STATISTICAL ANALYSIS PLAN

Study Title:	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
Sponsor	Momenta Pharmaceuticals, Inc. 301 Binney Street Cambridge, MA 02142 USA
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LIST OF ABBREVIATIONS

AChR	Acetylcholine Receptor
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Class (from WHODRUG dictionary)
BMI	Body mass index
CRF	Case Report Form
CMH	Cochran–Mantel–Haenszel
COVID-19	2019 novel coronavirus
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of Variation
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
FSH	Follicle stimulating hormone
GCP	Good Clinical Practices
gMG	generalized Myasthenia Gravis
ICH	International Council for Harmonisation
ICU	Intensive care unit
Ig	Immunoglobulin
ITT	Intent to Treat
K-M	Kaplan-Meier
LOCF	Last observation carried forward
MCAR	Missing Completely At Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Affairs
MG-ADL	Myasthenia Gravis - Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post-intervention Status
MG-QoL15r	Myasthenia Gravis Quality of Life - 15 Scale
mITT	Modified Intent-to-Treat
MMRM	Mixed-effects Model Repeated Measures
MNAR	Missing Not At Random

MuSK	Muscle-Specific Kinase
nADA	Neutralizing ADA
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QMG	Quantitative Myasthenia Gravis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System/Software
SI	International System of Units
TEAE	Treatment Emergent Adverse Event
WHODRUG	World Health Organization Drug

1 INTRODUCTION

This document describes the data analysis specifications for Momenta Pharmaceuticals, Inc. protocol MOM-M281-004 entitled "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."

This version of the statistical analysis plan (SAP) was prepared in accordance with the latest protocol MOM-M281-004 version 3.1 (dated 5 July 2019) and 3.2 (for EU only, dated August 28, 2019). The regional version of the protocol does not affect the statistical analysis.

The purpose of this SAP is to provide a framework in which answers to the protocol objectives may be achieved in a statistically rigorous fashion, without bias or analytical deficiencies, following methods identified prior to database lock. Specifically, this plan has the following purposes:

To outline the types of analyses and presentations of data that will form the basis for conclusions.

To explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry. Any deviations from these guidelines must be substantiated by sound statistical reasoning and documented in writing in the final clinical study report.

To detail the changes to the planned analysis as a result of the COVID-19 pandemic.

The original study design included an interim analysis that was to be conducted when approximately 30 enrolled patients had completed their Day 57 assessments. The results were to be used to adjust the sample size, if necessary, and to guide future development activities. Very rapid enrollment towards the end of the enrollment period led the Sponsor instead to plan to conduct the interim analysis on all randomized patients. However, the COVID-19 global pandemic, which halted study operation prematurely and impeded completion of study visits for some patients, rendered execution of this plan infeasible. Therefore, a new interim analysis of the data, described in Section 10 of this document, will be implemented.

2 OVERVIEW OF STUDY DESIGN

MOM-M281-004 is a multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of M281 compared with placebo when administered by intravenous (IV) infusion to patients with generalized Myasthenia Gravis (gMG).

Following a Screening Period of up to 4 weeks, approximately 60 eligible patients will be randomized 1:1:1:1:1 to one of 5 treatment groups (approximately 12 per group). The randomization will be stratified first by autoantibody type (anti-muscle-specific kinase

(MuSK) vs anti-acetylcholine receptor (AChR)), and for patients positive for anti-AChR, the randomization will be further stratified by Baseline Myasthenia Gravis - Activities of Daily Living (MG-ADL) score (≤10, >10). The treatment groups are as follows:

- Group 1: placebo once every 2 weeks (Q2W)
- Group 2: 5 mg/kg M281 once every 4 weeks (Q4W)
- Group 3: 30 mg/kg M281 Q4W
- Group 4: 60 mg/kg M281 as a single dose
- Group 5: 60 mg/kg M281 Q2W

During the Treatment Period, patients will attend clinic visits beginning at Baseline (Day 1) and every other week for 8 weeks to receive study drug (placebo or M281) and undergo safety, efficacy, PK, PD, and immunogenicity assessments. To maintain the study blind with respect to assigned treatment and treatment regimen, all patients will receive an IV infusion (either placebo or M281) every other week; thus, all patients will receive a total of 5 infusions (See Table 1 below). Patients in the placebo group will receive an infusion Q2W beginning on Day 1. Patients in the M281 5 mg/kg Q4W, and 30 mg/kg Q4W dose groups will receive a placebo infusion at the Day 15 and Day 43 visits to maintain blinding of the study. Patients in the M281 60 mg/kg single-dose arm will receive placebo infusions on Days 15, 29, 43, and 57. Only patients in the M281 60 mg/kg Q2W group will not receive any placebo infusions. Infusions will be administered on the designated infusion days at the study facility after completion of all assessments specified for the given infusion day as shown on the Schedule of Study Assessments (Section 13). The infusions will be administered without regard to meal times. The infusion time is noted in the Infusion Manual. Guidelines for management of infusion reactions are provided in the study manual. The date of infusion, start and end times, the volume administered, and the time of the first infusion rate change (if applicable) for all doses are to be recorded.

Pharmacokinetic samples, vital signs, and an electrocardiogram (ECG) will be obtained before the start of the infusion. Patients will be observed for safety after the first 3 infusions per the Infusion Manual; if no clinically relevant adverse events (AEs) related to the infusion are observed in these first 3 infusions, the post-infusion observation period is no longer needed. The last infusion will be administered at the Day 57 visit. During the Follow-up Period (the 8-week period after the last infusion), clinic visits will be conducted for all patients at Day 85 and Day 113 for further safety, efficacy, PK, PD, and immunogenicity assessments needed to characterize the anticipated prolonged effects of M281. Serum biomarkers may be explored.

Upon completion of the study at Day 113, patients have the option to enroll in a separate open-label extension study where they would receive treatment with M281.

An independent Drug Safety Monitoring Board (DSMB) will be responsible for oversight of patient safety during the study.

Table 1 Selection and Timing of Infusions for Each Treatment Group

	Infusion Timepoints				
Treatment Group	**Day 1 Visit**	**Day 15 Visit**	**Day 29 Visit**	**Day 43 Visit**	**Day 57 Visit**
Placebo Q2W	Placebo	Placebo	Placebo	Placebo	Placebo
M281 5 mg/kg Q4W	M281	Placebo	M281	Placebo	M281
M281 30 mg/kg Q4W	M281	Placebo	M281	Placebo	M281
M281 60 mg/kg single dose	M281	Placebo	Placebo	Placebo	Placebo

Abbreviations: Q2W = every 2 weeks; Q4W = every 4 weeks.

2.1 Primary Objectives

The primary objectives are to evaluate:

- The safety and tolerability of treatment with M281 in patients with gMG who have an insufficient clinical response to ongoing, stable standard of care therapy, and
- The efficacy of M281 for gMG as measured by the change in MG-ADL score.

2.2 Secondary Objectives

The secondary objectives are to evaluate:

- The efficacy of M281 as measured by changes in the Quantitative Myasthenia Gravis (QMG) score and the revised Myasthenia Gravis Quality of Life - 15 Scale (MG-QoL15r),
- The PK of M281, and
- The PD activity of M281 as measured by effects on total serum immunoglobulin (Ig)G concentrations.

2.3 Exploratory Objectives

The exploratory objectives are to:

- Evaluate the PD activity of M281 as measured by effects on serum concentrations of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE;
- Evaluate the PD activity of M281 as measured by effects on serum levels of pathogenic autoantibodies associated with gMG (anti-AChR and anti-MuSK);
- Characterize pathogenic MG autoantibodies (anti-AChR and anti-MuSK) and their potential for disease modification and possible relationship with clinical status;
- Evaluate the immunogenicity of M281 as assessed by the presence of total and neutralizing anti-M281 antibodies in patients with gMG;

- Evaluate the response to treatment with M281 in patients with gMG, as measured by exploratory efficacy endpoints, including, but not limited to, use of rescue therapy, time to response, duration of response, and number of MG exacerbations; and
- Evaluate the potential relationship between change in MG-ADL score and change in anti-AChR levels in patients treated with M281, for patients positive for anti-AChR antibodies only.

2.4 Primary Endpoints

2.4.1 Primary Safety Endpoint

M281 safety and tolerability will be evaluated in terms of the incidence of AEs (including Serious AEs (SAEs) and AEs of Special Interest (AESIs)) compared with placebo.

Analysis of all safety data will be performed on the Safety Population and will be presented by the treatment received. Adverse events will be coded using a standardized medical dictionary (Medical Dictionary for Regulatory Activities [MedDRA]). Analysis of AEs in terms of incidence by severity and by relatedness will also be provided. Prior and concomitant medications will be coded by the World Health Organization Drug Dictionary Enhanced and will be summarized. Medical history will be listed by patient and coded using MedDRA and will be summarized. Descriptive statistics and a summary of abnormalities using shift tables will be presented for safety laboratory tests, vital signs, ECGs, other laboratory parameters, and the Columbia-Suicide Severity Rating Scale (C-SSRS). For vital signs and ECGs, descriptive statistics at each visit and change from Baseline at each visit will be provided. Physical examinations will be summarized as shift tables. Listings will also be provided for each type of safety data.

2.4.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Day 57 in the total MG-ADL score for each treatment group compared with placebo. The details on the statistical analyses for the primary efficacy endpoint are described in Section 8.4.1.1.

2.5 Secondary Endpoints

The study's secondary efficacy endpoints are listed with their corresponding analysis methods in Section 8.4.1.2.

2.6 Exploratory Endpoints

The study's exploratory efficacy endpoints are listed with their corresponding analysis methods in Section 8.4.2.

3 SAMPLE SIZE

Approximately 60 patients will be randomized 1:1:1:1:1 to one of the 5 treatment arms of the study. Allowing for 15% attrition, it is expected that approximately 50 patients (10 per arm) will be evaluable for the primary efficacy endpoint.

The study is designed to have at least 80% power and experiment-wise one-sided type I error of 5% to detect a difference from placebo in MG-ADL at Day 57 with 12 patients (10 evaluable) per arm in the placebo, M281 5 mg/kg Q4W, M281 30 mg/kg Q4W, and M281 60 mg/kg Q2W arms, using a dose-responsive test with the doses sorted in ascending order. The M281 60-mg/kg single-dose arm was not included in the powering as its relationship to other doses is not defined. The change from baseline in MD-ADL in the placebo and 60 mg/kg Q2W arms were assumed to be -2 and -6.0 points, respectively, and the common standard deviation was assumed to be 3 points. Additionally, the ratio of within- to between-patient variance was assumed to be 0.2. Power was estimated via simulations performed in R 3.4.4 (R Core Team, 2018).

The study design originally allowed the sample size to be increased by up to 30 additional patients based on the results of the interim analysis. However, due to the rapid enrollment rate and also due to COVID-19, the need for sample size adjustment will no longer be assessed in the interim analysis (see Section 10 and Section 11.2).

4 RANDOMIZATION, BLINDING, AND REPLACEMENT OF PATIENTS

Eligible patients 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 a web-based interactive response system to obtain the randomization number for each eligible patient.

The study is double-blinded. The patient, investigator, and Sponsor will be blinded to study treatment for the duration of the study. An unblinded site pharmacist will be responsible for preparing the study drug for infusion while the remainder of site personnel will remain blinded.

Laboratory measurements related to expected PD activity and immunogenicity of M281 (i.e., total serum IgG and IgG subtypes [IgG1, IgG2, IgG3, and IgG4], anti-AChR and anti-MuSK autoantibodies, albumin, and anti-M281 antibodies) will be blinded to the patient, investigator, and Sponsor and not provided during study conduct with the exception of total serum IgG at the Day 113 Visit if the patient does not enter the MOM-M281-005 open-label extension study.

If an emergency occurs that necessitates knowledge of a patient's treatment assignment, the Investigator can obtain the information via the web-based interactive response system.

An unblinded interim analysis will be conducted as described in Section 10. An unblinding plan detailing the unblinding process will be finalized and signed off before unblinding.

5 DEFINITIONS OF PATIENT POPULATIONS

The Intent-to-Treat (ITT) Population will include all randomized patients. Efficacy analysis will be performed using the ITT Population in the final analysis.

The modified Intent-to-Treat (mITT) Population will include all randomized patients who have at least one postbaseline efficacy assessment, and whose data are suitable for analysis (see Section 11.2 for details). The interim analysis will use the mITT population for efficacy analyses.

The Safety Population will include all patients who received any amount of M281 or placebo. All safety analysis will be performed using the Safety Population.

The PK Population will include all randomized patients in the Safety Population with at least one evaluable plasma concentration of M281.

The Per Protocol (PP) Population is a subset of the ITT Population and will include patients who complete the study with no major protocol deviations impacting safety, efficacy, or PD assessments. Assignment to the PP Population will be determined prior to unblinding the study.

6 DEFINITIONS, COMPUTATIONS, DATA CONVENTIONS

6.1 Key Definitions and Computations

Start of Treatment

Date and start time of the first infusion of the study drug.

Baseline

Baseline represents the procedures or assessments done prior to the administration of study treatment. The Baseline value will be the value obtained closest to and prior to the first administration of study treatment (Day 1). These values can occur on the same day as the first administration of study treatment (or in the Screening visit), as long as they are measured before the study treatment is administered.

Visit Structure and Visit Names

Section 13 displays the schedule of study assessments taken from the protocol (pages 25-27) that defines the visit structure and visit names. Patient listings and summary tables will follow as closely as possible the visit structure and naming conventions outlined in Section 13.

Adverse Event (AE) and Treatment-Emergent Adverse Event (TEAE)

Reporting of AEs will start following the patient signing the informed consent form and end at the final visit.

The AEs and SAEs are defined as follows:

- Adverse event is any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.
- Serious Adverse Event is any adverse event occurring at any dose that results in any of the following outcomes: Death, a life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious AE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition**.**

Treatment-emergent adverse events (TEAE) are defined as any AE occurring during or after the initiation of the first infusion of study drug.

The severity of AE will be graded using Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 and the degree of certainty about causality will be graded into definitely, probably, possibly related, unlikely to be related, and not related.

Adverse Event of special interests (AESI) are defined as any CTCAE Grade 3 or higher event of severe infection and any CTCAE Grade 3 or higher event of hypoalbuminemia.

See Section 6.1.1 of the study protocol for more details.

Anti-drug Antibody Seroconversion

Anti-drug Antibody (ADA) seroconversion will be considered as any subject who begins with an antibody titer below the limit of quantification (including ADA screening assay negative) and at any point after Start of Treatment has an antibody titer above the limit of quantification.

6.2 Conventions

- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded up to 1 significant digit (tenths) for purposes of presentation.
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded up to 1 significant digit (tenths) for purposes of presentation.
- 1 pound = 0.454 kg.
- 1 inch = 2.54 cm.
- Investigational Product (Study Drug) is M281.
- Study Drug Administration: Duration of treatment is defined as the last dose date minus the first dose date of the study treatment plus 1.
- The software used for all summary statistics and statistical analyses will be Statistical Analysis System/Software (SAS) Version 9.3 or later.

- Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 7).

7 MISSING DATA AND DROPOUTS

All data will be analyzed as they were collected in the clinical database. Hence, missing values will generally not be imputed except for in the specific situations described in the subsections below.

7.1 Partial/Missing Dates

When tabulating AE data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment. No imputation will be applied to the incomplete AE end date.

To summarize time since MG diagnosis, partial dates will be handled as follows. If the day of the month is missing, the day is set to the fifteenth (15^{th}) of the month. If the day and month are both missing, the day and month will be assumed to be June 15^{th} .

Imputed dates will be noted in the patient data listings. Any imputed dates undertaken post-database lock will be fully described in the clinical study report.

7.2 Missing MG-ADL, QMG, and MG-QOL15 Individual Item Scores

In case any individual item scores in MG-ADL, QMG, and MG-QOL15 are missing, the total score will be imputed with the following method.

- For any scale, any patient at any timepoint, if the score is missing for 3 or more items, the total score for the scale will not be imputed and considered as missing in the analysis.
- If an individual item in any scale for the same patient is missing 3 or more times, the total scale score for those timepoints will not be imputed and will be considered as missing in the analysis
- Otherwise, for each patient, each missing item score, the missing item score will be imputed as the mean of the nonmissing scores of the same item in the timepoints immediately before and immediately after the missing score. If there is no data available after the timepoint, then the score from the previous timepoint will be carried forward. Baseline or screening data can be considered in this algorithm. The calculated mean score will be rounded to the nearest integer. The total score of the scale will be recalculated from the imputed scores.

7.3 Missing MG-ADL and QMG total scores

MG-ADL and QMG total scores can be missing due to several reasons:

- Patient discontinuation due to AEs, compliance, lack of efficacy, voluntary withdrawal. This missing data pattern will be considered Missing Not At Random (MNAR)
- Inability to assess some items (see Section 7.2), This missing data pattern will be considered MNAR
- Inability to perform the assessment due to COVID-19 pandemic related operational challenges. These missing data will be considered as Missing Completely At Random (MCAR)

Because of mixed missing data patterns, the efficacy analysis will be performed using Multiple Imputation Markov Chain Monte Carlo (MCMC) method. The details are provided in Section 10.

8 DESCRIPTION OF STATISTICAL ANALYSES

8.1 General Principles

Unless otherwise noted, data will be summarized in tabular format by treatment group. All study data documented on the case report forms (CRFs) will be included in the study data listings.

All output will be incorporated into Microsoft rtf or Excel files, or Adobe Acrobat portable document format (PDF) files, sorted and labeled according to the International Council for Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

All data listings that contain an evaluation date will contain a relative study day (Study Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication, which is designated as Day 1; the preceding day is Day -1, and the day before that is Day -2, etc.

Statistical tests will be two-sided, with a type 1 error rate of 5%, unless otherwise stated (e.g. one-sided test for the dose response analyses). All confidence intervals (if constructed) will be constructed at the 95% confidence level. Any inferential statistical tests conducted in this study are considered exploratory in nature; therefore, no p-value adjustments for multiplicity analyses will be made.

Tabulations will be produced for appropriate demographic, baseline, efficacy, PK, and safety parameters. Summary (i.e. descriptive) statistics will include number of patients, mean, standard deviation, median, range (minimum, maximum) values and, where appropriate, coefficient of variation (CV%) for continuous variables and frequencies, and percentages for categorical variables. Time-to-event analyses will be summarized using Kaplan-Meier survival analysis and graphs for the estimated median time.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 7).

8.2 Patient Enrollment, Disposition, Protocol Deviations

Patient disposition will be tabulated and will include:

- Number enrolled
- Number of patients in analysis populations (ITT, Safety, and PP)
- Number completing the study treatment and the primary reason for treatment discontinuation
- Number completing the study and the primary reason for study discontinuation

A by-patient data listing of study completion information, including the reason for study withdrawal, will be presented.

A protocol deviation is any noncompliance with the clinical trial protocol or Good Clinical Practice (GCP). The noncompliance may be either on the part of the patient, the investigator, or the study site staff. Protocol deviations will be identified and documented by Momenta/designee study monitors/project manager based on reviews of data listings prior to database lock.

The Sponsor or designee will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file), in collaboration with the data monitoring group as applicable; this file will include a description of the protocol deviation.

All protocol deviations will be presented in a data listing.

8.3 Demographic, Baseline Characteristics, and Medical History

Demographics, baseline characteristics, and medical history will be summarized and presented overall and by treatment group for the ITT and Safety Populations. Age, height, weight, body mass index (BMI) and baseline MG-ADL, QMG, MG-QoL15r scores will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum).

The number and percentage of patients in each age, sex, race and ethnicity category, baseline Myasthenia Gravis Foundation of America (MGFA) classification, and randomization stratum will also be presented. No formal statistical comparisons will be performed.

MG Disease history will include time since diagnosis, time since symptom onset, number of MG crises, and number of past episodes of clinical deterioration which will be summarized using descriptive statistics. The antibody status will be presented using the counts and percentages.

Medical history will be coded using MedDRA and will be summarized by treatment group.

All demographic, baseline, and medical history data, including disease history, previous MG medications/therapies, and pregnancy test results will be provided in data listings.

8.4 Efficacy, Pharmacokinetic and Pharmacodynamic Analyses

8.4.1 Efficacy and Pharmacodynamic Analyses

Efficacy analyses will be conducted using the ITT population in the final analysis, and the mITT population in the interim analysis. Analysis of Primary and Key Secondary endpoints will be repeated for the PP Population and anti-AChR positive patients.

8.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline to Day 57 in the total MG-ADL score for each treatment group compared with placebo.

The primary efficacy endpoint will be evaluated via dose-response analyses, as well as mixed-effects model repeated measures (MMRM) analyses, using data at Days 15, 29, 43, and 57. Dose-response analyses will include one-sided tests of linear trend and rank-based association. Models of MG-ADL Day 57 change score versus dose will be explored. MMRM analyses will include variables for baseline MG-ADL score, treatment-by-study week interaction, and autoantibody type, with variance-covariance structure assumed as compound symmetry. Covariates such as corticosteroids dose, use of immunosuppressants, and duration since MG diagnosis may be added to the model, and different variance-covariance structures may be explored. For MMRM analyses, two-sided tests with type I error rate of 5% are used.

8.4.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints and their corresponding analysis methods are included in Table 2.

Table 2 Secondary Efficacy Endpoints

Endpoints	Analysis Methods
Total MG-ADL score change from Baseline and difference from placebo in relationship to total serum IgG percent of Baseline Total MG-ADL score change from Baseline and difference from placebo during the study as a response to percent change in total serum IgG (patients with positive anti-AChR antibodies only) Total QMG score change from Baseline and difference from placebo in relationship to total serum IgG percent of Baseline Total QMG score change from Baseline and difference from placebo during the study as a response to percent change in total serum IgG (patients with positive anti-AChR antibodies only)	Analysis will be described in a separate analysis plan.
Responder analysis: number of patients with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥8-point improvement in total MG-ADL score from Baseline to Day 57 • Responder analysis: number of patients with a 3-, 4-, 5-, 6-, 7-, or ≥8-point improvement in total QMG score over time after the last dose	Fisher's exact test comparing each active treatment group vs. placebo group
• Change in total QMG score from Baseline to Day 57 • Change in total MG-QoL15r score from Baseline to Day 57 • Change in total serum IgG from Baseline to Day 57	MMRM (same as the primary endpoint)
• Change in total MG-ADL, QMG, and MG-QoL15r scores over time after the last dose • Change in total serum IgG over time after the last dose	MMRM (same as the primary endpoint)
• Shift in MGFA classification from Baseline to Day 57 • Shift in MGFA classification over time after the last dose	CMH

Abbreviations: AChR = Acetylcholine Receptor; IgG = Immunoglobulin G; MG-ADL = Myasthenia Gravis - Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MMRM = Mixed-effects Model Repeated Measures; Myasthenia Gravis Quality of Life - 15 Scale; QMG = Quantitative Myasthenia Gravis.

8.4.2 Exploratory Efficacy and Pharmacodynamic Endpoints

The exploratory efficacy and PD endpoints and their corresponding analysis methods are included in Table 3.

Table 3 Exploratory Efficacy and PD Endpoints

Endpoints	Analysis Methods
• Change in serum concentration of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE over time	Descriptive statistics only
• Change in gMG-related serum autoantibody titers over time	Descriptive statistics only
• Potency and other characteristics of pathogenic MG antibodies may be assayed and possible relationship with clinical status may be explored	Analysis will be performed when the data is available
• The incidence of ADA and nADA seroconversion over time	Descriptive statistics only
• Need for increase (rescue) in glucocorticosteroid use before Day 57 and before Day 113	Fisher's exact test
• Need for rescue therapy before Day 57 and before Day 113	Fisher's exact test
• Number of patients with clinical deterioration before Day 57 and before Day 113	Fisher's exact test
• Number of episodes of myasthenic exacerbation (hospitalizations, ICU admissions, and length of stay)	CMH
• Number of patients with a durable response, defined as ≥4 consecutive weeks with improvement ≥2 on MG-ADL • Number of patients with a durable response, defined as ≥4 consecutive weeks with improvement ≥3 on QMG	Fisher's exact test
• Duration of response, defined as number of consecutive weeks that the patient has an improvement ≥2 on MG-ADL • Duration of response, defined as number of consecutive weeks that the patient has an improvement ≥3 on QMG	Descriptive statistics only
• Number of patients with change in MGFA classification status at Day 57 and over time	CMH
• A model-based analysis of MG-ADL score change from Baseline, change from placebo in relationship to anti-AChR titer, for patients positive for anti-AChR antibodies only	Analysis will be described in a separate analysis plan.

Table 3 Exploratory Efficacy and PD Endpoints

Endpoints	Analysis Methods
• A simultaneous model of all score-based measurements (QMG, MG-ADL) over time by IgG change from Baseline	Analysis will be described in a separate analysis plan.
• Proportion of patients with minimal manifestations, and change in status at Day 57 and Day 113 per MGFA-PIS	This analysis will not be performed as the data was not collected as planned
• Time to response defined as time from first infusion to the first time with improvement ≥2 on MG-ADL • Time to maximum improvement in MG-ADL • Time from maximum improvement in MG-ADL to rebound • Time to response defined as time from first infusion to the first time with improvement ≥3 on QMG • Time to maximum improvement in QMG	Descriptive statistics

Abbreviations: AChR = Acetylcholine Receptor; ADA = Antidrug Antibodies; CMH = Cochran–Mantel–Haenszel ; gMG = Generalized Myasthenia Gravis; ICU = Intensive Care Unit; IgG = Immunoglobulin G; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis - Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MGFA-PIS = Myasthenia Gravis Foundation of America Post-intervention Status; MMRM = Mixed-effects Model Repeated Measures; Myasthenia Gravis Quality of Life - 15 Scale; nADA = Neutralizing Antidrug Antibodies; QMG = Quantitative Myasthenia Gravis.

8.4.3 Pharmacokinetic (PK) Analysis

Plasma concentrations of M281 will be summarized by treatment groups and nominal time point using descriptive statistics (number of patients, number of samples above the limit of quantification, arithmetic mean, standard deviation, coefficients of variation, geometric mean, geometric coefficient of variation, median, minimum, and maximum). No PK parameters will be calculated.

8.5 Safety Analysis

Safety analyses will be conducted using the safety population. No inferential statistical tests will be done for the safety endpoints.

8.5.1 Adverse Events

Adverse Events will be coded using the latest MedDRA dictionary and displayed in tables and listings using System Organ Class and Preferred Term. Severity of AEs was determined by study Investigators using CTCAE v5.0 criteria.

Adverse events will be summarized for those events that are considered treatment-emergent, where treatment-emergent is defined per protocol as any AE occurring during or after the initiation of the first infusion of study drug.

The number and percentage of patients with any treatment-emergent adverse event (TEAE), further identified by maximum severity, with any TEAE assessed by the Investigator as related to study drug, with any TEAE with a CTCAE severity Grade ≥ 3, with any treatment-emergent SAE, with any treatment-related treatment-emergent SAE, with any TEAE leading to discontinuation of study drug, with any TEAE leading to death, and with any AE of Special Interest will be presented. In these tabulations, each patient will contribute only once (i.e., the maximum severity and the strongest relationship), regardless of the number of episodes. AEs with missing relationship will be considered "Related" to study treatment.

Additional summary tables by System Organ Class and Preferred Term that include all TEAEs, TEAEs assessed by the Investigator as related to treatment, treatment-emergent SAEs, SAEs assessed by the Investigator as related to treatment, TEAEs by CTCAE severity grade, TEAEs with a CTCAE severity Grade ≥ 3, and AEs of Special Interest. TEAEs, sorted by Preferred Term in descending order of incidence in the overall safety population will be also be presented.

All AEs occurring on-study will be listed in a patient data listing. By-patient listings will also be provided for the following: AEs leading to patient death, SAEs, and AEs leading to discontinuation of treatment.

8.5.2 Study Drug Exposure and Dose Modifications

Study drug exposure will be determined by duration and total volume administered and will be summarized by treatment group using descriptive statistics.

Duration of study drug exposure will be calculated by the number of days patients were administered study drug, as determined below.

Duration of Study Drug Exposure = (Date of last dose – Date of first dose) +1

Study drug administration data for each patient will also be presented in a data listing.

8.5.3 Laboratory Tests

Safety laboratory tests that include hematology, chemistry, coagulation function, and urinalysis tests will be evaluated at all scheduled visits.

Laboratory data will be summarized by NCI-CTCAE v5.0 toxicity grade when possible. The CTCAE grade will be calculated for all applicable analytes as described in Table 4 in Section 12.

Clinical laboratory values will be expressed in International System of Units (SI).

The actual value and change from baseline to each on-study evaluation will be summarized for each clinical laboratory parameter. In the event of repeat values, the worst value per study visit will be used.

Shift tables will be produced that summarize the changes from baseline to worst value, using CTCAE toxicity grades for relevant laboratory parameters.

All laboratory data will be provided in data listings. A subset listing will be presented for laboratory results with CTCAE severity ≥ Grade 3.

8.5.4 Vital Signs and Weight

Vital signs (temperature, systolic blood pressure and diastolic blood pressure, and pulse rate) will be collected at all scheduled visits with time points of pre-infusion and 30 minutes post-infusion for the first 3 infusions, and pre-infusion only for the following infusions.

Vital sign variables and weight will be summarized using descriptive statistics by treatment group.

The actual value and change from baseline to each scheduled visit/time point will be summarized using descriptive statistics. Vital sign measurements will be presented for each patient in a data listing.

8.5.5 Physical Examinations

Full physical examinations are performed at Screening, Baseline, and Day 113, and a focused physical examination at all other visits. A shift table from baseline to the worse post-baseline value (abnormal being the worst) will be provided for each body system by treatment group. Physical examination results will also be presented in a data listing.

8.5.6 Electrocardiograms (ECG)

Electrocardiograms (ECG) will be collected at all scheduled visits. On infusion days, ECG will be assessed immediately prior to the beginning of the infusion. For the first infusion, a single 12-lead ECG will also be conducted within 10 minutes after the infusion has been completed.

Electrocardiogram variables measured on a quantitative scale (PR, RR, QRS, QT, QTcB, and QTcF) will be summarized using descriptive statistics for the actual value and change from baseline to each visit/timepoint by treatment group.

In addition, a shift table will be provided for interpretation from baseline to the worst post-baseline value with the number and percentage of patients.

All ECG tests including overall ECG interpretation will be included in by-patient listings for further medical review.

8.5.7 Columbia-Suicide Severity Rating Scales (C-SSRS)

Post-baseline C-SSRS responses to suicidal ideation and suicidal behavior questions (yes/no) will be summarized by treatment group and by visit. A shift table with categories of 'No suicidal ideation or behavior', 'Suicidal ideation', and 'Suicidal behavior' will be utilized to summarize the change from baseline to worst post-baseline value (suicidal behavior being the worst value).

All C-SSRS data will be presented in by-patient listings.

8.5.8 Myasthenia Gravis Exacerbation

Myasthenia gravis exacerbations were to be collected in the AE page. Myasthenia gravis exacerbations will be presented in a by-patient listing. The counts of exacerbation events by treatment will be summarized (number of subjects with an event and number of events).

8.5.9 Concomitant Therapy and Procedures

For the purpose of this analysis, concomitant medications/therapies are defined as those medications taken after first dose of study drug. Specifically, for any medication that did not end prior to first dose or the end date is missing or the medication is ongoing, the medication will be considered concomitant. Prior medication/therapy is defined as any medication that started and ended prior to the first dose of study drug.

These medications will be coded using World Health Organization Drug (WHODrug) Dictionary Version Mar2018. The number and percentage of patients in the Safety population using different concomitant or prior medications will be tabulated separately by treatment group and summarized in a table by WHODrug anatomical class (ATC) and preferred drug name. These data will also be presented in patient listings.

9 TESTING/VALIDATION PLAN AND SOFTWARE SYSTEM

Statistical Analysis System/Software (SAS) version 9.3 or later will be used to analyze the data, and create summary tables, patient data listings, and graphical representations of the data. All SAS programs will be validated using industry standard validation procedures.

10 INTERIM ANALYSIS

The interim analysis described here represents a change from the protocol specified analysis plan due to rapid enrollment and COVID-19 pandemic (see Section 11 for further details). Under the current interim analysis plan, all efficacy and safety analyses planned for the original final analysis, as detailed in Section 8, will be performed. All efficacy analyses will be performed based on the mITT population, and all safety analyses will be performed based on the Safety Population.

The primary and secondary efficacy endpoints will be analyzed using Analysis of Covariance (ANCOVA), with the average score collected on Day 43 and Day 57 as the response variable, and the stratification factor as covariate. If only one of the assessments (Day 43 or

Day 57) is available, then that assessment will be used. For patients who took rescue medication, their data after the rescue medication will be disregarded in the efficacy analysis. Missing data will be imputed with Last Observation Carried Forward (LOCF) method and Multiple Imputation Markov Chain Monte Carlo (MCMC) method. Random seed number 42365 will be used in MCMC procedure. Individual M281 treatment groups will be compared against placebo. Combinations of treatment arms (for example, comparing the combination of the highest two groups, 60 mg/kg Q2W and 30 mg/kg Q4W, against placebo) may also be explored. All statistical analyses will be evaluated on nominal p-value without adjustment of multiple comparison.

The originally proposed MMRM method will also be performed as a sensitivity analysis.

The efficacy analysis will be repeated for anti-AChR patients only.

The efficacy analysis will also be repeated excluding those patients whose data was affected by COVID-19.

11 STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

The study originally had a planned interim analysis after approximately 30 patients had completed the Day 57 assessments. The results were to be used to adjust the sample size, if necessary, and to guide future development activities. Very rapid enrollment towards the end of the enrollment period led the Sponsor instead to plan to conduct the interim analysis on all randomized patients. However, the COVID-19 pandemic, which halted operation in the study and impeded completion of study visits for many patients, made this revised plan infeasible and led to the implementation of the current interim analysis described in Section 10.

The COVID-19 pandemic has caused significant changes to the study conduct:

- Study drug administration was stopped April 17, 2020, 8 patients did not receive the final Day 57 dose.
- Some patients missed or delayed Day 57, Day 85, or Day 113 visits.
- Some patients had remote visits and as a result MG-ADL was assessed remotely and QMG was not assessed.
- Data collection process was disrupted. Data entry and source data verification were delayed.

As a result of these events, the following changes to the planned analysis will be implemented in the final and interim analyses. All changes are documented and finalized before unblinding.

11.1 Final Analysis

The final analysis will be performed as planned in the protocol, with additional missing data handling being needed in the primary and secondary efficacy analysis. See Section 7 for details.

11.2 Interim Analysis

Unblinding: The interim analysis will be performed and the unblinded aggregated results will be disclosed. Individual patient level data will remain blinded to everyone except the unblinded team. The unblinding process is described in a separate Unblinding Plan, which is also finalized before unblinding.

Analysis Population: The interim analysis will be based on the mITT population, which consists of all randomized patients who had post-baseline efficacy assessments and are suitable for analysis. A patient is considered suitable for analysis if the patient data from the following list of selected CRFs has been entered and either source verified or remotely monitored.

- Demographics form;
- Baseline MG history form;
- Randomization form;
- All MG-ADL and QMG forms up to D43 or the last dosing visit;
- Study drug administration form;
- Central lab samples related to clinical safety and IgG;
- End of treatment form;

The list of patients suitable for analysis will be established before unblinding.

The details are described and finalized in the Unblinding Plan. Patients excluded from the mITT population and the reason for exclusion will be finalized before unblinding and tabulated.

Scope of Analysis: The primary and secondary efficacy endpoints (MG-ADL and QMG) will be regarded as reliable and representative of the entire study population. Safety, other efficacy endpoints, and exploratory endpoints will also be analyzed but considered preliminary.

Primary Analysis Method: Details are provided in Section 10. The COVID-19 global pandemic has created complex missing data patterns, which may limit the suitability of the originally proposed MMRM method. Therefore, the primary analysis method was changed to ANCOVA, rules for handling of missing data were specified, and new sensitivity analyses were also specified.

While the original analysis included some flexibility for fine tuning statistical models by including baseline covariates, the inclusion of these covariates may no longer be feasible due to current data availability. However, such analyses may be performed later when the rest of the data becomes available.

Day 85 and Day 113 Data: Analysis of D85 and D113 data will still be performed but caution is required in interpretation as the data might have not been fully verified.

12 REFERENCE

Table 4. CTCAE Toxicity Laboratory Grading Chart

Panel	Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v5.0)
Hematology	WBC count	10^9/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 3.0 × 10^9/L Grade 2: < 3.0 – 2.0 × 10^9/L Grade 3: < 2.0 – 1.0 × 10^9/L Grade 4: < 1.0 × 10^9/L
Hematology	ANC	10^9 cells/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 1.5 × 10^9/L Grade 2: < 1.5 – 1.0 × 10^9/L Grade 3: < 1.0– 0.5 × 10^9/L Grade 4: < 0.5 × 10^9/L
Hematology	Lymphocyte count	10^9cells/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 0.8 × 10^9/L Grade 2: < 0.8 – 0.5 × 10^9L Grade 3: < 0.5 – 0.2 × 10^9/L Grade 4: < 0.2 × 10^9/L
Hematology	Hemoglobin	g/L	Increase	Grade 0: ≤ ULN Grade 1: > 20 g/L + ULN Grade 2: > 20 – 40 g/L +ULN Grade 3: > 40 + ULN Grade 4: Not defined
		g/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 100 g/L Grade 2: < 100 – 80 g/L Grade 3: < 80 Grade 4: Not defined
Hematology	Platelet count	10^9/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 75 × 10^9/L Grade 2: < 75 – 50 × 10^9/L Grade 3: < 50 – 25 × 10^9/L Grade 4: < 25 × 10^9/L
Chemistry	Albumin	g/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 30 g/L Grade 2: < 30 – 20 g/L Grade 3: < 20 g/L Grade 4: Not defined

Table 4. CTCAE Toxicity Laboratory Grading Chart

Panel	Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v5.0)
Chemistry	Alk Phos	U/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 2.5 × ULN Grade 2: > 2.5 – 5.0 × ULN Grade 3: > 5.0 – 20.0 × ULN Grade 4: > 20.0 × ULN
Chemistry	ALT	U/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 3.0 × ULN Grade 2: > 3.0 – 5.0 × ULN Grade 3: > 5.0 – 20.0 × ULN Grade 4: > 20.0 × ULN
Chemistry	AST	U/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 3.0 × ULN Grade 2: > 3.0 – 5.0 × ULN Grade 3: > 5.0 – 20.0 × ULN Grade 4: > 20.0 × ULN
Chemistry	Total Bilirubin	micromol/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 1.5 × ULN Grade 2: > 1.5 – 3.0 × ULN Grade 3: > 3.0 – 10.0 × ULN Grade 4: > 10.0 × ULN
Chemistry	Creatinine	micromol/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 1.5 × ULN Grade 2: > 1.5 – 3.0 × ULN Grade 3: > 3.0 – 6.0 × ULN Grade 4: > 6.0 × ULN
Chemistry	Calcium	mmol/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 2.9 mmol/L Grade 2: > 2.9 – 3.1 mmol/L Grade 3: > 3.1 – 3.4 mmol/L Grade 4: >3.4 mmol/L
			Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 2.0 mmol/L Grade 2: < 2.0 -1.75 mmol/L Grade 3: < 1.75 – 1.50 mmol/L Grade 4: < 1.50 mmol/L

Table 4. CTCAE Toxicity Laboratory Grading Chart

Panel	Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v5.0)
Chemistry	Phosphorus	mmol/L	Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 0.8 mmol/L Grade 2: < 0.8 – 0.6 mmol/L Grade 3: < 0.6 – 0.3 mmol/L Grade 4: < 0.3 mmol
Chemistry	Glucose	mmol/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 8.9 mmol/L Grade 2: > 8.9 – 13.9 mmol/L Grade 3: > 13.9 – 27.8 mmol/L Grade 4: >27.8 mmol/L
			Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 3.0 mmol/L Grade 2: < 3.0 -2.2 mmol/L Grade 3: < 2.2 – 1.7 mmol/L Grade 4: < 1.7 mmol/L
Chemistry	Uric Acid	umol/L	Increase	Grade 0: ≤ ULN Grade 1: >ULN – 590 umol/L Grade 2: > 590 umol/L Grade 3: undefined Grade 4: undefined
Chemistry	Sodium	mmol/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 150 mmol/L Grade 2: > 150 – 155 mmol/L Grade 3: > 155 – 160 mmol/L Grade 4: > 160 mmol/L
			Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 130 mmol/L Grade 2: Not defined Grade 3: < 130 – 120 mmol/L Grade 4: < 120 mmol/L
Chemistry	Potassium	mmol/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 5.5 mmol/L Grade 2: > 5.5 – 6.0 mmol/L Grade 3: > 6.0 – 7.0 mmol/L Grade 4: > 7.0 mmol/L

Table 4. CTCAE Toxicity Laboratory Grading Chart

Panel	Analyte	Standard Unit	Directional Change of Interest	Toxicity Grades (CTCAE v5.0)
			Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 3.0 mmol/L Grade 2: Not defined Grade 3: < 3.0 – 2.5 mmol/L Grade 4: < 2.5 mmol/L
Chemistry	Magnesium	mmol/L	Increase	Grade 0: ≤ ULN Grade 1: > ULN – 1.23 mmol/L Grade 2: Not defined Grade 3: > 1.23 – 3.30 mmol/L Grade 4: > 3.30 mmol/L
			Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 0.5 mmol/L Grade 2: < 0.5 – 0.4 mmol/L Grade 3: < 0.4 – 0.3 mmol/L Grade 4: < 0.3 mmol/L
Urinalysis	pH		Decrease	Grade 0: ≥ LLN Grade 1: < LLN – 7.3 Grade 2: Not defined Grade 3: < 7.3 Grade 4: Not defined

13 SCHEDULE OF STUDY ASSESSMENTS

Study Day	Screening Period[a] -Day -28 to Day -1	Treatment Period					Follow-Up Period (No Study Treatment)	
		Baseline (Day 1)[b]	Day 15[b]	Day 29[b]	Day 43[b]	Day 57[b]	Day 85	Day 113
Visit Window (± Days)	--	--	± 1	± 3	± 3	± 3	± 7	± 7
Informed Consent	X							
Site Visit	X	X	X	X	X	X	X	X
Med History and Demographics	X							
Vital Signs[c]	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Height	X							
Physical Examination[d]	X[d]	X[d]	X	X	X	X	X	X[d]
12-Lead ECG[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X	X
C-SSRS	X	X		X		X	X	
Efficacy Assessments[f]								
MG-ADL	X	X	X	X	X	X	X	X
QMG	X	X	X	X	X	X	X	X
MG-QoL15r		X	X	X	X	X	X	X
MGFA Clinical Classification	X	X				X		X
MGFA-PIS – selected elements						X		X
Pregnancy test (women of childbearing potential, and menopausal females if FSH is not elevated)[g]	X	X						

Study Day	Screening Period[a] -Day -28 to Day -1	Treatment Period					Follow-Up Period (No Study Treatment)	
		Baseline (Day 1)[b]	Day 15[b]	Day 29[b]	Day 43[b]	Day 57[b]	Day 85	Day 113
Visit Window (± Days)	--	--	± 1	± 3	± 3	± 3	± 7	± 7
Blood sample for FSH (menopausal females only)[g]	X							
QuantiFERON-Gold TB Test[h]	X							
Blood sample for HIV-1 & 2, Hepatitis B (HBV core antibody), Hepatitis C	X							
Blood sample for anti-AChR and anti-MuSK autoantibody levels[i]	X[i]	X	X	X	X	X	X	X
Blood sample for exploratory biomarkers	--	X		X		X	X	X
Safety Laboratory Testing[j]	X	X	X	X	X	X	X	X
Blood sample for total and neutralizing anti- M281 antibodies		X	X	X	X	X	X	X
Blood sample for levels of total IgG and IgG subclasses	X	X	X	X	X	X	X	X[k]
Blood sample for IgA, IgM, and IgE levels		X		X		X		X
Confirm Patient Eligibility and Randomize[l]		X						
Serum PK[m]		X[m]	X[m]	X[m]	X[m]	X[m]	X	
Study Drug Infusion[b]		X	X	X	X	X		
AEs / Prior and Concomitant Medications/Rescue Therapy[n]	Monitored throughout the study							

Study Day	Screening Period[a] -Day -28 to Day -1	Treatment Period					Follow-Up Period (No Study Treatment)	
		Baseline (Day 1)[b]	Day 15[b]	Day 29[b]	Day 43[b]	Day 57[b]	Day 85	Day 113
Visit Window (± Days)	--	--	± 1	± 3	± 3	± 3	± 7	± 7

Abbreviations: AE = adverse event; anti-AChR= anti-acetylcholine receptor autoantibody; anti-MuSK = anti-muscle-specific kinase autoantibody; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HBV= hepatitis B virus; HCV = hepatitis C virus; HIV= human immunodeficiency virus; Ig = immunoglobulin; MG = myasthenia gravis; MG-ADL= Myasthenia Gravis – Activities of Daily Living; MGFA-PIS = Myasthenia Gravis Foundation of America Post-intervention status; MG-QoL15r= revised Myasthenia Gravis Quality of Life – 15 Scale; PD = pharmacodynamic; PK = pharmacokinetics; QMG = Quantitative Myasthenia Gravis scale; TB= tuberculosis.

[a] Patients who fail to meet all the entry criteria may be retested as noted in Section 4 of the Study Protocol and in the study manual, and/or rescreened after a period of at least 4 weeks. Details for rescreening procedures will be provided in the study manual.

[b] Infusion to be administered as specified in the Infusion Manual. Patients will be observed for safety after the first 3 infusions per the Infusion Manual; if no clinically relevant AEs related to the infusion are observed in these first 3 infusions, the post-infusion observation period is no longer needed.

[c] Vital signs (temperature, recumbent systolic blood pressure and diastolic blood pressure, and pulse rate) will be measured immediately prior to the start of each infusion. For the first infusion, vital signs will also be measured after completion of the infusion as specified in the Infusion Manual.

[d] Full physical examinations to be performed at Screening, Baseline, and Day 113, and a focused physical examination at all other 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.

[e] 12-lead ECGs will be conducted at every scheduled visit. On infusion days, the ECG will be taken immediately prior to the beginning of the infusion. For the first infusion, a single 12-lead ECG will also be conducted within 10 minutes after the infusion has been completed.

[f] The patient's acetylcholinesterase inhibitor dose must be withheld for approximately 10 hours or longer prior to performing the MG assessments (including those conducted during the Screening Period to determine patient eligibility). All MG assessments must be done starting at approximately the same time of day as performed at Screening, and prior to study drug administration on infusion days. The applicable MG assessments must be performed in the order shown in this Schedule of Study Assessments. Patients may take their dose of acetylcholinesterase inhibitor once the MG assessments are completed.

[g] Women of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 prior to infusion of study drug. Menopausal women must have an elevated follicle-stimulating hormone level (FSH) at Screening; if the FSH is not elevated, menopausal women must have a negative serum pregnancy test to be eligible, and a negative urine pregnancy test on Day 1 prior to infusion of study drug.

[h] Patients with a positive QuantiFERON®-TB Gold test result are excluded from this study. Patients with an equivocal QuantiFERON®-TB Gold test result at Screening will be allowed one retest; if the retest is negative, the patient is eligible. If the retest is positive or equivocal, the patient is excluded from this study.

[i] If the patient receives the first dose of M281 before the Screening results are available and the results are subsequently negative, the patient may be replaced.

[j] Includes chemistry, hematology, coagulation function (including prothrombin time), and urinalysis.

[k] For patients who do not enroll in the open-label extension study, if the total serum IgG is not at least 600 mg/dL at this visit, the investigator must continue to regularly follow the patient until total serum IgG is 600 mg/dL or higher.

[l] Confirmation of patient eligibility on Day 1 is based on the Baseline QMG and MG-ADL scores, Baseline C-SSRS, review of medications/therapies, and negative urine pregnancy test (performed at the study center) for women of childbearing potential before first administration of study drug. Menopausal women must have an elevated FSH or negative serum pregnancy test at Screening and negative urine pregnancy test on Day 1 before first administration of study drug to be eligible.

[m] On infusion days, blood samples for measurement of M281 serum concentrations will be taken immediately prior to the beginning of the infusion. After the first infusion and after the infusion on Day 57, blood samples for measurement of M281 serum concentrations will also be taken post-infusion (as specified in the Infusion Manual).

[n] All medications/therapies to be collected from the time of informed consent throughout the patient's participation in the study. Reporting of AEs will start following the patient signing the informed consent form. Administration of rescue therapy for worsening of MG-related symptoms should also be recorded.