 1.4 (Bharmal 2009) and covers domains of effectiveness, convenience, and global satisfaction. The instrument is scored by domain with scores ranging from 0-100 where a lower score indicates lower satisfaction. The recall period is "the last 2-3 weeks". It takes approximately 5 minutes to complete.

8.1.9. Digital Health – Actigraphy Measurements (at Selected Sites)

Actigraphy, a non-invasive method of monitoring human rest/activity patterns, will be performed using a wrist-worn actigraphy watch in newly screened participants post-Amendment 1 at select sites globally. Participants who will not prove eligible will return their actigraphy watch to the study site. Only accelerometry measurements will be collected from actigraphy watches, with the data utilized to assess physical activity, mobility, and sleep parameters. Participants will be asked to continuously wear the watch on the non-dominant wrist from Screening Visit until Week 24/ET/EOP of the double-blind placebo-controlled phase, and will download data from the watch prior to the site visit. Sites and participants will not have access to data generated from the use of the watch. All actigraphy watches will be collected from participants at their respective Week 24/ET/EOP visit.

8.2. Safety Assessments

Details regarding the independent Data Monitoring Committee are provided in Committees Structure in Appendix 4, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 5 (Section 10.5), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (Table 1, Table 2, Table 3, and Table 4).

8.2.1. Physical Examinations

Physical examinations will be performed by the investigator or designated physician, nurse practitioner or physician assistant as specified in the SoA (Section 1.3; Table 1, Table 2, Table 3, and Table 4). Any new, clinically significant finding (in the opinion of the investigator) must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

Height will be measured at screening only. Weight will be measured at screening, at Day 1, Week 4, and then every 4 weeks through the first 24 weeks of the OLE. Thereafter, weight will be measured every 12 weeks. A full physical examination will be performed visits specified in the Schedule of Activities (Section 1.3). At all other visits, a focused physical examination will be performed to determine if there has been any change in neurologic function, upper respiratory tract (ears, nose, throat, and sinuses), eyes and lungs, abdomen, or skin.

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device after the participant has been resting in the recumbent position for 3 to 5 minutes. Manual techniques will be used only if an automated device is not available.

At a study intervention administration visit, vital signs should be obtained before and 30 minutes after completion of the IV infusions, or if the participant reports any symptoms. Vital signs should also be obtained 1 hour after completion of the IV infusions for the first 3 visits in the double-blind placebo-controlled phase and the OLE phase as outlined in the Schedule of Activities (Section 1.3; Table 1, Table 2, and Table 3).

The investigator will determine if any of the vital sign measurements are clinically significant (CS) or not clinically significant (NCS). Clinical significance is defined as any variation in assessment results that have medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a CS change from a screening value is noted, the CS value and reason for clinical significance will be documented on the AE page of the patient's eCRF.

8.2.3. Electrocardiograms

A 12-lead electrocardiogram will be as specified in the Schedule of Activities (Section 1.3; Table 1, Table 2, Table 3, and Table 4). The investigator will determine if the ECG is CS or NCS.

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for safety laboratory assessments, such as serum chemistry, hematology, and lipid profiles and a random urine sample for urinalysis, will be collected as noted in Appendix 2 (Section 10.2), Clinical Laboratory Tests. The investigator must review the laboratory results, determine if abnormal clinical laboratory results are CS or NCS, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. As described in Section 6.3, data that may potentially unblind study intervention assignment will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized.

8.2.5. Pregnancy

Urine pregnancy testing will be done for women of childbearing potential only (performed locally), see definition in Section 10.6. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

8.2.6. Adverse Events Temporally Associated with Infusion

Any AE (except laboratory abnormalities) that occurs during or within the observation period after the IV infusion of study intervention will be carefully evaluated. Participants will be observed for safety 1-hour post-infusion after the first 3 infusions in the double-blind placebo-controlled phase; if no clinically relevant AEs related to the infusion are observed with these first 3 infusions, participants will be observed for 30 minutes after subsequent infusions for the duration of the phase. During the OLE phase, participants will be observed for safety 1-hour post-infusion after the first 3 infusions; if no clinically relevant AEs related to the infusion are observed with these 3 infusions, participants will be observed for 30 minutes after subsequent infusions.

8.2.7. Infusion-Reactions

An infusion reaction is defined as any AE that is reported by investigator to represent an infusion reaction.

Minor infusion-related AEs may be managed by slowing the rate of the IV infusion and/or treating with antihistamines and/or acetaminophen (paracetamol) as clinically indicated. If an IV infusion of study intervention is interrupted because of an AE that, in the opinion of the investigator, is not severe or does not result in a SAE, the infusion may be restarted with caution.

8.2.8. Hypersensitivity Reactions

Before any administration of study intervention at the study site, appropriately trained personnel and medications (eg, antihistamines, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. All participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension).

In the case of a severe allergic reaction (eg, anaphylaxis [Sampson 2006]), SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures are essential and must be available when study intervention is being administered. Participants who experience serious adverse reactions related to an injection or infusion should be discontinued from further study intervention administrations.

8.2.9. Suicidal Ideation and Behavior Risk Monitoring

Although preclinical and clinical studies with nipocalimab did not indicate any central nervous system effects, the C-SSRS will be used in this study as an additional safety assessment based on the recommendation by the United States Food and Drug Administration (US FDA) for all clinical studies involving the development of drugs or biologics for neurologic indications to assess suicide risk. The US FDA has provided guidance to prospectively assess suicidal ideation and behavior in clinical studies to ensure that participants in clinical studies who are experiencing suicidal ideation and behavior are properly recognized and adequately treated and to ensure the collection of more timely and more complete data on suicidal ideation and behavior than have been collected in the past (US FDA 2012)

Baseline assessment of suicidal ideation and behavior and intervention-emergent suicidal ideation and behavior will be assessed during the study using the C-SSRS. If a participant's C-SSRS results indicate active suicidal ideation and/or a plan/intent, the results should be discussed with the sponsor's medical monitor as soon as reasonably possible, unless urgency of the participant's medical situation prevents this, and the participant may be discontinued from the study at the discretion of the investigator. Appropriate medical interventions and measures should be undertaken in such cases by the investigator. Clinical findings based on C-SSRS should be reported as AEs/SAEs as applicable.

8.2.10. Benefit-Risk Balance

Benefit-risk balance of nipocalimab for adults with gMG will be explored. Refer to Section 9.4.6, Benefit-Risk Analysis for details.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaints (PQC), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQC can be found in Appendix 5, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious Adverse Events

All SAEs and AESIs, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 8 weeks after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

A **possible Hy's law Case** is defined by the occurrence of ALT/AST ≥3 x ULN, alkaline phosphatase <2 x ULN together with total bilirubin (Tbili) ≥2 x ULN or international normalized ratio (INR) >1.5 (if measured). Any possible Hy's Law case is considered an important medical event and should be reported to the sponsor within 24 hours, even before all other possible causes of liver injury have been excluded.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

Selected events including potential MACE will undergo adjudication by an Event Adjudication Committee (EAC). For such events, investigators will be asked to provide a specific package of information for evaluation. Further details will be provided in a procedural manual. The EAC will assess such events according to the committee's charter and will independently classify the events while blinded to treatment assignment.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or

PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 5, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events: myasthenia gravis crisis and myasthenia gravis.

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries/territories in which the studies are conducted.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. (see Appendix 6 [Section 10.6] Contraceptive and Barrier Guidance and Collection of Pregnancy Information and Appendix 5 [Section 10.5], Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting).

8.3.6. Adverse Events of Special Interest

Treatment-emergent AEs associated with the following situations are considered an AESI:

1. Infections that are severe (as defined in Section 10.5.3) or require IV anti-infective or operative/invasive intervention.
2. Hypoalbuminemia with albumin <20 g/L (<2.0 g/dL); applicable to participants who have albumin >20 g/L at previous assessments. Those who enter with <20 g/L and stay below this level should not be reported as an AESI. Those who enter with an albumin > 20g /L or those who enter with albumin <20g/L and then have an increase in albumin >20 g/L which subsequently decreases to <20 g/L should be reported as an AESI.

These AEs occurring after the first study intervention administration(s) in participants participating in this clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the event, according to the procedures in Appendix 5 (Section 10.5), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting, for SAEs. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Pharmacokinetics

Blood samples will be taken as described in the Schedule of Activities (Section 1.3; Table 1, Table 2, and Table 3) for measurement of serum nipocalimab concentrations to assess the PK of nipocalimab. Additionally, serum samples should also be collected at the end of treatment visit from participants who discontinued study intervention or were withdrawn from the study. At each sampling timepoint, aliquots of serum samples will be taken for PK, immunogenicity, and back-up, respectively.

8.4.1. Evaluations

Blood samples will be collected for measurement of serum concentrations of nipocalimab and should be drawn from a different arm than that of the IV infusion line if study agent is administered at that visit.

Blood samples will be collected and each serum sample will be divided into aliquots (for PK, anti-nipocalimab antibodies, and back-up). All pre-dose samples must be collected before study intervention administration at visits when a study intervention administration is scheduled. At study visits where postdose samples are collected, a blood sample will be collected 45 minutes (± 15 minutes) after the end of infusion. Samples collected for analyses of nipocalimab serum concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum

samples. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

8.4.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of nipocalimab using a validated, specific, and sensitive immunoassay method by the sponsor's bioanalytical facility or under the supervision of the sponsor. The sponsor, or it's designee, under conditions in which participants' identity remains blinded, will assay these samples.

8.5. Genetics and Pharmacogenomics

Pharmacogenomics and genetics are not evaluated in this study.

8.6. Biomarkers

Biomarker assessments will be performed to examine the biologic response to treatment and to identify biomarkers that are relevant to nipocalimab treatment and/or MG, where local regulations permit. Blood samples for biomarker research will be collected from participants who agree during the consenting process as specified in the SoA (Section 1.3; Table 1, Table 2, and Table 3). The samples will be used to address scientific questions related to circulating biomarkers thought to play a role in any effect of nipocalimab and/or MG, including research to help develop ways to detect, monitor or treat the disease. The analyses could use proteomics, RNA expression and/or metabolomics to understand disease characteristics and response to nipocalimab. No genetic analysis will be performed.

Sample collection and testing will comply with local regulations.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.6.1. Pharmacodynamics

Blood samples will be collected for measurement of concentrations of total serum IgG, IgG subtypes (IgG1, IgG2, IgG3, and IgG4), IgA, IgM, IgE, and levels of anti-AChR, anti-MuSK, and anti-LRP4 autoantibodies. In participants seronegative for anti-AChR and anti-MuSK autoantibodies, other autoantibodies that have been implicated in gMG may be assessed[m]. For stratification purposes, the levels of anti-AChR and anti-MuSK will be tested on all samples

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

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collected at Screening; anti-LRP4 will also be collected to assess seropositivity.[n] Blood samples will be collected at the time points specified in the Schedule of Activities (Section 1.3; Table 1, Table 2, and Table 3).

8.7. Immunogenicity Assessments

Antibodies to nipocalimab will be evaluated in serum samples collected from all participants according to the Schedule of Activities (Section 1.3; Table 1, Table 2, and Table 3). Additionally, serum samples should also be collected at the end of treatment visit from participants who discontinued study intervention or were withdrawn from the study. At each sampling timepoint, aliquots of serum samples will be taken for PK, immunogenicity, and back-up, respectively.

Serum samples will be screened for antibodies binding to nipocalimab and the titer of confirmed positive samples will be reported. Other analyses may also be performed to verify the stability of antibodies to nipocalimab and/or further characterize the immunogenicity of nipocalimab (such as for the incidence of NAb to nipocalimab).

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to nipocalimab will be performed using a validated method by the sponsor's bioanalytical facility or under the supervision of the sponsor. All samples collected for detection of antibodies to nipocalimab will also be evaluated for nipocalimab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s).

8.8 Medical Resource Utilization and Health Economics

Medical resource utilization data, associated with medical encounters, will be collected using the Healthcare Resource Use Questionnaire (HRUQ) on an ongoing basis whenever an encounter occurs and will be reviewed as indicated in the Time and Events Schedule. The HRUQ includes information regarding utilization of healthcare services (including the timing and type of services), enabling changes in level and quantity of services to be considered as a variable in economic models.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

[n] In China, anti-LRP4 autoantibody collection will only be tested at Screening.

9.1. Statistical Hypotheses

The primary hypothesis of this study is that IV nipocalimab is superior to placebo as measured by average change from baseline in the MG-ADL score over Weeks 22, 23, and 24 for participants who are seropositive (anti-AChR positive, anti-MuSK positive, and/or anti-LRP4 positive).

9.2. Sample Size Determination

Double-blind Placebo-controlled Phase

A sample size of 75 seropositive participants per group are 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 (Donohue 2020; Lu 2008). At least 150 eligible seropositive participants will be enrolled. Seronegative participants will also be enrolled[o].

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 6 below summarizes the between-group differences in proportions that can be detected with at least 90% (80%) power for the key secondary endpoint 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 6: 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 (*refer to Section 9.4.2.2*).

[o] Seronegative participants are no longer being recruited; all participants must have a positive serologic test for a gMG related pathogenic autoantibody (anti-AChR, anti-MuSK and/or anti-LRP4 autoantibodies), confirmed prior to randomization.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

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
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 nipocalimab in either the double-blind or OLE phase and have at least 1 valid post-dose blood sample drawn for PD analysis

9.4. Statistical Analyses

The SAP will be finalized prior to unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The primary and key secondary efficacy analyses will be tested at a two-sided significance level of 0.05 and point estimates and 95% confidence intervals will be presented. The testing strategy to control Type I error over the primary and key secondary endpoints is described in Section 9.4.2.2, below. A different testing strategy will be employed for submission to Japan and is described in Section 9.4.3.

Other secondary and exploratory endpoints will be summarized with estimates and 95% confidence intervals and/or descriptive statistics.

The analysis of the 24-week double-blind placebo-controlled phase will be performed after the last participant completes the Week 24 visit.

A final analysis, including the OLE phase, will be performed after the last participant, last visit in the OLE phase.

9.4.2. Double-blind Placebo-controlled Phase

9.4.2.1. Primary Endpoint

Primary Estimand (applicable to regions outside of the European Union [EU])

- Population: Seropositive participants with gMG who are on a stable MG therapy (or who discontinued MG therapy due to intolerance or lack of efficacy as defined in Inclusion Criterion #4).
- Endpoint: Average change from baseline (screening and Day 1) in MG-ADL total score over Weeks 22, 23 and 24.
- Intercurrent events and corresponding strategies:
  - Treatment discontinuation of study intervention only due to reasons other than initiation of rescue medication use (Hypothetical strategy: as if the intercurrent event had not occurred) (ICH Guidance E9 [R1] 2019)
  - Treatment discontinuation of both background MG medication and study intervention due to reasons other than initiation of rescue medication use (Hypothetical strategy: see above)
  - Treatment discontinuation of study intervention only due to initiation of rescue medication use (Hypothetical strategy: see above)
  - Treatment discontinuation of both background MG medication and study intervention due to initiation of rescue medication use (Hypothetical strategy: see above)

  - Change in background MG medication (Hypothetical strategy: see above)
- Summary measure: Difference between treatment means.
- Treatment: 30 mg/kg loading dose followed by 15 mg/kg q2w of nipocalimab versus placebo.

Primary Estimand (applicable to the EU)

- Population: Seropositive participants with gMG who are on a stable MG therapy (or who discontinued MG therapy due to intolerance or lack of efficacy as defined in Inclusion Criterion #4).
- Endpoint: Average change from baseline (screening and Day 1) in MG-ADL total score over Weeks 22, 23 and 24.
- Intercurrent events and corresponding strategies:
  - Treatment discontinuation of study intervention only due to reasons other than initiation of rescue medication use (Treatment policy: irrespective of the occurrence of an intercurrent event) (ICH Guidance E9 [R1] 2019)
  - Treatment discontinuation of both background MG medication and study intervention due to reasons other than initiation of rescue medication use (Treatment policy: see above)
  - Treatment discontinuation of study intervention only due to initiation of rescue medication use (Hypothetical strategy: as if the intercurrent event had not occurred)
  - Treatment discontinuation of both background MG medication and study intervention due to initiation of rescue medication use (Hypothetical strategy: see above)
  - Change in background MG medication (Treatment policy: see above)
- Summary measure: Difference between treatment means.
- Treatment: 30 mg/kg loading dose followed by 15 mg/kg q2w of nipocalimab versus placebo.

Analysis Under the Primary Estimands

Regions outside of the EU

The primary efficacy endpoint, the average change from baseline in MG-ADL total score over Weeks 22, 23 and 24 of the double-blind placebo-controlled phase, will be analyzed using an MMRM with weekly change from baseline as the dependent variable; factors for treatment, autoantibody status, region, week, and treatment-by-week interaction; baseline MGADL total score as a covariate and participant as a random effect. Baseline is defined as the arithmetic mean of the screening and Day 1 assessments. An unstructured variance-covariance matrix will be used first. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1). 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. Observations after the occurrence of an intercurrent event will not be included in the primary analysis, consistent with the hypothetical strategy for handling

intercurrent events. Missing data will be handled through the MMRM, assuming missing data are Missing at Random.

Sensitivity analyses will include a tipping point analysis using multiple imputation with delta adjustment. The frequency of the intercurrent events of treatment discontinuation and rescue medication use will be summarized.

EU

The analysis will proceed in the same manner as described above for regions outside of the EU, except for how observations collected after intercurrent events are handled. For intercurrent events addressed with the treatment policy strategy, observations collected after the intercurrent event will be included in the analysis. For intercurrent events addressed with the hypothetical strategy, observations collected after the intercurrent event will not be included in the analysis. Missing data that may result after an intercurrent event will be handled with a Copy Reference multiple imputation approach.

Sensitivity analyses will include a Jump to Reference multiple imputation approach.

The Statistical Analysis Plan may specify supplementary estimands in addition to the primary estimands specified above.

9.4.2.2. Secondary Endpoint(s)

Key Secondary Efficacy Endpoints

A fixed sequence approach will be applied to adjust for multiplicity and to control Type 1 error across the primary and the 5 key secondary efficacy endpoints. 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 endpoint. If the primary endpoint is statistically significant, the selected secondary endpoints will be assessed in the following order:

1. Average change from baseline in QMG score over weeks 22 and 24. Analyzed using a similar method (appropriate for the region) as for the primary efficacy endpoint, but since the QMG is not assessed at Week 23, the contrast will average the change from baseline over Weeks 22 and 24 of the double-blind placebo-controlled phase.
2. 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. 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 Week 22 or 23 in order to have a non-missing average score. A participant with a missing average score will be considered a nonresponder. Analyzed by Cochran-Mantel-Haenszel test controlling for the baseline MG-ADL total score randomization strata (≤9, >9), autoantibody status, and region.

3. Loading dose response, defined as percentage of participants with improvement in MG-ADL total score of ≥2 points at Week 1 and/or Week 2. A participant with a missing assessment at either time point will be considered a nonresponder at that time point. Analyzed by Cochran-Mantel-Haenszel test controlling for the baseline MG-ADL total score randomization strata (≤9, >9), autoantibody status, and region.
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 between Week 6 through Week 23 (excursions defined as loss of improvement in MG-ADL score of ≥2 points from baseline). A participant with a missing assessment at a time point will be considered a nonresponder at that time point. Analyzed by Cochran-Mantel-Haenszel test controlling for the baseline MG-ADL total score randomization strata (≤9, >9), autoantibody status, and region.
5. 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 50% 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 Week 22 or 23 in order to have a non-missing average score. A participant with a missing average score will be considered a nonresponder. Analyzed by Cochran-Mantel-Haenszel test controlling for the baseline MG-ADL total score randomization strata (≤9, >9), autoantibody status, and region.

Estimands for Responder-type Key Secondary Endpoints (applicable to all regions)

- Population: seropositive participants with gMG who are on a stable MG therapy (or who discontinued MG therapy due to intolerance or lack of efficacy as defined in Inclusion Criterion #4).
- Endpoint: As defined above for “response”, “loading dose response”, “minimum symptom expression”, and sustainability of therapeutic response.
- Intercurrent events and corresponding strategies:
  - Treatment discontinuation of study intervention only due to reasons other than initiation of rescue medication (Composite strategy: endpoint is defined as “non-response” at time points after the intercurrent event) (ICH Guidance E9 [R1] 2019)
  - Treatment discontinuation of both background MG medication and study intervention due to reasons other than initiation of rescue medication (Composite strategy: see above)
  - Change in background MG medication (Composite strategy: see above)
  - Treatment discontinuation of study due to initiation of rescue medication (Composite strategy; see above)
  - Treatment discontinuation of both background MG medication and study intervention due to initiation of rescue medication (Composite strategy; see above)
- Summary measure: Difference between proportion of responder in each treatment group.
- Treatment: 30 mg/kg loading dose followed by 15 mg/kg q2w of nipocalimab versus placebo.

The estimands for the QMG endpoint are similar to the primary estimand with the same intercurrent events and intercurrent events strategies.

Sensitivity analyses to evaluate missing data assumptions in the estimators of the key secondary endpoints will be described in the SAP.

Other Efficacy Endpoints

Between-group differences and 95% confidence intervals of the change from baseline in MG-ADL score at each time point will be estimated from the same MMRM described above (as appropriate for the region). Similar analyses will be conducted for QMG.

The percentage of MG-ADL responders, defined as improvement in the MG-ADL total score of ≥2 points, will be summarized at each time point. Participants with a missing value at a time point will be considered a non-responder at that time point. A similar analysis will be conducted for QMG, including sustainability of response as defined for MG-ADL above, where QMG response is defined as improvement of ≥3 points.

Time to first MG-ADL response in the double-blind, placebo-controlled period will be summarized with Kaplan-Meier estimates.

The percentage of participants with minimum symptom expression, defined as a MG-ADL total score of 0 or 1, will be summarized at each time point. The percent 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 24-week double-blind placebo-controlled phase will also be summarized.

Change from baseline in the Neuro-QoL Fatigue total score, MG-QoL15r total score, and PGI-S will each be analyzed using a similar MMRM described above for the primary efficacy endpoint. The frequency distributions of PGI-S and PGI-C scores will also be summarized at each time point. Descriptive statistics of the change from baseline in EQ-5D-5L visual analog scale and health status index will be summarized at each time point. The distribution of the level of responses (level 1, 2, 3, 4, and 5) for each of the EQ-5D-5L health dimensions of mobility, self-care, usual activity, pain and discomfort, and anxiety and depression will be summarized at each time point.

Analyses of the MG-ADL described above, and for selected secondary efficacy endpoints, will be repeated for the full analysis set (both seropositive and seronegative participants) and for the seronegative subgroup. Additional descriptive summaries of MG-ADL will be performed for each type of anti-autobody (anti-AChR, anti-MuSK, anti-LRP4) as the sample size in each subgroup allows.

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 on 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.

Additional actigraphy endpoints may be derived using emerging algorithms. Associations between actigraphy endpoints and other endpoints may be explored. All actigraphy-related analyses are considered exploratory and will be summarized in a separate report.

9.4.3. Testing Strategy for Japan

For submission in Japan 2 primary endpoint families of 3 statistical hypotheses will be tested:

Primary Endpoint Family 1

- Efficacy of 24 weeks of nipocalimab treatment compared to placebo for generalized myasthenia gravis (gMG), based on the MG-ADL scale, in seropositive participants when treatment is taken as directed.
- Efficacy of 24 weeks of nipocalimab treatment compared to placebo for generalized myasthenia gravis (gMG), based on the MG-ADL scale, in anti-AChR positive participants when treatment is taken as directed.

Primary Endpoint Family 2

- Efficacy of 24 weeks of nipocalimab treatment compared to placebo for generalized myasthenia gravis (gMG), based on the MG-ADL scale, in seropositive and seronegative participants when treatment is taken as directed.

The estimands for each hypothesis are the same as the primary estimand described above for regions outside of the EU with only the population changing depending on the hypothesis. The analysis under each estimand will be the same as the analysis under the primary estimand, employing the appropriate analysis set for the given estimand.

The primary analyses for Japan will be conducted at the 2-sided 0.05 level for both the seropositive and anti-AChR positive analysis sets. If both are statistically significant, the null hypotheses for 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 2-sided 0.05 level. If the analysis for either the seropositive analysis or the anti-AChR positive analysis is not statistically significant (at 2-sided 0.05), then the analysis for the full analysis set will not be conducted.

This serial gatekeeping strategy maintains Type I error control over the two families of 3 hypotheses at the 2-sided 0.05 level.

Further details about analyses specific for the Japan submission will be described in the Statistical Analysis Plan.

9.4.4. Open-label Extension Phase

All efficacy data will be summarized using descriptive statistics. Two treatment groups are defined for this phase based on the sequence of assigned treatments in the double-blind placebo-controlled phase: 1) nipocalimab 15 mg/kg q2w - nipocalimab 15 mg/kg q2w; 2) placebo - nipocalimab 15 mg/kg q2w.

Change from the double-blind placebo-controlled baseline over time will be summarized for MG-ADL, QMG, Neuro-QoL Fatigue total score, MG-QoL15r total score, and PGI-S.

The percentage of MG-ADL responders and QMG responders over time will be summarized. The percentage of participants with minimal symptom expression (MSE) will be summarized at each time point.

The frequency distributions of PGI-S and PGI-C scores will also be summarized at each time point. Descriptive statistics of the change from baseline in EQ-5D-5L visual analog scale and health status index will be summarized at each time point. The frequency distribution of level of responses (level 1, 2, 3, 4, and 5) for each of the EQ-5D-5L health dimensions of mobility; self-care; usual activity; pain and discomfort; and anxiety and depression will also be summarized at each time point.

The treatment groups may also be combined for summaries of OLE phase timepoints since all participants will be assigned the same nipocalimab dose for the first 6 months of the phase.

9.4.5. Safety Analyses

All safety analyses will be made on the full analysis set.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during a phase will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group. Separate summaries will be provided for each phase of the study. Participants who die, who discontinue treatment due to an AE, or who experience an SAE will be summarized separately. Listings of all participants with MACE (non-fatal myocardial infarction, stroke, and cardiovascular death) will be provided.

The TEAEs of special interest will be examined separately grouped in the following categories: Severe or serious infections, hypoalbuminemia <20 g/L. The AESIs will be further listed in the SAP.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Electrocardiogram

The ECG data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made. All clinically relevant abnormalities in ECG waveforms that are changes from the baseline readings will be reported.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, body weight measurements, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examinations

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

C-SSRS

The percentage of participants with suicidal ideation or suicidal behavior based on the C-SSRS will be summarized.

9.4.6. Other Analyses

Pharmacokinetic Analyses

For each intervention group, serum nipocalimab concentrations will be summarized over time to assess the PK of nipocalimab. Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for serum nipocalimab concentrations. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

Biomarkers Analyses

Changes in serum IgG, or other biomarkers over time will be summarized by intervention group. Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. Results of biomarker analysis will be presented in a separate report.

Immunogenicity Analyses

The incidence and titers of anti-nipocalimab antibodies will be summarized by treatment group for all participants who receive at least 1 dose of nipocalimab and have appropriate samples for detection of antibodies to nipocalimab.

A listing of participants who are positive for anti-drug antibodies to nipocalimab will be provided. The maximum titers of anti-drug antibodies to nipocalimab will be summarized for participants who are positive for anti-drug antibodies to nipocalimab.

The incidence of NAbs to nipocalimab will be summarized for participants who are positive for anti-drug antibodies to nipocalimab and have samples evaluable for NAbs to nipocalimab.

Pharmacokinetic/Pharmacodynamic Analyses

A pharmacometrics model-based analyses will be conducted to describe the relationships of PK, PD (IgG lowering), and efficacy (MG-ADL and/or QMG). Details will be given in a model-based PK/IgG/efficacy analysis plan, and results of the model-based PK/IgG/efficacy analysis will be presented in a separate technical report.

Benefit-Risk Analysis

Benefit-risk assessment of nipocalimab vs placebo for participants with gMG will be assessed using a structured framework approach. Benefits in the assessment may include the primary efficacy endpoint and improvement from baseline in measures of disease activity and functions, such as MG-ADL and QMG. Risks in the assessment may include clinically meaningful, treatment-emergent AEs or adverse drug reactions.

The benefit-risk assessment will be evaluated over the double-blind placebo-controlled period based on the between treatment differences (eg, risk difference or excess number of events) for efficacy and safety endpoints at Week 24. Kaplan-Meier Product-Limit estimates may also be used to display and evaluate benefits and risks over time. To compare efficacy and safety endpoints in similar units (proportions to proportions, or rates to rates), MG-ADL and QMG will be assessed as the proportions of participants which show a clinically meaningful change or response, and the risks will be shown as proportions or rates. Benefit-risk results will be depicted with effect tables and with other visual representations (eg, forest plots).

9.5. Interim Analysis

Analyses of the OLE data may be performed periodically to assess safety and/or efficacy.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AChR	acetylcholine receptor
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guerin
CIC	circulating immune complex
CK	creatine kinase
COVID-19	coronavirus disease 2019
CRF	case report form
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DMC	Data Monitoring Committee
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS-HDFN	early onset severe hemolytic disease of the fetus and newborn
EU CTR	European Union Clinical Trial Regulation
EQ-VAS	EQ visual analogue scale
FcRn	neonatal Fc receptor
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IRB	Institutional Review Board
IV	Intravenous
IVIg	intravenous immunoglobulin
IWRS	interactive web response system
LRP4	lipoprotein-related protein receptor 4
MACE	Major Adverse Cardiovascular Events

MAD	multiple ascending dose
MCID	minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis – Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15r	Revised Myasthenia Gravis Quality of Life – 15 Scale
MMRM	mixed effects model repeated measures
MSE	minimum symptom expression
MuSK	muscle-specific kinase
Nab	neutralizing antibody
NCS	not clinically significant
Neuro-QoL Fatigue	fatigue items of the quality of life in neurological disorders scale
OLE	open-label extension
PD	Pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PG-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
q2w	every 2 weeks
q4w	every 4 weeks
QMG	Quantitative Myasthenia Gravis
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIPPM	site investigational product procedures manual
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication;
ULN	upper limit of normal
US	United States
US FDA	United States Food and Drug Administration
wAIHA	warm autoimmune hemolytic anemia
WOCBP	woman of child bearing potential

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory. As in all clinical studies, in the event a local lab is required, it would be entered into the eCRF as an unscheduled lab.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)</td><td>Total and Direct bilirubin
Alkaline phosphatase
Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Phosphate
Glucose
Albumin
Total protein
Lipid panel (total cholesterol, HDL, LDL [calculated], triglycerides)</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Appendix 7 Liver Safety.

Possible Hy’s Law case reporting requirements are defined in Section 8.3.1.</td></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td colspan="3"><u>Dipstick</u>
Glucose
Protein
Blood</td></tr>
<tr><td colspan="3">If dipstick result is abnormal, microscopy will be used to measure sediment.
In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory.
Red blood cells, white blood cells, epithelial cells, crystals, casts, and bacteria will be measured using microscopy.
Crystals, casts and bacteria will only be reported if they are present.</td></tr>
<tr><td>Other Screening Tests</td><td colspan="3">• Serum/Urine Pregnancy Testing for women of childbearing potential only, including premenopausal or perimenopausal women (ie, not postmenopausal where postmenopausal where postmenopausal is defined as amenorrhea for 12 months or greater), and also including those with a follicle-stimulating hormone ≤40 IU/L or 40 mIU/mL.</td></tr>
</table>

	• Serum follicle-stimulating hormone (for female participants exhibiting amenorrhea for approximately 12 months (ie, perimenopausal) at screening only). • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], anti-HBc antibody, anti-HBs antibody, and hepatitis C virus test [including HCV ribonucleic acid test if necessary) at screening only.

10.3. Appendix 3: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA test is **negative**, the participant ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this protocol.

These eligibility criteria based on HBV test results are also represented in Table 1 below. For participants who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines.

Table 1: Eligibility based on hepatitis B virus test results

HEPATITIS B TEST RESULT			
Hepatitis B surface antigen (HBsAg)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	**STATUS**
negative	negative	negative	**Eligible**
negative	(+)	negative	
negative	(+)	(+)	
(+)	negative *or* (+)	negative *or* (+)	**Not eligible**
negative	negative	(+)	**(Require testing for presence of HBV DNA*)**

* If HBV DNA is detectable, the participant is not eligible for this protocol. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, the participant is not eligible for the protocol.

For participants who **are not eligible for this protocol due to HBV test results**, consultation with a physician with expertise in the treatment of HBV infection is recommended.

10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

10.4.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country- or territory-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the

situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.4.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.4.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. Each participant must be legal age of consent in the jurisdiction in which the study is taking place, at the time of consent. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent must be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent must be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

10.4.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete, or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory PD, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.4.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Remaining study samples may be used to help develop ways to better understand the effect of nipocalimab and/or ways to detect, monitor or treat the disease. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.4.6. Committees Structure

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) and Major Adverse Cardiovascular Events (MACE) Event Adjudication Committee (EAC) will be established to monitor data on an ongoing basis and to ensure the continuing safety of the participants enrolled in this study. The DMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. Committee membership responsibilities, authorities, and procedures of each committee will be documented in separate DMC and EAC charters.

10.4.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding nipocalimab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of nipocalimab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there

will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.4.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory data from a central laboratory, and direct transmission of efficacy data from an eCOA/ePRO vendor into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.4.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into

CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.4.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that PROs are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or

- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

10.4.11. Monitoring

The sponsor will use a combination of monitoring techniques: central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.4.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.4.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. For trials performed under Regulation [EU] No. 536/2014, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.4.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.5. Appendix 5: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.5.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is Medically Important.*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For nipocalimab, the expectedness of an AE will be determined by whether or not it is listed in the IB. For standard of care medication (that is required to be continued along with the study intervention) with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.

10.5.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator.

The assessment of causality must consider the following factors:

- Temporal relationship
- Clinical characteristics of event
- Pharmacological plausibility
- Confounding risk factors:
  - Concomitant medication
  - Underlying/concurrent disease
  - Family/social history
- Challenge:
  - De-challenge: Did the reaction improve when the investigational product was withdrawn, in the absence of any other treatment?
  - Re-challenge: What happens if participant is re-challenged with investigational product?
- Other considerations: Participant characteristics and past medical history, and quality of information

The following selection must be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.5.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.5.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

10.5.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the

AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

The cause of death of a participant in a study within 8 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

10.5.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.5.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.6. Appendix 6: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 5 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

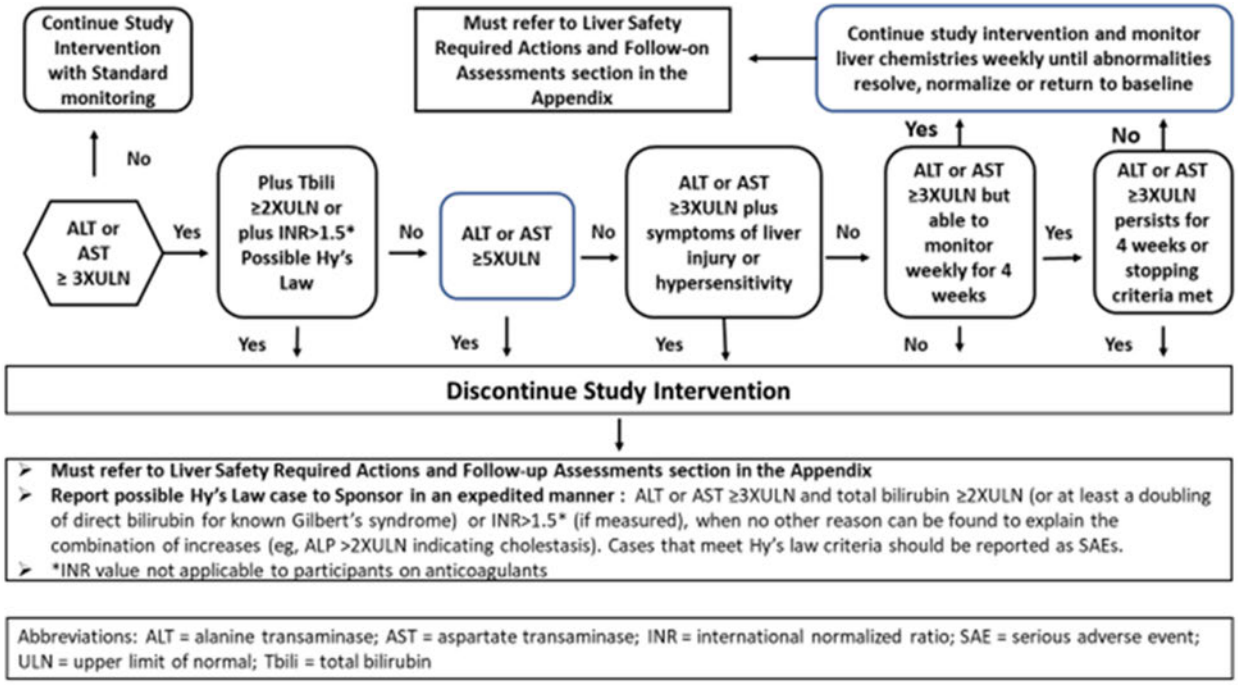
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.7. Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments

10.7.1. STOPPING ALGORITHM

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm (no preexisting liver disease)



10.7.2. Follow-Up Assessments

B. FOLLOW-UP ASSESSMENTS

Liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT/AST-absolute	ALT or AST ≥5×ULN
ALT/AST Increase	**If not able to monitor:** ALT or AST ≥3×ULN and cannot be monitored weekly for 4 weeks **Or if able to monitor:** ALT or AST ≥3×ULN persists for ≥4 weeks
Total bilirubin[1, 2]	ALT or AST ≥3×ULN **and** total bilirubin ≥2×ULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome)

INR[2]	ALT or AST ≥3×ULN **and** international normalized ratio (INR) >1.5, if INR measured
Symptomatic[3]	ALT or AST ≥3×ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring and Follow-up Assessments

Actions	Follow-Up Assessments
• **Immediately** stop study intervention • Report the event to the sponsor **within 24 hours** • Complete the eCRF according to eCRF completion guidelines, and complete an SAE data collection tool if the event also met the criteria for an SAE[2] • Perform follow-up assessments as described in the Follow-Up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) **MONITORING:** **If ALP<2×ULN, ALT or AST ≥3×ULN AND total bilirubin ≥2×ULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or INR >1.5 (if measured):** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total and direct bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **If ALT or AST ≥3×ULN AND total bilirubin <2×ULN and INR ≤1.5 (if measured):** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total and direct bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis 45 minutes after the most recent dose[5] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin • Fractionate bilirubin • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the eCRF as per eCRF completion guidelines • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications) • Record alcohol use on the eCRF as per eCRF completion guidelines **<u>If ALT or AST ≥3×ULN AND total bilirubin ≥2×ULN or INR >1.5 (if measured)</u>** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential

RESTART/RECHALLENGE – **If liver event causality is determined to be "not related", restart may be permitted upon written approval of the sponsor.** See restart guidelines	acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete eCRF per eCRF completion guidelines • Liver biopsy may be considered and discussed with local specialist if available: – In participants when serology raises the possibility of autoimmune hepatitis (AIH) – In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In participants with acute or chronic atypical presentation • If liver biopsy conducted complete eCRF as per eCRF completion guidelines

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3×ULN **and** total bilirubin ≥2×ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALP <2×ULN, ALT or AST ≥3xULN **and** total bilirubin ≥2 x ULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or ALP <2×ULN, ALT or AST ≥3 ×ULN **and** INR >1.5 (if measured) may indicate severe liver injury **(possible 'Hy's law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis).** The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAgG and HBcAB; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criterion and Actions with Continued Study Intervention	
Criterion	**Actions**
ALT or AST ≥3×ULN and <5×ULN **and** total bilirubin <2×ULN or INR<1.5 (if measured)**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the sponsor within **24 hours** of learning of the abnormality to discuss participant safety • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize or return to baseline • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1.1 • If, after 4 weeks of monitoring, ALT or AST<3×ULN and total bilirubin <2×ULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline

References

James LP, Letzig L, Simpson PM, et al, Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

10.8. Appendix 8: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation or quarantine of participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

Temporary measures may be implemented for study-related participant management in the event of disruption to the conduct of the study as determined appropriate by the investigator to maintain continuity of patient care and study integrity. This guidance does not supersede any local or government guidelines or requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

If, as a result of the COVID-19 pandemic, visits cannot be conducted in person at the study site, they may be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical monitor or designee to discuss plans for administration of study intervention, performing study assessments, and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the CSR.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
  - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures (eg, those related to safety monitoring / efficacy evaluation

  - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
  - other procedures may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.
  - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in eCRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

10.9. Appendix 9: Criteria for Assessing Potential Cases of Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled (Sampson 2006):

1. **Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)**
   AND AT LEAST ONE OF THE FOLLOWING:
   a. **Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)**
   b. **Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)**
2. **Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):**
   a. **Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)**
   b. **Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)**
   c. **Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)**
   d. **Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)**
3. **Reduced BP after exposure to known allergen for that participant (minutes to several hours):**
   a. **Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP***
   b. **Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline**

Key: BP=blood pressure; PEF=Peak expiratory flow.

***Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.**

10.10. Appendix 10: Country/Territory-specific Requirements

10.10.1. Requirements for EU Region (EUR)

Requirements for EUR		
Section	**Requirement**	**Amendment Number**
1.1 Synopsis, Open-label Extension Phase; 4.1 Overall Design; 4.4 End of Study Definition; 6.6 Continued Access to Study Intervention After the End of the Study	**Study Completion Definition** A participant will be considered to have completed the study if the participant has completed assessments at the last visit of the OLE phase. Participants entering the OLE phase will continue until 240 Weeks after the double-blind phase of the study has been completed	2

10.10.2. Requirements for FRANCE (FRA)

Requirements for FRA		
Section	**Requirement**	**Amendment Number**
6.8.1 Prohibited Therapies	Therapies to be Administered with Caution: The following medications may interfere with the function of the neuromuscular junction and worsen the clinical symptoms of MG per the National Protocol of Diagnosis and Care (PNDS) Autoimmune Myasthenia gravis (PNDS 2015). Clinical judgement and the risk-to-benefit ratio of the drug should be taken into consideration before prescribing the following: • Aminoglycosides, colimycin, polymyxin, telithromycin, injectable cyclins, macrolides, fluoroquinolones • Quinines, quinidine, hydroxychloroquine, procainamide • Beta-blockers (even eye drops) • Diphenyl-hydantoin, trimethadione • Dantrolene • D-penicillamine • Magnesium • Curarisants: the use of non-depolarizing molecules of rapid degradation, such as	2

	atracurium, is allowed, but precise monitoring is needed • Benzodiazepines • Neuroleptics (phenothiazine) • Carbamazepine • Lithium • Allopurinol • Injection of iodine for radiological contrast examination • Interferon alpha and beta • Nicotine patches • Statins	

10.11. Appendix 11: Protocol Amendment History

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

Amendment 2 (11 January 2023)

Overall Rationale for the Amendment: To revise the key secondary endpoints, to CCI [redacted] and to update the protocol based on EU Clinical Trial Regulation (EU CTR).

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis	Added a summary of the benefit-risk assessment.	To align with the EU CTR requirements.
1.1 Synopsis, Objectives and Endpoints; 1.1 Synopsis Statistical Methods; 3 Objectives and Endpoints; 4.2 Scientific Rationale for Study Design; 9.4.2.2 Secondary Endpoint(s)	Revised key secondary endpoint for sustained response and moved from #5 to #4. Added a new key secondary endpoint (#5) to evaluate the effect of nipocalimab compared to placebo on symptom improvement based on the MG-ADL scale, in seropositive gMG participants when treatment is taken as directed. Moved MSE to other secondary endpoints.	Minimal symptom expression, as defined by the MG-ADL, is a desired treatment goal and retained as a secondary endpoint. Since the final score achieved on MG-ADL may vary depending on the baseline score, relative symptom improvement defined as ≥50% improvement on MG-ADL score from the baseline score will be evaluated as a key secondary.
1.1 Synopsis, Objectives and Endpoints; 3 Objectives and Endpoints	Clarified description for key secondary objective #2 from clinically important individual response to the minimum clinically important difference (MCID) or better.	The MCID is the accurate term for the smallest clinically important individual response; this is formally stated now.
1.1 Synopsis, Overall Design; 1.1 Synopsis, Number of Participants; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 5 Study Population; 9.2 Sample Size Determination	Increased overall sample size to 190 to allow additional enrollment of seronegative participants.	The sample size change does not impact the primary analysis of 150 seropositive participants with gMG; the change reflects only an increase in the cohort of seronegative participants with gMG.
1.1 Synopsis, Objectives and Endpoints; 1.1 Synopsis, Overall Design Open-label Extension phase; 1.1 Synopsis, Intervention Groups and Duration, Open-label Extension Phase; 1.2 Schema; 1.3 Schedule of Activities, Table 2, Note, Table 3 Column Headings and Note; 3 Objectives and Endpoints; 4.1 Overall Design, Open-label Extension Phase; 4.2 Scientific Rationale for Study Design, Study	CCI [redacted]	To streamline visit schedule and IMP administration, the OLE dosing sections are updated to allow only q2w dosing in the OLE.

Section Number and Name	Description of Change	Brief Rationale
Phase/Periods Intervention Group; 4.3 Justification of Dose; 6.1 Study Intervention(s) Administered, Open-label Extension Phase; 6.5 Dose Modification		
1.1 Synopsis, Objectives and Endpoints; 1.1 Synopsis, Statistical Methods; 3 Objectives and Endpoints; 4.2 Scientific Rational for Study Design; 9.4.2.2 Secondary Endpoints	Changed "symptom remission" to "minimum symptom expression"	To reflect the preferred term used by clinicians for an MG-ADL score of 0 or 1.
1.1 Synopsis, Other Efficacy Endpoints; 9.4.2.2 Secondary Endpoints	Added clarifying text for sustainability of response for QMG.	To clarify definition of sustained response.
1.1 Synopsis, Overall Design; 1.3 Schedule of Activities, Table 1 Footnote "b"; 1.3 Schedule of Activites, Table 4; 4.1 Overall Design; 7.1 Discontinuation of Study Intervention	Text describing discontinuation of study intervention was clarified to indicate when participants are eligible to rollover to the OLE and when the ET visit must be completed.	Clarification that participants who discontinue study intervention during the double-blind placebo-controlled phase for any reason other than Clinical Deterioration requiring hospitalization or rescue therapy must complete the 24 weeks of study procedures to rollover to the OLE.
1.1 Synopsis, Statistical Methods; 4.1 Overall Design; 4.2 Scientific Rationale; 5 Study Population 9.4.2.1 Primary Endpoint; 9.4.2.2 Secondary Endpoint(s)	Added text within protocol to clarify, as specified in Inclusion Criterion #4, participants must be on stable MG therapy **or** discontinued corticosteroids and/or immunosuppressants ≥4 weeks prior to screening due to intolerance or lack of efficacy.	Original language from inclusion Criterion #4 was re-stated within protocol sections to further emphasize that study participants who discontinued prior standard of care MG therapy due to intolerance or lack of efficacy are also permitted in the study as per the original protocol.
1.1 Synopsis, Statistical Methods; 9.2 Sample Size Determination	Deleted text describing sample size re-estimation.	Due to current estimates of the dropout rate, sample size re-estimation will not be performed and has been removed from the SAP.
1.1 Synopsis, Overall Design; 1.1 Synopsis, Number of Participants; 1.1 Synopsis, Sample Size Determination; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 5. Study Population; 5.1.1 Inclusion Criteria for Double-blind Placebo	Added footnote to clarify that the study is no longer recruiting seronegative participants.	Enrollment of seronegative participants has been completed.

Section Number and Name	Description of Change	Brief Rationale
Controlled Phase, Criterion 2 9.2 Sample Size Determination		
1.3 Schedule of Activities, Table 1 Footnote "h" Table 2 Footnote "e" Table 3 Footnote "a"; 8.1.1 Myasthenia Gravis – Activities of Daily Living; 8.1.2 Quantitative Myasthenia Gravis	Added clarification that the investigator should attempt to reschedule the visit within the per protocol visit window if acetylcholinesterase inhibitors were taken <12 hours prior to visits where MG-ADL and QMG assessments are performed.	Clarification added as acetylcholinesterase inhibitors can have an impact on the MG-ADL and QMG assessment. MG-ADL and QMG are the primary and key secondary endpoints of the study and as such all efforts should be made to collect objective data with no confounding factor.
1.3 Schedule of Activities, Table 1 Footnote "n" Table 1 Footnote "u" Table 2 Footnote "i" Table 2 Footnote "q"	Text requiring FSH testing was clarified in Table 1 footnote "n" and Table 2 footnote "i". Added new footnote to define menopausal status and clarify required FSH testing.	To clarify when FSH testing is required.
1.3 Schedule of Activities, Table 1 Footnote "m"	Clarified that lipid labs at screening are not required to be non-fasting.	Lipid labs at screening can be non-fasting, but are not required to be.
1.1 Synopsis, Overall Design; 1.1 Synopsis, Open-label Extension Phase; 4.1 Overall Design; 4.4 End of Study Definition; 6.6 Continued Access to Study Intervention After the End of Study	Added reference to new Appendix (Appendix 10.10.1) for sites in the EU.	Prior local country amendments are now consolidated within the global protocol and aligned with EU CTR requirements; region-specific requirements for the EU have been moved to an appendix.
6.1 Study Intervention(s) Administered	Added table with descriptions and classifications for all medicinal products used in the study.	To align with the EU CTR requirements.
6.1 Study Intervention(s) Administered. 6.8 Concomitant Therapy	Moved text describing standard of care MG medications from Section 6.8 to Section 6.1.	To align with the EU CTR requirements.
6.3 Measures to Minimize Bias: Randomization and Blinding	Text added to last paragraph to clarify when the double-blind, placebo-controlled phase is complete.	To clarify end of double-blind phase
6.8.1 Prohibited Therapies	Added botulinum toxin to list of prohibited therapies.	Botulinum toxin is a product contraindication in MG and has been added to the examples of prohibited medications for clarity.
6.8.1 Prohibited Therapies	Added reference to new Appendix (Appendix 10.10.2) for sites in France.	To provide a consolidated protocol and align with EU CTR requirements, country-specific requirements for France have been moved to an appendix.
6.8.2 Rescue Medication/Therapy/Clinical Deterioration	Added clarification that: • IVIg and plasmapheresis are the only rescue treatments permitted. • For participants who require rescue treatment during the double-blind,	To provide clarification regarding permitted rescue treatments, the potential for subsequent treatment with

Section Number and Name	Description of Change	Brief Rationale
	placebo controlled phase EOP visit must be completed prior to OLE entry. • For participants requiring rescue treatment during the OLE, continued OLE participation must be discussed with the sponsor's medical monitor.	nipocalimab, and required study visits for these participants.
8.1.1 Myasthenia Gravis – Activities of Daily Living; 8.1.2 Quantitative Myasthenia Gravis	Added clarifying text to circumstances regarding unavoidable changes in raters.	To clarify circumstances where a change in rater is unavoidable.
8.2.10 Benefit Risk Balance; 9.4.6 Other Analyses	Added sections for benefit-risk balance	To align with nipocalimab protocols for other indications
9.2 Sample Size Determination	Removed MSE from sample size determination.	MSE moved from key secondary endpoint to a secondary endpoint.
1.1 Synopsis, Statistical Methods; 9.3 Population Analysis Sets	Revised text and table describing analysis sets for consistency with the SAP.	Alignment edit.
10.10.1 Requirements for EUR; 10.10.2 Requirements for FRA	New Appendix (Appendix 10.10.2) for Country/Territory Specific requirements was added to include regional requirements specific to EU and country-specific requirements for France.	To provide a consolidated protocol and align with EU CTR requirements, region-specific requirements for the EU and country-specific requirements for France have been moved to an appendix.
10.2 Appendix 2: Clinical Laboratory Tests	Added bicarbonate to clinical chemistry Added clarifying text to routine urinalysis section of the table.	To include missing protocol template text.
11 References	New references added.	To include additional references.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (21 July 2022)

Overall Rationale for the Amendment: To add an exploratory endpoint for the use of an actigraphy watch to assess physical activity, mobility, and sleep at selected sites. Two additional exclusion criteria were added to align with standard language across the nipocalimab program. In addition, clarifying edits from the latest sponsor protocol template and edits to align with standard language across the nipocalimab program were made throughout the protocol.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis, Exploratory Objectives; 1.1 Synopsis, Efficacy Evaluations; 1.1 Synopsis, Statistical Methods; 1.3. Schedule of Activities (SoA) Table 1 ;	Added an assessment of physical activity using actigraphy watch-collected data (at selected sites) throughout the relevant sections of the protocol.	This exploratory outcome measure will allow analysis of changes in digital parameters in nipocalimab compared to placebo on daily physical activities in seropositive gMG participants when treatment is taken as directed (at selected sites).

Section number and Name	Description of Change	Brief Rationale
3. Objectives and Endpoints; New section 8.1.9. Digital Health – Actigraphy Measurements (at Selected Sites); 9.4.2.2 Secondary Endpoint(s)		
2.3.1. Risks for Study Participation	Updated risk language in Table 5 and removed overdose as a potential risk of clinical significance from the table.	To align with nipocalimab IB.
5.2. Exclusion Criteria, Criterion 33	Added new exclusion criterion regarding BCG vaccination.	To ensure the safety of participants and to provide sufficient details and better guidance to study investigators to determine whether participants are eligible for the study. This aligns with standard language across the nipocalimab program.
5.2. Exclusion Criteria, Criterion 34	Added new criterion for granulomatous infection.	Criterion added to disallow participants with a history of active granulomatous infection before screening. This aligns with standard language across the nipocalimab program
5.1.1 Inclusion Criteria for Double-blind Placebo-Controlled Phase Entry, Criterion 1 and Criterion 15; 5.1.2 Inclusion Criteria for Open-label Extension Phase Entry, Criterion 6; 10.4.3 Informed Consent Process	Revised to clarify that participants must be ≥18 years of age and the legal age of consent in their jurisdiction.	Clarification that only adult participants as per the legal age of consent in that jurisdiction will be eligible to participate in the study.
5.1.1. Inclusion Criteria for Double-blind Placebo-Controlled Phase Entry, Criterion 9	Criterion removed.	Male or female is no longer an inclusion criterion. Standard requirement for all sponsor protocols.
5.1.1 Inclusion Criteria for Double-blind Placebo-Controlled Phase Entry, Criterion 4	Added clarification to types of discontinued immuno-agents as well as timing for changes to background medications.	To clarify that background medications must be optimized and unchanged for the duration specified in Criterion 4 prior to screening and/or baseline visits.
5.1.1 Inclusion Criteria for Double-blind Placebo-Controlled Phase Entry, Criterion 8; 5.1.1 Inclusion Criteria for Open-label Extension Phase Entry, Criterion 4	Added text regarding recommendation for COVID-19 vaccination	Aligned with update to sponsor COVID-19 guidance.
5.1.1 Inclusion Criteria for Double-blind Placebo-Controlled Phase Entry, Criterion 11	Updated the length of time a woman of childbearing potential must practice a highly effective method of contraception to 30 days after last administration of study intervention.	To align with nipocalimab protocols for other indications. Added for clarification

Section number and Name	Description of Change	Brief Rationale
	Added text clarifying that labeling requirements for concomitant treatment will supersede if more stringent	
5.2. Exclusion Criteria, Criterion 17	Updated language for time for administration of live vaccine.	To align with recommendations available from the CDC Advisory Committee on Immunization Practices, the Infectious Diseases Society of America, and the half-life of nipocalimab.
5.2. Exclusion Criteria, Criterion 17	Added language to refer to exclusion criterion #33	For clarity, provided reference to new criterion
5.2. Exclusion Criteria, Criterion 1	Revised to provide further detail to excluded disease history.	To align with nipocalimab protocols for other indications.
5.1.1 Inclusion Criteria for Double-blind Placebo-Controlled Phase Entry, Inclusion Criterion 13; 10.6 Appendix 6: Contraceptive and Barrier Guidance	Revised instructional text regarding contraception	Incorporation of clarifying edits from the latest sponsor protocol template update
5.2 Exclusion Criteria, Criterion 3	Clarified that to be eligible for the study, participants should not meet the definition of Clinical Deterioration as noted in Section 6.8.2.	Clarification of exclusion criteria
5.2 Exclusion Criteria, Criterion 15	Added eculizumab or other novel therapeutic agents to prohibited therapies.	Provided for clarification.
5.2 Exclusion Criteria Criterion 31	Criterion deleted.	Criterion is redundant with text added to exclusion criterion #1.
5.2 Exclusion Criteria	Added note following exclusion criterion #29 to clarify appropriate medical interventions and measures to be followed should a participant meet criterion #29.	Clinical findings based on C-SSRS should be reported as adverse events/serious adverse events as applicable.
8.2.9 Suicidal Ideation and Behavior Risk Monitoring	Added text to clarify appropriate medical interventions and measures to be followed should a participant's C-SSRS results indicate active suicidal ideation and/or a plan/intent. Clarified that clinical findings based on C-SSRS should be reported as AEs or SAEs, as applicable.	Clinical findings based on C-SSRS should be reported as adverse events/serious adverse events as applicable.
1.1 Synopsis; 4.1 Overall Design; 8. Study Assessments and Procedures; 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 9.4.5 Safety Analyses; 10.4.6 Committee Structure	Added text related to major adverse cardiovascular events (MACE) and the Event Adjudication Committee (EAC).	Potential MACE events will undergo review by an event adjudication committee in alignment with the overall nipocalimab program
5.2 Exclusion Criteria Criterion 31	Criterion deleted.	Criterion is redundant with text added to exclusion criterion #1.

Section number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Added note following exclusion criterion #29 to clarify appropriate medical interventions and measures to be followed should a participant meet criterion #29.	Clinical findings based on C-SSRS should be reported as adverse events/serious adverse events as applicable.
8.2.9 Suicidal Ideation and Behavior Risk Monitoring	Added text to clarify appropriate medical interventions and measures to be followed should a participant's C-SSRS results indicate active suicidal ideation and/or a plan/intent. Clarified that clinical findings based on C-SSRS should be reported as AEs or SAEs, as applicable.	Clinical findings based on C-SSRS should be reported as adverse events/serious adverse events as applicable.
1.1 Synopsis; 4.1 Overall Design; 8. Study Assessments and Procedures; 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 9.4.5 Safety Analyses; 10.4.6 Committee Structure	Added text related to major adverse cardiovascular events (MACE) and the Event Adjudication Committee (EAC).	Potential MACE events will undergo review by an event adjudication committee in alignment with the overall nipocalimab program
5.2 Exclusion Criteria Criterion 31	Criterion deleted.	Criterion is redundant with text added to exclusion criterion #1.
5.2 Exclusion Criteria	Added note following exclusion criterion #29 to clarify appropriate medical interventions and measures to be followed should a participant meet criterion #29.	Clinical findings based on C-SSRS should be reported as adverse events/serious adverse events as applicable.
8.2.9 Suicidal Ideation and Behavior Risk Monitoring	Added text to clarify appropriate medical interventions and measures to be followed should a participant's C-SSRS results indicate active suicidal ideation and/or a plan/intent. Clarified that clinical findings based on C-SSRS should be reported as AEs or SAEs, as applicable.	Clinical findings based on C-SSRS should be reported as adverse events/serious adverse events as applicable.
1.1 Synopsis; 4.1 Overall Design; 8. Study Assessments and Procedures; 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 9.4.5 Safety Analyses; 10.4.6 Committee Structure	Added text related to major adverse cardiovascular events (MACE) and the Event Adjudication Committee (EAC).	Potential MACE events will undergo review by an event adjudication committee in alignment with the overall nipocalimab program
Synopsis, Statistical Methods; 9.4.2.1. Primary Endpoint	Multiple imputation methods for the primary estimand for EU were revised.	To specify multiple imputation methods that are more consistent with the treatment policy estimand.

Section number and Name	Description of Change	Brief Rationale
9.4.2.1. Primary Endpoint	Corrected text under the primary estimand for EU for intercurrent events due to change in background MG medication to 'Treatment Policy'	Intercurrent events due to change in background MG medication will be handled by Treatment Policy.
1.1 Synopsis; 3. Objectives and Endpoints	Removed the outcome measure: evaluate the potential relationship between change in QMG scores.	For consistency in outcomes for exploring the effects of nipocalimab on MG disease biomarkers
1.3 Schedule of Activities, Table 2	Added urine drug screen at screening visit	The lab is supportive information for the determination of eligibility per exclusion criterion #14; was present in Double-blind screening but missing in OLE screening.
1.3 Schedule of Activities Table 4	Added urine pregnancy test, Ig, serum for nipocalimab concentrations, ADA, and NAb to safety follow-up assessments.	Consistency across nipocalimab protocols.
1.1 Synopsis; 4.1 Overall Design; 8. Study Assessments and Procedures; 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 9.4.5 Safety Analyses; 10.4.6 Committee Structure	Added text related to major adverse cardiovascular events (MACE) and the Event Adjudication Committee (EAC).	Potential MACE events will undergo review by an event adjudication committee in alignment with the overall nipocalimab program
Synopsis, Statistical Methods; 9.4.2.1. Primary Endpoint	Multiple imputation methods for the primary estimand for EU were revised.	To specify multiple imputation methods that are more consistent with the treatment policy estimand.
9.4.2.1. Primary Endpoint	Corrected text under the primary estimand for EU for intercurrent events due to change in background MG medication to 'Treatment Policy'	Intercurrent events due to change in background MG medication will be handled by Treatment Policy.
1.1 Synopsis; 3. Objectives and Endpoints	Removed the outcome measure: evaluate the potential relationship between change in QMG scores.	For consistency in outcomes for exploring the effects of nipocalimab on MG disease biomarkers
1.3 Schedule of Activities, Table 2	Added urine drug screen at screening visit	The lab is supportive information for the determination of eligibility per exclusion criterion #14; was present in Double-blind screening but missing in OLE screening.
1.3 Schedule of Activities Table 4	Added urine pregnancy test, Ig, serum for nipocalimab concentrations, ADA, and NAb to safety follow-up assessments.	Consistency across nipocalimab protocols.
1.1. Synopsis; 1.3 Schedule of Activities; 3. Objectives and Endpoints	Added footnotes to clarify that in China, anti-LRP4 autoantibody collection will only be tested at screening.	To consider local practice feasibility
1.3 Schedule of Activities Table 4; 8.6.1. Pharmacodynamics	Added a footnote to clarify that exploratory biomarker is not applicable in China.	To consider local practice feasibility

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.3 Schedule of Activities, Table 1 Footnote “r” Table 2 Footnote “n” Table 3 Footnote “j” 3 Objectives and Endpoints; 4.2 Scientific Rationale for Study Design	Modified the footnote to clarify that exploratory biomarker is not applicable in China.	To provide additional clarification regarding exploratory biomarker collection.
1.3. Schedule of Activities, Table 1 Footnote “j” Table 2 Footnote “f” Table 3 Footnote “b”	Added abdomen or skin to list of focused physical examination body systems	Correction to align with text in Section 8.2.1.
1.3 Schedule of Activities, Table 1 Footnote "k", Table 2 Footnote "g", and Table 3 Footnote "c"; 8.2.2 Vital Signs; 9.4.5 Safety Analyses	Respiratory rate added to vital signs. "Immediately" was removed from vital sign collection time in the SoA footnotes	Correction to add respiratory rate to list of vital signs to be collected. Additionally, "immediately" was removed from the vital sign collection time in the SoA footnotes for consistency with Section 8.2.2
1.3. Schedule of Activities, Tables 1, 2, and 3	A statement regarding requirements to confirm a woman is menopausal to determine whether a pregnancy test is required (Table 1 and Table 2), and that additional serum pregnancy testing is at the discretion of the investigator or if required by local regulations was added.	Clarification and further information on when pregnancy tests are required in women of childbearing potential.
8.2.2. Vital Signs	Text “oral” has been removed from temperature collection requirement.	There are other preferred alternatives and the study eCRF accommodates other anatomical locations for temperature collection.
1.3. Schedule of Activities Table 1	Removed exploratory biomarker sample during Screening.	Exploratory biomarker samples are not required at the Screening phase.
1.3. Schedule of Activities, Table 1 and Table 2.	Added collection of serum Ig sample at Screening.	Total IgG should be measured at Screening.
1.3. Schedule of Activities, Table 2	Added ECG at week 24 of the OLE phase.	To make the OLE ECG schedule consistent with the double-blind phase.
1.3. Schedule of Activities, Table 2 Footnote “h” Table 3 Footnote “d”	Footnote observation time after infusion in OLE was updated.	Clarification that all participants receiving their first 3 infusions will need to be monitored for safety 1-hour post-infusion, regardless of being in the DB or OLE phase (as some would have come from placebo arm).
1.3. Schedule of Activities, Table 1 Footnote “p” 8.4.1. Evaluations	Added text to clarify that postdose samples will be collected 45 minutes (± 15 minutes) after the end of infusion.	Clarification on the time windows for the post dose samples collection
Synopsis, Overall Design; Synopsis, Intervention Groups and Duration; 1.3. Schedule of Activities Tables 2 and 3; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 6.1 Study Intervention(s) Administered;	Corrected Title and statement in note of Table 2, Table 3 to Week 24 and added clarifying text.	Correction of the time after which a change in dosing is permitted and to clarify that the new dosing schedule must align with the original q12w/q24w visit schedule as well as to match the participant’s visit schedule

Section number and Name	Description of Change	Brief Rationale
6.5 Dose Modification;		
3. Objectives and Endpoints	Modified text to "could use".	For consistency with Section 8.6.
4.2.1. Study-Specific Ethical Design Considerations; 8. Study Assessments and Procedures	Added text to clarify volume of blood collected covers the full duration of the double-blind placebo-controlled phase and 2 years of OLE.	To provide clarification of total volume of blood to be collected.
5.3 Lifestyle Considerations	Added third criterion regarding timing of live vaccines (including BCG).	For consistency with the exclusion criteria.
5.4 Screen Failures	Added text to clarify rescreening is permitted once with approval of sponsor's medical monitor.	To clarify when rescreening is permitted.
6.1 Study Intervention(s) Administered	Additional language to describe how nipocalimab and placebo are sourced and supplied centrally and locally.	Consistency across nipocalimab protocols
6.3 Measures to Minimize Bias: Randomization and Blinding	Updated masking information for select laboratory parameters, including the study phases where the parameters remain masked. Added clarifying text.	To clarify the masking of selected laboratory data.
6.8.3 Vaccinations (Including COVID-19)	New section added.	To provide guidance for timing of non-live vaccine administration
6.8.1 Prohibited Therapies	Deleted text requiring mandatory discontinuation of study intervention. Added text to clarify the medical monitor and/or sponsor should be consulted prior to starting any biologic or other advanced therapies.	The original intent of the prohibited medications section 6.8.1 is unchanged. The text was deleted, because the decision on whether a participant can continue study participation or must be discontinued if they take a prohibited medication may depend on the reason a medication was given, whether this was a single-use or sustained treatment, and the half-life of the prohibited medication.
5.1.2 Inclusion Criteria for Open-label Extension Phase; 6.5 Dose Modification; 6.8.2 Rescue Medication/Therapy/Clinical Deterioration	Added text to clarify that in instances where participants who require rescue treatment during the double-blind phase and enter the OLE phase based on investigator's discretion after completion of an EOP Visit. Also clarified, the EOP visit assessments must not be combined with those of the OLE Day 1 assessments and while there is no fixed duration limit between EOP and OLE Day 1, in instances where the interval is greater than 4 weeks, the investigator should assess if it is appropriate to continue treatment in the OLE phase in consultation with the sponsor's medical monitor.	To inform the investigator on how to classify completion of double-blind treatment for participants who require rescue medication and to assess whether treatment should be continued in the OLE.
7.1 Discontinuation of Study Intervention	The list of reasons for discontinuation is revised to include a description of severe allergic reaction and/or severe infusion reaction related to the study intervention.	To address severe allergic reaction and/or severe infusion reaction as a reason for study discontinuation

Section number and Name	Description of Change	Brief Rationale
8.1.1 Myasthenia Gravis-Activities of Daily Living; 8.1.2 Quantitative Myasthenia Gravis	Added information regarding unavoidable changes in raters.	To address circumstances where a change in rater is unavoidable.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 10.2 Appendix 2 Clinical Laboratory Tests; 10.7 Appendix 7 Liver Safety: Suggested Actions and Follow-up Assessments, Footnote “2”	Corrected the definition of possible Hy’s Law cases and added text to clarify safety reporting. Revised terminology to clarify and align with the rest of the protocol.	Incorporation of clarifying edits from the latest sponsor protocol template update and consistency of the description of "possible Hy's Law" within the protocol.
8.3.6 Adverse Events of Special Interest	Revised first numbered bullet point.	To align definitions with nipocalimab protocols for other indications.
8.4 Pharmacokinetics	Added text to clarify PK samples should be collected at the end of treatment visit from participants who discontinued study intervention or were withdrawn from the study.	To provide clarification regarding collection of PK samples.
8.6.1 Pharmacodynamics	Added clarification that anti-LRP4 will also be collected and used to assess seropositivity.	To provide clarification regarding autoantibody testing.
8.7 Immunogenicity Assessments	Removal of language describing the storage time (up to 1 month) after approval of the final Clinical Study Report	Removal of language to maintain consistency with storage time mentioned in Section 10.4.5
10.2 Appendix 2 Clinical Laboratory Tests	Added glucose as a parameter for collection for clinical chemistry	Glucose has been added as a laboratory parameter
10.4.3 Informed Consent Process	Added language to inform participants who have received previous treatment with rituximab that they may be at an increased risk of infection during the study.	To provide consistency for all nipocalimab protocols
10.4.4 Data Protection	Updated the text on Privacy of Personal Data based on EU CTR.	To align with sponsor protocol template update.
10.8 Appendix 8 Study Conduct During a Natural Disaster	Updated to include latest guidance regarding study conduct regarding COVID-19.	To enhance participant safety.
10.10 Appendix 10: Criteria for Assessing Potential Cases of Anaphylaxis	Added an appendix for criteria for assessing potential cases of anaphylaxis	To provide criteria for determining and assessing cases of anaphylaxis
6.4 Study Intervention Compliance	Removed reference to visiting nurse.	For consistency within the protocol. Home infusion is not permitted in the study.
2. Introduction	Updated text	Added information and additional references
Throughout the protocol	Added territory(ies) to country(ies).	To align with sponsor protocol template update.
Throughout the protocol	The term “should” was replaced with “must” where the text has an intrinsic	To enhance scientific rigor by incorporation of clarifying edits where the text has an intrinsic mandatory

Section number and Name	Description of Change	Brief Rationale
	mandatory component instead of a probability or expectation.	component instead of a probability or expectation.
Throughout the protocol	Minor editorial changes including grammar, spelling and formatting were made	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	15-Aug-2024 13:16:01 (GMT)	Document Approval