Janssen Research & Development

Statistical Analysis Plan

An Open-label Extension Study of MOM-M281-004 to Evaluate the Safety, Tolerability, and Efficacy of M281 Administered to Patients with Generalized Myasthenia Gravis

Protocol MOM-M281-005; Phase 2

JNJ-80202135; M281 (nipocalimab)

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

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	7 July 2021	Not Applicable	Initial release

1. INTRODUCTION

This document summarizes the planned analyses for study MOM-M281-005 which was an open-label extension study of the randomized, double-blind study MOM-M281-004.

Because of the coronavirus disease 2019 (COVID-19) pandemic, all study drug administrations in both the 004 and 005 studies were stopped as of 17 April 2020 and the 005 study was subsequently terminated. Because of the termination, only 37 of a possible 65 patients who completed the 004 study entered the 005 study. The planned treatment duration for a patient was to be approximately 1 year, but because of the termination of dosing, no patient had more than 9 months of study drug exposure and approximately 50% of patients had <3 months of study drug exposure. Given the reduced number of patients enrolled and reduced duration of exposure, limited summaries of efficacy results are planned for this study.

1.1. Objectives and Endpoints

Primary objective

- To evaluate the long-term safety and tolerability of nipocalimab in generalized myasthenia gravis (gMG).

Secondary objectives

- To evaluate the long-term efficacy of nipocalimab
- To evaluate the long-term immunogenicity of nipocalimab
- To evaluate the long-term pharmacodynamic (PD) activity of nipocalimab

Exploratory objectives

- To evaluate the effect of nipocalimab on fatigue and physical activity
- To evaluate the long-term PD activity of nipocalimab on serum concentrations of immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin E (IgE)
- To evaluate the long-term PD activity of nipocalimab on serum titers of pathogenic autoantibodies associated with gMG (anti-AChR and/or anti-MuSK)
- To evaluate the long-term response to treatment with nipocalimab in relation to other treatment(s) and/or clinical studies
- To evaluate the potential relationship between change in the Myasthenia Gravis – Activities of Daily Living (MG-ADL) total score and change in anti-AChR antibody levels

1.2. Study Design

MOM-M281-005 is a long-term, open-label extension study of patients who completed the MOM-M281-004 study without discontinuing study drug during the 004 study for reasons other than the need for rescue therapy as specified in the 004 protocol, and who completed the protocol-specified 8 weeks of follow-up after the last dose of study drug in the 004 study.

Eligibility for the 005 study was assessed and enrollment into the 005 study occurred (at the earliest) after completion of assessments at the patient's last follow-up visit in the 004 study (the Day 113 visit of the 004 study). Thus, the Day 113 visit of the 004 study can be Day 1 for the 005 study; patients who meet the eligibility criteria for the 005 study could receive their first open-label infusion of nipocalimab on the same day.

Patients enrolled in the 005 study initially received nipocalimab 30 mg/kg every 4 weeks (q4w) by intravenous (IV) infusion. This dose was one of the doses evaluated in the 004 study. After at least 8 weeks of treatment on a stable dose of nipocalimab, the dose and/or dosing frequency of nipocalimab could have been individually adjusted for a given patient at the discretion of the investigator and previous consultation with the medical monitor, based on the patient's tolerability to nipocalimab and the patient's MG status. The individually adjusted dose could not exceed 60 mg/kg and the dosing frequency could not exceed every 2 weeks (q2w).

2. STATISTICAL HYPOTHESES

No statistical hypothesis is specified for this study. The objective of the study is to estimate the frequency of adverse events, laboratory abnormalities, and vital signs abnormalities with long term exposure to nipocalimab.

3. SAMPLE SIZE DETERMINATION

The sample size of the 005 study depended on the enrollment in the 004 study. In the 004 study, 68 patients were randomized and given at least one administration of study drug and 65 patients completed the Day 113 visit.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	**Description**
Enrolled	All patients who sign the ICF
Full Analysis Set (FAS)	The full analysis set (FAS) includes all patients who received at least 1 dose of study drug.
Safety	The safety analysis set includes all patients who received at least 1 dose of study drug.
Immunogenicity Analysis Set	The immunogenicity analysis set is defined as all patients who received at least 1 dose of study drug and had 1 or more samples obtained after their first study drug administration for the assessment of antibodies to nipocalimab.

5. STATISTICAL ANALYSES

5.1. General Considerations

The reference start date for the calculation of study day is defined as the date of the first infusion in the 005 study. Study day of a visit or start/end date of an event is defined as the visit/start/end date – reference start date + 1.

The Day 113 visit of the 004 study is the baseline visit of the 005 study. For assessments not collected at the Day 113 visit of the 004 study or collected at both the Day 113 visit of the 004 study and the Day 1 visit of the 005 study, the Day 1 visit of the 005 study will serve as baseline.

Analysis visit windows are not defined. Results collected per visit will be summarized by nominal visit.

Results will be summarized by 2 subject groups, 1 for patients who were randomized to the placebo group in the 004 study and 1 for patients who were randomized to a nipocalimab group in the 004 study:

- Placebo-Nipocalimab
- Nipocalimab-Nipocalimab

All tables will also include an "All Nipocalimab" column, which combines the "Placebo-Nipocalimab" and "Nipocalimab-Nipocalimab" subject groups.

5.2. Participant Dispositions

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

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

- Patients who received study drug
- Patients who completed the study
- Patients who discontinued study drug
- Reasons for discontinuation of study drug
- Patients who terminated study prematurely
- Reasons for termination of study

5.3. Primary Endpoint(s) Analysis

The primary endpoints for this open-label extension study are safety- and tolerability-related. See Section 5.6 for definitions.

5.4. Secondary Endpoint(s) Analysis

Secondary endpoints will be summarized using the full analysis set.

5.4.1. Definition of Endpoint(s)

5.4.1.1. Myasthenia Gravis – Activities of Daily Living (MG-ADL)

The MG-ADL is an 8-item questionnaire administered by a qualified healthcare professional that assesses the severity of the impairment of 8 activities (talking, chewing, swallowing, breathing, impairment of ability to brush teeth or comb hair, impairment of ability to arise from a chair,

double vision, and eyelid droop) on a 4-point scale (0 = normal, 1, 2, or 3 = severe) (Wolfe 1999). See Appendix 11 for definitions of each score for each function. The MG-ADL is assessed at Weeks 4, 8, and 12, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

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

Change from baseline in MG-ADL total score will be calculated for each post-baseline visit.

5.4.1.2. Quantitative Myasthenia Gravis (QMG) Test

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

The QMG total score is defined as the sum of the 13 individual item scale scores (range: 0 to 39). The total score is missing if any item is missing. Higher scores indicate greater impairment.

Change from baseline in QMG total score will be calculated for each post-baseline visit.

5.4.1.3. Revised Myasthenia Gravis Quality of Life 15 (MG-QoL-15r)

The MG-QoL-15r is a 15-item, health-related quality of life measure designed to assess limitations related to living with MG. Responses to each item are rated by the patient, using a reflection period of "over the past few weeks" on a 3-point scale (0 = not at all, 1 = somewhat, and 2 = very much). See Appendix 13 for a list of the 15 items. The MG-QoL-15r is assessed at Weeks 4, 8, and 12, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

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

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

5.4.1.4. Clinical Global Impression of Severity (CGI-S)

The CGI-S scale is the clinician/physician's global assessment of a patient's illness severity in response to the question "Considering your total clinical experience, how do you rate the current severity of the patient's MG?". The rating is given on a 7-point scale with higher scores indicating greater severity (1 = Normal, not at all ill; 2 = Borderline illness; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients). If the assessment was not performed, a score of 0 is assigned; 0 scores will be treated as missing. The CGI-S is assessed at Day 1; Weeks 4, 8, and 12; then every 12 weeks, at the end of treatment visit, and at the end of study visit.

Change from baseline in CGI-S will be calculated for each post-baseline visit.

5.4.1.5. Clinical Global Impression of Improvement (CGI-I)

The CGI-I scale is the clinician/physician's global assessment of the change in severity of the patient's gMG since starting the OLE study in response to the question "Compared to the beginning of the MOM-M281-005 study, how would you rate the current severity of the patient's MG?". The rating is given on a 7-point scale with lower scores indicating greater improvement (1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse). If the assessment was not performed, a score of 0 is assigned; 0 scores will be treated as missing. The CGI-I is assessed at Weeks 4, 8, and 12, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

5.4.1.6. Myasthenia Gravis Foundation of American (MGFA) Classification

The MGFA system classifies a patient's MG severity into one of 5 classifications of increasing severity from Class I (ocular muscle weakness only) to Class V (the patient is intubated) (Jaretzki 2000). Classes II through IV are each further divided into 2 subclasses ('a' or 'b') based on which muscle groups are primarily affected (see Appendix 14). The MGFA classification is assessed at Weeks 8 and 12, then every 24 weeks, and at the end of treatment visit.

5.4.2. Analysis Methods

Descriptive statistics (mean, standard deviation, median, minimum, maximum) of values and changes from baseline at each visit will be provided for the MG-ADL total score, QMG total score, MG-QoL-15r total score, and CGI-S by subject group and overall. Plots of mean (±SE) values and changes over time for each endpoint will also be provided.

The distribution of the CGI-S ratings, CGI-I ratings, and MGFA classification will be summarized with the number and percentage of patients with each value at each visit. The shift from baseline MGFA classification to the classification at each post-baseline visit will also be summarized.

The number and percentage of patients with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥8-point improvement in MG-ADL total score will be summarized at each post-baseline visit. In addition, the number and percentage of patients with an MG-ADL total score of 0 or 1 will be summarized at each post-baseline visit.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

Tertiary/exploratory endpoints will be summarized using the full analysis set.

5.5.1. Definition of Endpoint(s)

5.5.1.1. 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 assess patient-reported fatigue and associated impact on physical, mental, and social activities during the past 7 days. Each item is graded on a 5-point scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always). The Neuro-QoL fatigue is assessed

at Day 1; Weeks 4, 8, and 12; then every 12 weeks, at the end of treatment visit, and at the end of study visit.

The Neuro-QoL fatigue total score is defined as the sum of the 19 individual items (range: 19 – 95). The total score is missing if any item is missing. Higher scores indicate more fatigue.

Change from baseline in Neuro-QoL fatigue total score will be calculated for each post-baseline visit.

5.5.1.2. Myasthenia Gravis Foundation of America Post-intervention Status (MGFA-PIS)

The MGFA-PIS is a measure of the patient's MG status after treatment/intervention. In this study, the investigator assessment of minimal manifestations is collected in which the investigator indicates (yes or no) if "[t]he patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles." The assessment is collected every 12 weeks, at the end of treatment visit, and at the end of study visit.

5.5.1.3. Measurement of Physical Activity

The patient's physical activity was measured during the study via a removable digital health device (Embrace) worn on the wrist. The Embrace device is licensed in the US for use in neurology. It provides sleep, rest, and physical activity analysis.

5.5.2. Analysis Methods

Descriptive statistics (mean, standard deviation, median, minimum, maximum) of values and changes from baseline at each visit will be provided for the Neuro-QoL fatigue total score by subject group and overall. Plots of mean (±SE) values and changes over time will also be provided.

MGFA-PIS result will be provided in a listing.

Results from the Embrace device were deemed to be of little utility given the study termination and will not be summarized or listed.

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set.

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

5.6.1. Extent of Exposure

The number and percentage of patients who receive study drug will be summarized. The number and percentage of patients at each dose level and dose frequency will also be summarized by visit.

Descriptive statistics for duration of study drug (N, mean, SD, median, and range (minimum, maximum)) will be provided. Patient-years of intervention are calculated as days of intervention/365.25. Patient-years will be presented by subject group.

Duration of intervention will be summarized in the following duration categories:

- <3 months (<90 days)
- ≥3 to <6 months (≥90 to <180 days)
- ≥6 to <9 months (≥180 to <270 days)

Duration of intervention is defined as (date of last infusion – date of first infusion) + 1.

Descriptive statistics will be presented for the following parameters:

- Number of infusions
- Cumulative total dose. Cumulative total dose is the total dose in mg a patient received over all infusions in the study. The dose in mg for a given infusion is the dose level administered in mg/kg multiplied by the patient's weight.

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

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial infusion of study drug through the day of last infusion plus 56 days is considered to be treatment emergent. If the event occurs on the day of the initial infusion of study drug, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of patients who experience at least 1 occurrence of the given event will be summarized by subject group.

Summary tables will be provided for treatment-emergent adverse events:

- AEs
- AEs by NCI-CTCAE toxicity grade
  - AEs with CTCAE toxicity grade ≥3
- AEs by relationship to study drug

Five patients had 5 SAEs in the study and no patient discontinued study drug because of an adverse event. One patient had an adverse event with onset after the sponsor discontinued all treatment because of the Covid-19 pandemic and that adverse event ultimately had a fatal outcome. Summary tables will not be provided for these events. Listings will be provided for patients who:

- Had SAEs
- Had AEs with a fatal outcome
- Had onset or worsening of symptoms of gMG (clinical deterioration). These include patients with AEs coded to the preferred term "myasthenia gravis".

Incidence of other treatment-emergent adverse events of clinical or special interest will be summarized. See Appendix 8 for the list of adverse events in each category. Listings of patients with adverse events of clinical or special interest will be provided.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the patients included in the safety analysis set.

Descriptive statistics will be presented for all chemistry, hematology, and urinalysis (pH and specific gravity) laboratory tests at scheduled time points.

Change from baseline to each scheduled time point will be summarized for chemistry, hematology, and urinalysis (pH and specific gravity) tests and displayed by subject group. Percent change from baseline to each scheduled time point will also be summarized for albumin and total cholesterol and displayed by subject group. Boxplots and plots of mean (±SE) value, change, and percent change from baseline to each scheduled time point will be provided for albumin and total cholesterol. Plots of mean (±SE) value and change to each scheduled time point will be provided for ALT (alanine aminotransferase), AST (aspartate aminotransferase), and total bilirubin.

Abnormality criteria based on normal ranges will be applied to baseline and postbaseline values. The number and percentage of patients with a maximum post-baseline value greater than the upper limit of normal (ULN) and the number and percentage of patients with a minimum post-baseline value less than the lower limit of normal (LLN) will be summarized. Shift tables will be provided summarizing the shift in laboratory values from baseline to the maximum post-baseline value and to the minimum post-baseline value with respect to the abnormality criteria (low, normal, high).

The number and percentage of patients with a markedly abnormal laboratory post-baseline value will be presented by subject group. A listing of markedly abnormal laboratory values will be provided.

The markedly abnormal laboratory findings to be reported for albumin and liver function-related tests are described below:

- Albumin <20 g/L
- ALT ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- AST ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- ALP (alkaline phosphatase) ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN

Markedly abnormal criteria for additional selected tests are provided in Appendix 10.

A listing of patients meeting the biochemical Hy's Law criteria will be provided:

- ALT or AST ≥3xULN, and
- Either total bilirubin ≥2xULN or INR>1.5

5.6.3.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, weight, pulse, blood pressure (systolic and diastolic), and Body Mass Index (BMI) will be summarized at each assessment time point. BMI will be calculated as weight (kg)/(height (m))^2 at each time point that body weight is measured. The height measurement collected at screening will be used in the calculation. Change from baseline will be summarized at each assessment time point. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented.

Incidence of treatment-emergent markedly abnormal vital signs during intervention, as defined in Table 2, will be summarized for patients who had a baseline assessment and at least 1 postbaseline assessment for that vital sign. A listing of patients with treatment-emergent markedly abnormal vital signs will be presented.

Pulse, blood pressure, and temperature were measured in the recumbent position prior to every infusion and at selected time points after the first 2 infusions (15 minutes, 30 minutes, 1 hour, 2 hours or at end of infusion, 4 hours or at least 2 hours after end of infusion). Descriptive statistics of values and change from baseline will be summarized for pre-infusion time points only. Identification of clinically important vital signs will consider both pre- and post-infusion time points.

Table 2: Markedly Abnormal Vital Signs

Vital Sign	Criteria
Pulse	≥120 bpm and with ≥15 bpm increase from baseline
	≤50 bpm and with ≥15 bpm decrease from baseline
Systolic blood pressure	≥160 mmHg and with ≥20 mmHg increase from baseline
	≤90 mmHg and with ≥20 mmHg decrease from baseline
Diastolic blood pressure	≥100 mmHg and with ≥15 mmHg increase from baseline
	≤50 mmHg and with ≥15 mmHg decrease from baseline

5.6.3.3. Electrocardiogram

A single 12-lead ECG was obtained prior to each infusion, after the patient was in the supine position for at least 5 minutes. A central ECG service measured and interpreted all ECG recordings except those obtained at the follow-up visit, which were evaluated by the investigator. At the Day 1 visit, a post-infusion ECG was also obtained. The Day 1 ECG prior to the infusion will be used as Baseline for the calculation of change.

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

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

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

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

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

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

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

Postbaseline abnormalities will be compared with their corresponding baseline result:

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

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

- Heart rate (bpm): ≤50 and ≥120
- PR interval (msec): <120 and >200
- RR interval (msec): <600 and >1200

- QRS interval (msec): >120

The interpretation of the ECGs as determined by the central ECG service will be displayed by the number and percentage of patients meeting the abnormality criteria. The interpretation will be summarized over time. Findings from the ECGs as determined by the central ECG service will be displayed by the number and percentage of patients with at least one occurrence of each finding.

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

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

The C-SSRS was administered by trained study personnel at Day 1; Weeks 2, 4, 8, and 12; then every 12 weeks. On visits when an infusion was given, the C-SSRS was administered prior to the infusion. The C-SSRS is a semi-structured clinician-administered questionnaire designed to solicit the occurrence, severity, and frequency of suicide-related ideation and behaviors during the assessment period.

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

Suicidal Ideation (1-5)

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

Suicidal Behavior (6-10)

- Category 6: Preparatory acts or behavior
- Category 7: Aborted attempt
- Category 8: Interrupted attempt
- Category 9: Non-fatal suicide attempt
- Category 10: Completed suicide

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

The shift from baseline category to worst post-baseline category will be summarized with categories defined as ‘no suicidal ideation or behavior’, ‘suicidal ideation’, and ‘suicidal behavior’.

5.7. Other Analyses

5.7.1. Immunogenicity

Blood samples for antibodies to nipocalimab were to be collected at Weeks 4, 8, and 12, then every 12 weeks, at the end of treatment visit and at the end of study visit.

Patients evaluable for immunogenicity are defined as patients who received at least 1 dose of study drug and had 1 or more post-treatment serum samples evaluable for antibodies to nipocalimab.

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

Patients who were positive for antibodies to nipocalimab will include patients who were positive for treatment-boosted or treatment-induced antibodies to nipocalimab at any time after their first nipocalimab administration in study 005.

1. Patients with treatment-induced antibodies to nipocalimab had a negative ADA sample prior to nipocalimab administration and at least one post-treatment sample positive for ADA.
2. Patients with treatment-boosted antibodies to nipocalimab had a positive ADA sample prior to nipocalimab administration and at least one post-treatment sample positive for ADA with titer at least 2-fold higher (i.e., ≥2-fold) than the titer of the baseline sample.

Patients who were negative for antibodies to nipocalimab will include patients with no post-treatment samples positive for ADA, patients with post-treatment samples positive for ADA with titers remaining the same as the baseline titers, or patients with post-treatment samples positive for ADA with reduced or disappeared titers. Patients who had no appropriate samples available for immunogenicity assessment following intervention will be classified as “patients with baseline ADA samples only”.

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

Incidence of antibodies to nipocalimab (evaluable, treatment-emergent ADA positive, ADA negative) and peak titers of ADA will be summarized. In addition, listings of patients with baseline positive ADA samples and patients who are classified as positive for treatment-emergent antibodies to nipocalimab will be provided.

In addition, a list of patients who were positive for antibodies to nipocalimab (treatment-emergent or treatment-boosted) will be provided with individual IgG, MG-ADL, and infusion-site reactions (if any).

The efficacy and infusion-site reactions will be summarized by patient ADA status (positive and negative).

5.7.2. Pharmacodynamics

5.7.2.1. Immunoglobulin G

Blood samples for levels of total immunoglobulin G (IgG) were collected at Weeks 2, 4, 8, and 12, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

Descriptive statistics of the value, change from baseline, percent change from baseline, and percent of baseline value will be presented at each scheduled time point. Plots of mean (±SE) percent of baseline value and percent change from baseline at each scheduled sampling time point will be provided.

The number and percentage of patients with IgG ≤1 g/L will be summarized and a listing of patients meeting that criteria will be provided. A listing of IgG levels will be provided for patients who had an infection adverse event of special interest (see Appendix 8).

5.7.2.2. Immunoglobulin A, M, and E

Blood samples for levels of immunoglobulin A, M, and E were collected every 12 weeks and at the end of treatment visit.

Descriptive statistics of value, change from baseline, percent change from baseline, and percent of baseline value will be presented at each scheduled time point.

5.7.2.3. Anti-AChR and Anti-MuSK Autoantibodies

Blood samples for levels of anti-AChR and anti-MuSK autoantibodies were collected at Weeks 4, 8, and 12, then every 12 weeks, at the end of treatment visit, and at the end of study visit.

For anti-AChR autoantibodies, descriptive statistics of value, change from baseline, percent change from baseline, and percent of baseline value will be presented at each scheduled time point. Plots of mean (±SE) percent of baseline value and percent change from baseline at each scheduled time point will be provided.

No anti-MuSK positive patient entered the 005 study. Therefore, no summaries or listings of anti-MuSK antibodies will be presented.

5.7.3. Myasthenia Gravis Medication Usage

A listing of myasthenia gravis medications taken to treat the onset or worsening of symptoms of gMG (rescue therapy for clinical deterioration) will be provided.

Usage of myasthenia gravis medications will be displayed graphically over time for each patient, with lines for each medication extending from the start day to the end day relative to the date of the first infusion of nipocalimab in the study.

5.7.4. Definition of Subgroups

The frequency of treatment-emergent adverse events will be summarized by the following subgroups:

Subgroup	Definition
Age Group	• <45 • 45-64 • ≥65
Sex	• Female • Male

5.8. Interim Analyses

No interim analysis was performed

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

A Data Safety Monitoring Board performed periodic review of safety data from the 005 study.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AChR	acetylcholine receptor
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
CGI-I	Clinical global impression – improvement
CGI-S	Clinical global impression – severity
CRF	case report form
C-SSRS	Columbia – Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
FAS	full analysis set
gMG	generalized myasthenia gravis
ICF	informed consent form
IgG	Immunoglobulin G
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MG-ADL	Myasthenia Gravis – Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MG-QoL-15r	Revised Myasthenia Gravis Quality of Life
MuSK	muscle-specific kinase
NAb	neutralizing antibodies
NCI	National Cancer Institute
PD	pharmacodynamic(s)
QMG	Quantitative Myasthenia Gravis
SAE	serious adverse event
SD	standard deviation
SE	standard error
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

The secondary endpoint of the incidence of neutralizing anti-drug antibody seroconversion over time will not be summarized because neutralizing anti-drug antibody data was not available.

The exploratory endpoint of quantitative level of physical activity over time (based on data from the Embrace device) and changes over time will not be summarized because the data from the device was not deemed useful given the study termination due to the Covid-19 pandemic.

The exploratory model-based analysis of MG-ADL score change from baseline in relationship to total serum IgG and anti-AChR titer will not be performed because of the limited number of subjects and limited duration of exposure as a result of the study termination due to the Covid-19 pandemic.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of patients in each analysis set will be summarized and listed by subject group and overall. In addition, the distribution of patients by country and site ID will be presented.

Table 3 presents a list of the demographic variables that will be summarized by subject group and overall for the safety analysis set.

Table 3: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (18-25 years, 26-50 years, 51-64 years, and >=65 years)	Frequency distribution with the number and percentage of patients in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2)	

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

Table 4 presents a list of the baseline characteristic variables that will be summarized by subject group and overall for the full analysis set.

Table 4: Baseline Characteristic Variables

Continuous Variables:	**Summary Type**
Baseline MG-ADL total score	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Baseline QMG total score	
Categorical Variables	
Baseline MGFA Clinical Classification	Frequency distribution with the number and percentage of patients in each category.

6.4. Appendix 4 Protocol Deviations

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

- Inclusion criteria (enrolled despite failing an inclusion criteria)
- Exclusion criteria (enrolled despite meeting an exclusion criteria)
- Study drug (e.g., incorrect drug assignment, preparation, or administration, etc.)
- Assessment – Safety (e.g., missing or incorrectly performed safety assessment)
- Lab/Endpoint data (e.g, lab sample or efficacy assessment not performed per protocol)
- Visit window (visit out of protocol-specified window)
- Informed consent (ICF) (patient not consented properly)
- Missed visit (when an entire visit is missed)
- Prohibited co-medication
- Overdose/mis-use
- Withdrawal criteria (patient met withdrawal criteria; or, study drug stopping rule was met; or, study drug interruption rule was met and patient was not withdrawn or study drug was not stopped/paused)
- Other

Visits or assessments not conducted or conducted remotely because of the Covid-19 pandemic will be identified as such in the protocol deviation description with the prefix "COVID-19:".

6.5. Appendix 5 Prior and Concomitant Medications

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

Summaries of concomitant medications will be presented by ATC term and subject group. The proportion of patients who receive each concomitant medication will be summarized as well as the proportion of patients who receive at least 1 concomitant medication.

A separate summary of concomitant medications that comprise background therapy for myasthenia gravis will also be provided.

Prior medications will be summarized by subject group and ATC term. A summary of prior medications for myasthenia gravis (medications started and stopped before entry into the 005 study) will also be provided.

6.6. Appendix 6 Medical History

The verbatim terms used in the CRF by investigators to identify medical history events and diseases will be coded using MedDRA. For each medical history preferred term, the number and percentage of patients with at least 1 ongoing occurrence of the given event/disease will be summarized by subject group and overall.

6.7. Appendix 7 Intervention Compliance

Not applicable

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE Special Interest Category	SOC	Additional condition
Infections	Infection and Infestations	≥Grade 3 and/or serious

AE Special Interest Category	Preferred term	Additional condition
Hypoalbuminaema	Hypoalbuminaemia	≥Grade 3

Other adverse events of clinical interest are defined as follows:

AE of Clinical Interest Category	Preferred term	Additional condition
Infusion site reaction	Any preferred term containing "infusion site" or "vessel puncture site"	
Serum sickness reaction	Serum sickness	
	Serum sickness-like reaction	

AE of Clinical Interest Category	SMQ	Additional condition
Opportunistic infections	Opportunistic infections	Narrow scope
Anaphylactic reaction	Anaphylactic reaction	Narrow and broad scope
Suicidal ideation/behavior	Suicide/self-injury	Narrow and broad scope
Drug related hepatic disorders	Drug related hepatic disorders – comprehensive search	Narrow scope

6.9. Appendix 9 Medications of Special Interest

Not applicable.

6.10. Appendix 10 Laboratory Toxicity Grading

Markedly abnormal criteria for selected laboratory tests are provided in the table below. Change and percent change are in reference to the baseline value.

		Markedly Abnormal Criteria	
Laboratory test	**Units**	**1 – High**	**2 - Low**
Albumin	g/L	High: Change >10 and value >60	Low: Change < -10 and value <25
Alkaline Phosphatase	U/L	High: Change >100 and value >250	
Alanine Aminotransferase	U/L	Value ≥3xULN	
Aspartate Aminotransferase	U/L	Value ≥3xULN	
Bicarbonate	mmol/L	High: Percent change >20 and value >34.9	Low: Percent change < -20 and value <15.1
Bilirubin	mcmol/L	High: Percent change >20 and value >45	
Blood Urea Nitrogen	mmol/L	High: Percent change >20 and value >17.9	
Calcium	mmol/L	High: Percent change >20 and value >3	Low: Percent change < -20 and value <1.5
Chloride	mmol/L	High: Change >5 and value >120	Low: Change < -5 and value <85
Creatinine	mcmol/l	High: Percent change >20 and value >250	
Gamma Glutamyl Transferase	U/L	High: Change >100 and value >300	
Glucose	mmol/L	High: Percent change >30 and value >16.7	Low: Percent change < -20 and value <2.2
Phosphate	mmol/L	High: Percent change >10 and value >2.6	Low: Percent change < -10 and value <0.6
Potassium	mmol/L	High: Percent change >20 and value >6	Low: Percent change < -10 and value <3
Protein	g/L		Low: Percent change < -20 and value <50
Sodium	mmol/L	High: Percent change >10 and value >155	Low: Percent change < -10 and value <125
Creatine Kinase	U/L	High: Percent change >20 and value >960	
Hematocrit	L/L	High: Percent change >15 and value >0.5(female) or >0.55 (male)	Low: Percent change < -15 and value <0.28
Hemoglobin	g/L	High: Percent change >10 and value >190	Low: Percent change < -10 and value <80
Neutrophils/Leukocytes	%	High: Percent change >30 and value >90	Low: Percent change < -30 and value <30
Monocytes/Leukocytes	%	High: Percent change >20 and value >20	
Eosinophils/Leukocytes	%	High: Percent change >20 and value >10	
Basophils/Leukocytes	%	High: Percent change >20 and value >6	
Lymphocytes/Leukocytes	%	High: Percent change >20 and value >60	Low: Percent change < -20 and value <8
Platelets	10^9/L	High: Percent change >20 and value >600	Low: Percent change < -20 and value <100
Erythrocytes	10^12/L	High: Percent change >20 and value >6.1(female) or >6.4(male)	Low: Percent change < -20 and value <3
Leukocytes	10^9/L	High: Percent change >20 and value >15	Low: Percent change < -10 and value <2.5
pH	pH	High: >7	

6.11. Appendix 11 Myasthenia Gravis – Activities of Daily Living

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

6.12. Appendix 12 Quantitative Myasthenia Gravis

Item	None = 0	Mild = 1	Moderate = 2	Severe = 3
Double vision on lateral gaze right or left, seconds	61	11-60	1-10	Spontaneous
Ptosis (upward gaze), seconds	61	11-60	1-10	Spontaneous
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete
Swallowing 4 oz. of water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9
Right arm outstretched (90-degree sitting), seconds	240	9—230	10-89	0-9
Left arm outstretched (90-degree sitting), seconds	240	9—230	10-89	0-9
Vital capacity, % predicted	≥80	65-79	50-64	<50
Right-hand grip (men), kgW	≥45	15-44	5-14	0-4
Right-hand grip (women), kgW	≥30	10-29	5-9	0-4
Left-hand grip (men), kgW	≥35	15-34	5-14	0-4
Left-hand grip (women), kgW	≥25	10-24	5-9	0-4
Head lifted (45-degree supine), seconds	120	30-119	1-29	0
Right leg outstretched (45-degree supine), seconds	100	31-99	1-30	0
Left leg outstretched (45-degree supine), seconds	100	31-99	1-30	0

6.13. Appendix 13 Revised Myasthenia Gravis Quality of Life

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

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

6.14. Appendix 14 Myasthenia Gravis Foundation of America Classification

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

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

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

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

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

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

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

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

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