Clinical Trial Protocol: MOM-M281-004

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
Study Number:	MOM-M281-004
Study Phase:	2
Product Name:	M281
IND Number:	138975
EudraCT Number:	2018-002247-28
Indication:	Generalized myasthenia gravis
Investigators:	Multicenter

Sponsor: Momenta Pharmaceuticals, Inc.
301 Binney Street
Cambridge, MA 02142 USA
Telephone: (617) 491-9700

Sponsor Contact: Santiago Arroyo, MD
Chief Medical Officer

Medical Monitor: PPD
Pharmaceutical Product Development, Inc

	Date
Original Protocol:	13 July 2018
Amendment 1:	26 October 2018
Amendment 2:	11 December 2018
Amendment 3:	04 June 2019
Amendment 3.2:	28 August 2019

SYNOPSIS

Sponsor:

Momenta Pharmaceuticals, Inc.

Name of Finished Product:
M281

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

Study Number:
MOM-M281-004

Study Phase: 2

Primary Objective(s):
The primary objectives are to evaluate:

- The safety and tolerability of treatment with M281 in patients with generalized myasthenia gravis (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 Myasthenia Gravis – Activities of Daily Living (MG-ADL) score.

Secondary Objective(s):
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 pharmacokinetics (PK) of M281, and
- The pharmacodynamic (PD) activity of M281 as measured by effects on total serum immunoglobulin (Ig)G concentrations.

Exploratory Objective(s):
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-acetylcholine receptor [anti-AChR] and anti-muscle-specific kinase [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.

Study Design:
This multicenter, randomized, double-blind, placebo-controlled study is designed to evaluate the safety, tolerability, efficacy, PK, PD, and immunogenicity of M281 compared with placebo when administered by intravenous (IV) infusion to patients with 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-MuSK vs anti-AChR), and for patients positive for anti-AChR, the randomization will be further stratified by Baseline 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. Pharmacokinetic samples, vital signs, and an electrocardiogram (ECG) will be obtained before the start of each 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.

Study Population:
Approximately 60 randomized patients with gMG. The sample size may be increased by up to 30 additional patients based on the results of the interim analysis.

Test Product, Dose, and Mode of Administration:
M281 for IV infusion at doses of 5 mg/kg (Q4W), 30 mg/kg (Q4W), 60 mg/kg (Q2W), and 60 mg/kg as a single dose

Placebo for IV infusion

Duration of Treatment:
8 weeks

Efficacy Assessments:
Efficacy will be assessed using the following measures in the following order: MG-ADL, QMG, MG-QoL15r, Myasthenia Gravis Foundation of America (MGFA) Clinical Classification, and selected elements of the MGFA Post-intervention Status (MGFA-PIS).

Safety Assessments:
Safety assessments include collection of AEs and serious AEs (SAEs), vital signs, physical examinations, clinical laboratory testing (including chemistry, hematology, coagulation, and urinalysis), ECG findings, and the Columbia-Suicide Severity Rating Scale (C-SSRS). After the patient has signed the informed consent, any new clinically relevant finding or worsening of a pre-existing condition will be reported as an AE.

Events of severe infection and hypoalbuminemia (Grade 3 or higher according to the Common Terminology Criteria for Adverse Events [CTCAE] v5.0) will be considered AEs of special interest (AESIs).

Pharmacokinetic Assessments:
Blood samples will be drawn for analysis of M281 concentrations.

Assessments of Pharmacodynamics and Biomarkers:
Blood samples will be drawn for analysis of the following PD parameters: concentrations of total serum IgG, and titers of anti-AChR and anti-MuSK autoantibodies. Exploratory PD will evaluate changes in serum concentrations of IgG subclasses (IgG1, IgG2, IgG3, IgG4), and IgA, IgM, and IgE. Additional blood samples will be drawn to explore characteristics of pathogenic MG antibodies (anti-AChR and anti-MuSK).

Immunogenicity Assessments:
Total and neutralizing anti-M281 antibodies will be assessed, as applicable.

Statistical Methods:
Adverse events will be coded using a standardized medical dictionary (Medical Dictionary for Regulatory Activities [MedDRA]) and tabular summaries of proportions of patients with AEs in each treatment group will be presented. 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 C-SSRS.

The primary efficacy endpoint is change from baseline to Day 57 in the total MG-ADL score for each treatment group compared with placebo. A mixed-effect model repeat measures (MMRM) analysis including data at Days 15, 29, 43, and 57 will be used for the primary efficacy analysis.

Serum concentrations of M281, PD parameters, and immunogenicity results will be summarized using descriptive statistics. Selected serum biomarkers will be assayed and their potential relationship to clinical status may be explored.

An interim analysis will be performed when approximately 30 patients have completed the Day 57 assessments. The results will be used to adjust the sample size, if necessary, and to guide future development activities. If the model adjusted standard deviation of MG-ADL change from baseline is >4.0, up to 30 additional patients may be recruited.

Date of Protocol Amendment 3.2: 28 August 2019

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AChR	acetylcholine receptor
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CK	creatine kinase
CRA	clinical research associate
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
D5W	dextrose 5% in water
DSMB	Drug Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
FcRn	neonatal Fc receptor
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IVIG	intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis

MG-ADL	Myasthenia Gravis – Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post-intervention Status
MG-QoL15r	Revised Myasthenia Gravis Quality of Life – 15 Scale
MMRM	mixed-effects model repeated measures
MuSK	muscle-specific kinase
nADA	neutralizing anti-drug antibody
NCS	not clinically significant
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
Q2W	every 2 weeks
Q4W	every 4 weeks
QMG	Quantitative Myasthenia Gravis
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SAP	statistical analysis plan
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
US FDA	United States Food and Drug Administration

1 INTRODUCTION

Myasthenia gravis (MG) is a rare, heterogeneous, neuromuscular disease characterized by fluctuating, fatigable muscle weakness. Generalized myasthenia gravis (gMG) is characterized by the fluctuating and variable combination of weakness in ocular, bulbar, limb, neck, and respiratory muscles. Myasthenia gravis is caused by pathogenic autoantibodies directed against proteins in the postsynaptic membrane of the neuromuscular junction. In most patients (approximately 85% of cases), circulating antibodies target the acetylcholine receptor (AChR); to a lesser extent (<10% of cases), antibodies to the muscle-specific kinase (MuSK), or lipoprotein-related protein 4 are present (Meriggioli and Sanders 2012; Zhang et al 2012).

Preferred symptomatic treatment is with the acetylcholinesterase inhibitor, pyridostigmine. However, to meet the treatment goals of restoring or maintaining full or nearly full physical function and high quality of life, most patients with MG also require treatment with immunosuppressive medication(s) (Gilhus 2016; Gilhus et al 2016; Mantegazza and Antozzi 2018). This includes treatment aimed at reducing the production of autoantibodies, such as immunosuppression with corticosteroids and second-line agents (azathioprine, cyclophosphamide, mycophenolate mofetil/mycophenolic acid, and B cell modification/ablation), as well as those aimed at increasing autoantibody removal such as plasma exchange, immunoadsorption, or immunomodulatory doses of intravenous immunoglobulin (IVIG) (Sanders et al 2016; Gilhus 2016; Gilhus et al 2016).

While many patients with gMG can be managed with current therapies, 10%-15% of patients fail to respond adequately to or cannot tolerate multiple therapies for MG and continue to suffer profound muscle weakness and severe disease symptoms that limit function and can be life-threatening (Silvestri and Wolfe 2014; Howard et al 2013; Howard et al 2017; Sanders et al 2016; Sathasivam 2014; Mantegazza and Antozzi 2018), and up to 80% fail to achieve complete and stable remission (Mantegazza 2018). Despite medical advances in patient care, a recent analysis of data from patient registries indicates that gMG is still associated with increased mortality compared to the general population, with an estimated mortality rate ratio of 1.4 (range 1.24–1.60) (Hansen et al 2016). Thus, there is a clear unmet medical need for new safe and effective treatments for gMG.

Momenta Pharmaceuticals, Inc. (Momenta) is developing M281 for the treatment of MG, with an initial focus on patients with gMG. M281 is a fully human, aglycosylated immunoglobulin (Ig)G1 antibody that targets the neonatal Fc receptor (FcRn) IgG binding site with high affinity, thereby interfering with the binding of native IgG. In cells of the reticuloendothelial system, FcRn binding of IgG protects it from degradation and contributes to its long half-life. Interference with FcRn function leads to a decrease in IgG levels. In patients with gMG, M281 is expected to reduce circulating levels of antibodies by blocking IgG recycling, including the pathogenic autoantibodies that cause MG, and to ameliorate manifestations of the disease.

The efficacy of blocking FcRn with anti-FcRn antibodies has been demonstrated in an experimental animal model of autoimmune MG. In this study, administration of an anti-rat

FcRn monoclonal antibody resulted in a dose-dependent amelioration of disease symptoms induced by administration of an anti-AChR monoclonal antibody, and a corresponding reduction in serum concentration of pathogenic antibody (Liu et al 2007).

In humans, intravenous (IV) administration of an anti-FcRn IgG4 monoclonal antibody (rozanolixizumab) was shown to decrease IgG levels in healthy volunteers to approximately 50% of baseline following a single 7-mg/kg dose (Kiessling et al 2017). Similar results were observed in a Phase 1 study of the humanized IgG4 monoclonal antibody, SYNT001, where single IV infusions at doses of 1, 3, 10, and 30 mg/kg produced dose-dependent reductions in IgG, with a nadir of 47% in the 30 mg/kg dose group (Blumberg et al 2017), and a Phase 1 study of the antibody Fc-fragment, ARGX-113, where a single IV infusion of 10 mg/kg drug reduced IgG by 50% and multiple infusions (up to 4 weekly infusions) reduced IgG by up to 85% (Argenx 2017). Preliminary data from an ongoing Phase 2, double-blind, placebo-controlled study of ARGX-113 (4 weekly IV infusions of 10 mg/kg ARGX-113 vs placebo) in patients with gMG showed promising results, with 75% of patients in the ARGX-113 group showing a clinically meaningful and statistically significant improvement in symptoms as measured by the Myasthenia Gravis – Activities of Daily Living (MG-ADL) scale for a period of at least 6 consecutive weeks (versus 25% of patients on placebo) (Argenx 2017). These clinical studies demonstrate that interference with IgG binding to FcRn rapidly decreases IgG to low but predictable steady state levels, and thus should rapidly and effectively decrease circulating levels of pathogenic autoantibodies to ameliorate pathology and morbidity associated with gMG.

Potential Risks and Plans for Mitigation

Reduction of Serum Albumin Levels:

Asymptomatic decreases in serum albumin concentrations to a mean of 20% to 25% decrease from baseline were observed in the Phase 1 clinical study (MOM-M281-001). This mild hypoalbuminemia was self-limited over the duration of dosing of M281 and recovered rapidly following dose cessation. To mitigate any potential risk of hypoalbuminemia in the present study, patients need to have a normal serum albumin level to be eligible for entering the study. Serum albumin levels and clinical symptoms related to hypoalbuminemia will be monitored throughout the study, and hypoalbuminemia-related adverse event (AE) stopping rules are included in Section 6.7.1 of this protocol.

Reduction of Circulating IgG Levels:

In the Phase 1 clinical study (MOM-M281-001), subjects administered with M281 showed dose-dependent reduction of circulating IgG levels, which is an anticipated pharmacodynamic (PD) effect of M281 and contributes to its potential benefit in MG. It is important to note that the normal immune response to produce IgM and IgG in response to a foreign antigen proceeds during treatment with FcRn blockers (Nixon et al 2015). To date, M281 has not been associated with an increase in infection-related events in nonclinical or clinical studies. Published clinical studies of other investigational agents that interfere with FcRn have not revealed an increase in incidence or severity of infections (Kiessling et al 2017; Argenx 2017; Blumberg et al 2017; Robak et al 2017). These observations are

suggestive, but not definitive, that the risk for infections associated with M281 administration may prove to be low. Given the theoretical potential for increased infection risk with reduced circulating IgG levels, procedures have been included in this protocol to mitigate the theoretical risk, including related criteria for study eligibility and infection-related AE stopping rules.

Elevation of Serum Creatine Kinase (CK):

Transient and asymptomatic elevations in serum CK levels were observed in 3 subjects in the 15 mg/kg multiple-ascending-dose cohort in the Phase 1 study. No CK elevations were observed in any of the preclinical studies of M281. To mitigate any potential risk in the present study, patients who have serum CK level ≥2 × upper limit of normal (ULN) are excluded from entering the study. Serum CK levels will be monitored during the study and CK-related AE stopping rules are included in Section 6.7.1 of this protocol.

Altogether, the current evidence from animal and human studies of FcRn blockade suggests that inhibition of FcRn-mediated IgG recycling by M281 may prove to be an effective treatment for patients with gMG. A completed study of M281 in healthy volunteers (MOM-M281-001) showed that M281 was well tolerated at single doses up to 60 mg/kg (the highest single dose tested) and at multiple doses up to 30 mg/kg (the highest repeat dose tested). This first study in patients with gMG will evaluate the therapeutic potential of single (60 mg/kg) and repeat doses of M281 (5, 30, and 60 mg/kg) for the treatment of patients with gMG, with the goal of determining the optimal dose and regimen for the Phase 3 study.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study 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 of this study 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 pharmacokinetics (PK) of M281, and
- The PD activity of M281 as measured by effects on total serum IgG concentrations.

2.3 Exploratory Objective(s)

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.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This multicenter, randomized, double-blind, placebo-controlled study is designed to evaluate the safety, tolerability, efficacy, PK, PD, and immunogenicity of M281 compared with placebo when administered by IV infusion to patients with 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-MuSK vs anti-AChR), and for patients positive for anti-AChR, the randomization will be further stratified by Baseline 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. Pharmacokinetic samples, vital signs, and an electrocardiogram (ECG) will be obtained before the start of each infusion. 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. 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.

The Schedule of Study Assessments is provided in Section 6.

3.2 Rationale for Study Design and Control Group

The study will enroll patients with gMG who have an insufficient clinical response (defined as a QMG score of ≥12 and MG-ADL score of ≥4) to ongoing, stable standard of care therapy. Considering the intended effects of M281 on IgG levels and the role of pathogenic autoantibodies in gMG, these patients are likely to benefit from treatment with M281 and are likely to represent the target population.

A randomized, double-blind, placebo-controlled, parallel group study design was chosen because it is the most robust study design. A placebo comparator arm was chosen for this study as it provides the most valid comparison versus active treatment for the analyses of safety, efficacy, PK, PD, and immunogenicity. A placebo arm is warranted because patients in this study are not required to stop their current standard of care medications; patients can remain on stable doses of their current pharmacologic therapies (eg, glucocorticosteroids, acetylcholinesterase inhibitors, immunosuppressants, other remedies/supplements) throughout the study. The parallel group design allows recruitment of patients for all treatment arms with the same time frame, thus avoiding the potential problem of imbalance when cohorts are recruited sequentially.

The doses of M281 chosen for administration during this study (5 mg/kg Q4W, 30 mg/kg Q4W, 60 mg/kg single dose, 60 mg/kg Q2W) were selected to ensure safety and tolerability while attempting to map the efficacious dose and dose regimen range for the treatment of patients with gMG. The doses consider safety, tolerability, and potential efficacy using data derived from nonclinical studies in nonhuman and data from the completed Phase 1 study of M281 in healthy normal volunteers, MOM-M281-001. The no observed adverse effect level in the 26-week, repeat-dose, Good Laboratory Practice-compliant toxicology study in cynomolgus monkeys was the highest dose tested of 300 mg/kg, which is 5-fold higher than the maximum proposed dose in this study (60 mg/kg Q2W) on a dose basis and 10-fold higher on a dose-per-week basis. Moreover, all dose levels administered in the Phase 1 study

in humans (up to 60 mg/kg single doses and up to 30 mg/kg once weekly for up to 4 weeks) were considered safe and well tolerated. Analysis of PK data following single doses at 60 mg/kg indicates that negligible accumulation will occur with Q2W dosing, suggesting that the clinically observed maximum serum concentration and area under the concentration-time curve are not likely to be exceeded. No accumulation is anticipated with Q4W dose regimens.

The efficacy of M281 in gMG is expected to be related to total serum IgG lowering. Therefore, IgG lowering was examined to select the doses to predict efficacy. The highest dose of 60 mg/kg Q2W was selected to saturate the FcRn target for the full dosing interval (thereby minimizing total serum IgG concentration), while the lowest dose of 5 mg/kg Q4W was selected to target minimally differentiated IgG lowering from placebo at trough. Intermediate doses were selected with the goal of maximizing the potential for differentiation with the percentage of total serum IgG lowering. A single-dose arm at the highest planned dose level for this study (60 mg/kg) is included based on observations in the first-in-human study and simulations that indicate a profound IgG lowering effect at this dose level.

The effects of M281 on IgG levels and the potential for symptom improvement are anticipated to be rapid; therefore, an 8-week Treatment Period is deemed sufficient for this study. The 8-week Follow-up Period will allow for full characterization of the duration of efficacy and PK after the last infusion of M281 and will allow for observation of the return of PD parameters.

3.3 Study Duration and Dates

The study includes a Screening Period of up to 4 weeks, an 8-week Treatment Period, and an 8-week Follow-up Period (beginning after the last infusion) for a total study duration of 20 weeks.

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 60 patients with gMG will be enrolled in this study among approximately 60 study centers internationally.

4.2 Inclusion Criteria

Each patient must meet the following criteria to be eligible for this study.

1. Is a male or female outpatient ≥18 years of age.
2. Has a documented history of gMG and clinical signs/symptoms of gMG.
3. Has a documented diagnosis of gMG by a positive serologic test for a gMG-related pathogenic autoantibody (anti-AChR or anti-MuSK autoantibodies), confirmed prior to randomization, and is on stable therapy for MG. 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.

4. Has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II, III, or IVa at Screening.
5. Has a QMG score of ≥12 and MG-ADL score of ≥4 at Screening and Baseline.
6. If taking a glucocorticosteroid, the patient must provide/obtain documentation showing the dose and regimen has been stable for at least 4 weeks prior to Screening.
7. If taking an acetylcholinesterase inhibitor, the patient must provide/obtain documentation showing the dose and regimen has been stable for at least 2 weeks prior to randomization on Day 1.
8. If taking statins at Screening, the patient must provide/obtain documentation showing the dose and regimen has been stable for at least 2 months prior to Screening.
9. If currently receiving immunosuppressants, the patient must provide/obtain documentation showing that the patient has been on the given immunosuppressant for ≥6 months and has been on a stable dose for ≥3 months prior to Screening. Allowed concomitant immunosuppressants are azathioprine, mycophenolate mofetil/ mycophenolic acid, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide.
10. Has total serum IgG at or higher than the lower limit of normal at Screening. However, if the patient is on immunomodulatory agents, the patient may be included as long as the IgG level is not lower than 75% of the lower limit of normal.
11. Has serum albumin and serum calcium concentrations within the normal range of the reference laboratory at Screening.
12. Has sufficient venous access to allow drug administration by infusion and blood sampling as per the protocol.
13. Is up to date on all age-appropriate vaccinations as per routine local medical guidelines.
14. *[This inclusion criterion was removed under Amendment 3.2; original numbering was retained.]*
15. Women of childbearing potential, defined as women physiologically capable of becoming pregnant, must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at Baseline. Menopausal women must have an elevated serum follicle-stimulating hormone level (FSH) at Screening; if the FSH is not elevated, they are considered to be of childbearing potential and must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline to be eligible.
16. Women of childbearing potential (including menopausal women who do not have elevated FSH) must agree to remain totally abstinent (ie, refrain from sexual intercourse during the study) or to consistently use a reliable and highly effective method of contraception (eg, condom plus diaphragm, condom plus spermicide, diaphragm plus spermicide, or intrauterine device or oral/injectable/implanted hormonal contraceptive used in combination with an additional barrier method) during the study and for 30 days after the last study treatment.
    Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.
17. Male patients must agree to remain totally abstinent (ie, refrain from sexual intercourse during the study) or to consistently use a reliable and highly effective method of contraception (eg, condom plus diaphragm, condom plus spermicide, diaphragm plus spermicide, or intrauterine device or oral/injectable/implanted hormonal contraceptive

used in combination with an additional barrier method) to avoid pregnancy of the patient's partner(s) during the study and for 100 days following the last study treatment, unless the patient provides documentation of a vasectomy at least 6 months prior to Screening. Male patients must also abstain from sperm donation during the study and for 100 days following the last treatment.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

18. A patient using herbal, naturopathic, and traditional Chinese remedies and ayurvedic and nutritional supplements is eligible if the use of these medications is acceptable to the Investigator. These remedies must be at a stable dose and regimen using the same preparation for ≥2 months prior to Screening.
19. Is able to understand and voluntarily provide written informed consent to participate in the study and comply with all study procedures.

4.3 Exclusion Criteria

Patients who meet any of the following criteria (at Screening unless otherwise specified) will be excluded from the study.

1. Has MGFA Class I, IVb, or V disease, or presence of MG crisis (MGFA Class V) at Screening or Baseline, history of MG crisis within 1 month of the Screening visit, or fixed weakness (and/or 'burnt out' MG). If the clinical status of the patient changes such that the patient meets Inclusion Criterion #4 (MGFA Clinical Class II, III, or IVa), the patient can be re-screened once.
2. Has received rituximab or eculizumab within 12 months prior to Screening.
3. Has received plasmapheresis, immunoadsorption therapy, or IVIG within 6 weeks prior to randomization on Day 1. The patient may be re-screened after the exclusionary period of 6 weeks has passed.
4. Has a gastric tube or is ventilator dependent.
5. Has an unresected thymoma (based on imaging results) or any history of malignant thymoma.
6. Has had a thymectomy within 12 months prior to Screening, or thymectomy is planned during the study.
7. Has a history of any neurologic disorder other than MG that might interfere with the accuracy of study assessments, including but not limited to any chronic neurodegenerative disease, major congenital neurologic defect or Lambert-Eaton myasthenic syndrome, drug-induced MG, or hereditary forms of myasthenic syndrome.
8. Has an altered level of consciousness, dementia, or abnormal mental status.
9. Has current suicidal ideation evidenced by a "yes" response to Questions 4 or 5 in the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening or Baseline, or a history of active suicidal ideation or suicidal behavior in the past year prior to Screening.

10. Is currently breastfeeding, pregnant, intends to become pregnant during the study, or is planning egg donation during the study or within 30 days after the last dose of study drug.
11. Has a serious or clinically significant infection (eg, pneumonia, biliary tract infection, diverticulitis, *Clostridium difficile* infection) requiring parenteral anti-infectives and/or hospitalization, within 8 weeks prior to Screening. The patient may be re-screened after the 8-week exclusionary period has passed. Any patient with an infection requiring oral anti-infectives, (eg, sinusitis, bronchitis, uncomplicated urinary tract infection), within the 4 weeks prior to Screening will be excluded, but may be subsequently re-screened after the 4-week exclusionary period has passed.
    Note: An uncomplicated, presumably viral, upper respiratory tract infection (eg, 'the common cold') is not an exclusion.
12. Has a chronic infection (eg, bronchiectasis, chronic osteomyelitis, chronic pyelonephritis) or requires chronic treatment with anti-infectives (eg, antibiotics, antivirals).
13. Has received a live vaccine within 3 months prior to Screening, or has a known need to receive a live vaccine during the study or within at least 3 months after the last dose of study drug in this study. The patient can be re-screened after the 3-month exclusionary period has ended.
14. Has any confirmed or suspected clinical immunodeficiency syndrome not related to treatment of his/her gMG, including human immunodeficiency virus (HIV) infection, or has a family history of congenital or hereditary immunodeficiency unless confirmed absent in the patient.
15. Has a positive or equivocal QuantiFERON®-TB Gold test, and/or a known close exposure to family or individuals known to have tuberculosis (TB).
    Note: A patient with an equivocal QuantiFERON®-TB Gold test result will be allowed one retest; if the retest is negative, the patient is eligible. If the retest is positive, the patient is excluded from this study. If the retest remains equivocal and the patient has no known risk factors or exposures to TB, the patient can be included in the study after consultation with Medical Monitor.
16. Has a history of or positive test results for HIV-1 and HIV-2 antibodies, hepatitis B virus (HBV core antibody), or hepatitis C virus (HCV). Patients who have been treated for HCV and demonstrate a negative serum HCV ribonucleic acid level at 12 weeks or longer after the completion of HCV therapy may be included in the study after consultation with the Medical Monitor. Patients with spontaneous resolution of HCV (as confirmed by specialist) may be included in the study if demonstrating a negative serum HCV ribonucleic acid level after consultation with the Medical Monitor.
17. Has current alcohol/substance abuse/dependence, a history of alcohol/substance abuse/dependence within the 12 months prior to Screening, or in the Investigator's opinion, shows evidence of ongoing alcohol/substance abuse/dependence.
18. Is currently participating in another interventional clinical trial, or has received any investigational drug (eg, abatacept, belimumab) within five half-lives of the given investigational drug.
19. Has donated or had significant loss of whole blood (480 mL or more) within 30 days, or plasma within 14 days prior to Screening. The patient can be re-screened after the relevant exclusionary period has passed.

20. Had any major surgery within 3 months prior to Screening, or has plans for or has been scheduled for any elective surgery or any major dental procedure during the study.
21. Has a history of a major organ transplant (eg, heart, lung, kidney, liver), or hematopoietic stem cell/marrow transplant.
22. Received treatment for malignancy within the 5 years prior to Screening, with the exceptions of properly treated basal or squamous cell carcinoma of the skin or properly treated carcinoma in situ of the cervix.
23. Has a hypersensitivity to M281 or any constituent of the study drug solution.
24. Has had a prior severe drug reaction that included shock or severe hypersensitivity.
25. Has liver impairment with Child-Pugh Class B or C.
26. Has a history of severe and/or uncontrolled hepatic, gastrointestinal, renal, pulmonary, cardiovascular, psychiatric, or musculoskeletal disorder, hypertension, or any other medical or autoimmune disorder that, in the opinion of the Investigator, might interfere with patient's full participation in the study, or might jeopardize the safety of the patient or the validity of the study results.
27. Has any other medical condition(s) likely to require treatment with oral or parenteral glucocorticosteroids (eg, severe asthma), or has required oral or parenteral glucocorticosteroids in the past 3 months (inhalational, intra-articular, topical or ocular glucocorticosteroids are not exclusionary), or taking any immunosuppressive agents not being used to treat MG.
28. Is receiving a systemic biologic antibody for any concurrent disease.
29. Has a QT interval corrected for heart rate (QTc) of >450 msec for males or >470 msec for females; or QTc >480 msec in patients with Bundle Branch Block, by the Fridericia formula.
30. Has any of the following abnormal laboratory values at Screening: aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase ≥2× ULN; or bilirubin ≥1.5× ULN (isolated bilirubin greater than 1.5× ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%, or if there is a prior diagnosis of Gilbert disease without any condition that causes elevation of bilirubin). Note: AST, ALT, alkaline phosphatase, or bilirubin levels that lead to exclusion can be re-tested once within the Screening Period and within 2 weeks of the first test. If the repeat test is still outside of the normal range, the patient can be re-screened once provided rescreening is approved by the Medical Monitor.
31. Has elevated CK ≥2× ULN at Screening. However, if the patient has CK ≥2× ULN and <5× ULN at Screening, and in the opinion of the investigator the patient has no CK-related disease and the CK level is believed to be the results of non-pathologic factors, the CK may be repeated and if stable/improved, the patient can be enrolled. Note: Patients who are ineligible because of elevated CK values can be re-tested as appropriate within the 4-week Screening Period. If the repeat test(s) is still outside of the normal range, the patient can be re-screened once.
32. Has had a splenectomy.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Study Drug

M281 is a sterile solution intended for IV infusion following dilution with dextrose 5% in water (D5W). It will be supplied in an open-label fashion to the study centers in 20-mL glass vials nominally containing 30 mg/mL (600 mg) of M281 protein in solution. The glass vial has a 20 mm chlorobutyl stopper and an aluminum overseal.

M281 is formulated to a target concentration of 30 mg/mL in 25 mM sodium phosphate, 25 mM sodium chloride, 8.7% weight/weight trehalose, 0.01% weight/volume polysorbate 80, pH 6.5.

5.1.2 Placebo

Placebo for IV infusion may be sourced by the study center or supplied by the Sponsor based on local regulations and availability.

5.2 Treatments Administered

M281 will be diluted with D5W and administered by IV infusion at doses of 5 mg/kg Q4W, 30 mg/kg Q4W, 60 mg/kg Q2W, or 60 mg/kg as a single dose based on the patient's body weight at Baseline. There will be no dosage adjustment for weight gained or lost during the study. Placebo will be administered in the same manner.

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.

Details for preparation of the infusion will be provided in the Drug Handling Manual. Infusion is to be administered as specified in the Infusion Manual.

5.3 Selection and Timing of Dose for Each Patient

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 over the 8-week treatment period as shown in Table 1. 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 (Table 2 in Section 6). 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.

Table 1. Selection and Timing of Infusions for Each Treatment Arm

Treatment Arm	Infusion Timepoints				
	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
M281 60 mg/kg Q2W	M281	M281	M281	M281	M281

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

5.4 Method of Assigning Patients to Treatment Groups

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.

5.5 Blinding

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 (ie, 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 8.8.

5.6 Concomitant Therapy

Patients must continue their baseline stable therapeutic regimen (standard of care) for gMG throughout the duration of the study and must maintain the same dose and regimen throughout the study, unless toxicity or safety issues mandate a change. All medications/therapies administered to patients at any time during the study (from the time the patient signs the informed consent), or changes to the dose/regimen of any medication/therapy, are to be recorded in the electronic case report form (eCRF).

Use of herbal, naturopathic, and traditional Chinese remedies, and ayurvedic and nutritional supplements may also continue during the study, if the patient is on a stable dose and regimen at study entry and the use of these medications is acceptable to the Investigator. The patient must maintain the same dose and regimen using the same preparation throughout the study.

5.7 Restrictions

5.7.1 Prior Therapy

Patients who received rituximab or eculizumab within 12 months prior to Screening are not eligible for the study. Patients who underwent plasmapheresis, received immunoadsorption therapy, or received IVIG within 6 weeks prior to Randomization are not eligible for the study (see Section 4.3, Exclusion Criteria).

Patients must continue their baseline stable therapeutic regimen (standard of care) throughout the duration of the study (see Section 4.2, Inclusion Criteria) with the exception that acetylcholinesterase inhibitors must be withheld for approximately 10 hours or longer at each study visit before the assessments of MG symptoms/status (efficacy assessments) are conducted. If possible, all efficacy assessments should be done at approximately the same time of day as performed at Screening, prior to study drug administration, and in the order defined in the Schedule of Study Assessments (Table 2 of Section 6). Patients may take their dose of acetylcholinesterase inhibitor once the efficacy assessments are completed.

5.7.2 Fluid and Food Intake

Patients are not required to be fasting at any time during the study and the study does not include any requirements with respect to food intake. Patients may only have room temperature food/fluids within 1 hour before the efficacy assessments are conducted and until efficacy assessments are completed.

5.7.3 Patient Activity Restrictions

Patients may continue their usual activities, including exercise, during the study, but patients should not begin any new exercise program during the study, or have excessive exertion on the day of or day before a study visit.

5.8 Treatment Compliance

Scheduled IV infusions of study drug will occur at the study center under observation by study staff, thus ensuring treatment compliance.

5.9 Packaging and Labeling

M281 will be supplied open-label in a carton labeled with the local language. Placebo will also be open-label and should be labeled as required per local regulations.

5.10 Storage and Accountability

Vials of M281 must be stored at 2°C to 8°C in a secure, controlled-access location. Placebo must be stored in a secure, controlled-access location. Storage temperatures for placebo will be detailed in the Drug Handling Manual. M281 and placebo must only be used for patients who have consented to participate in this trial.

At the end of the study, a final reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently destroyed or returned to the Sponsor. A written explanation must be provided for any discrepancies.

6 STUDY ASSESSMENTS AND PROCEDURES

The Schedule of Study Assessments is presented in Table 2.

Table 2. Schedule of Study Assessments

	Screening Period[a] -Day -28 to Day -1	Treatment Period					Follow-Up Period (No Study Treatment)	
Study Day		**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						
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							

Table 2. Schedule of Study Assessments

	Screening Period[a] -Day -28 to Day -1	Treatment Period					Follow-Up Period (No Study Treatment)	
Study Day		**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 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							

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 and 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.

6.1 Safety Assessments

Safety assessments include collection of AEs and serious AEs (SAEs), vital signs, physical examinations, clinical laboratory testing (including chemistry, hematology, coagulation, and urinalysis), ECG findings, and the C-SSRS. After the patient has signed the informed consent, any new clinically relevant finding or worsening of a pre-existing condition will be reported as an AE.

Severe infections and hypoalbuminemia will be considered AEs of special interest (AESIs).

6.1.1 Adverse Events

An AE can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can therefore be any unfavorable and unintended sign, symptom, disease, concurrent illness, or clinically significant abnormal laboratory finding that emerges or worsens (ie, aggravated in severity or frequency from the baseline condition) during the study. Clinically significant abnormal results of laboratory tests or diagnostic procedures are to be reported as AEs.

6.1.1.1 Performing Adverse Events Assessments

At each contact with the patient, the Investigator or designee will capture AEs by specific questioning and, as appropriate, by examination. Patients will be asked non-leading questions to capture medically related changes to their well-being. Participants will also be asked if they have been hospitalized, had any accidents, sought care from a health professional, used any new medications/therapies, or changed concomitant medication regimens (both prescription and over-the-counter) due to an AE.

6.1.1.2 Timing

Reporting of AEs (including SAEs) will start following the patient signing the informed consent form (ICF). Reporting of AEs will end at the final visit (Day 113).

6.1.1.3 Severity

The Investigator will grade the severity/intensity of each AE using the National Cancer Institute, Common Terminology Criteria for Adverse Events v5.0 (CTCAE) classifications (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

The CTCAE provides specific criteria for grading adverse events as well as laboratory tests; in general, the grades are as follows:

Grade 1, Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2, Moderate: minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living

Grade 3, Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4, Life-threatening consequences; urgent intervention indicated

Grade 5, Death related to AE

6.1.1.4 Relationship

The Investigator must assess all AEs for relationship to study drug by examining and evaluating the patient based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related – There is clear evidence to suggest a causal relationship to study drug; other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probably Related – There is evidence to suggest a causal relationship to study drug, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possibly Related – There is some evidence to suggest a causal relationship to study drug (eg, the event occurred within a reasonable time after administration of the study drug). However, other factors may have contributed to the event (eg, the patient's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship

improbable (eg, the event did not occur within a reasonable time after administration of the study drug) and in which other drugs or chemicals or underlying disease provides plausible explanations (eg, the patient's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

6.1.1.5 Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the Reference Safety Information in the Investigator's Brochure for M281.

6.1.1.6 Adverse Events of Special Interest

For this study, any CTCAE Grade 3 or higher event of severe infection or hypoalbuminemia will be considered an AESI. These cases will be handled similarly to an SAE for reporting purposes and reviewed by the DSMB as they occur.

6.1.1.7 Clinical Laboratory Adverse Events

Investigators will indicate on the laboratory report whether abnormal values are clinically significant (CS) or not clinically significant (NCS). All CS abnormal laboratory results will be considered as AEs and are to be reported in the eCRF.

6.1.1.8 Serious Adverse Events

DEFINITION

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes: death, 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 an SAE 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

REPORTING SERIOUS ADVERSE EVENTS

The Investigator will report to the Sponsor any SAE or AESI within 24 hours of becoming aware of the event, whether or not the event is considered related to study drug. The report

must include an assessment of whether there is a reasonable possibility that the study drug caused the event.

Send SAE and AESI reports to:

MMS Holdings 6880 Commerce Blvd Canton, MI 48187 USA	E-mail: MomentaPharmaDrugSafety@mmsholdings.com

The Sponsor will be responsible for notifying the regulatory authorities per local requirements of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, the Sponsor must notify the regulatory authorities and all participating investigators of any safety reports of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

It is the responsibility of the Sponsor to determine the reportability of SAEs.

All SAEs will be followed until satisfactory resolution or until the Investigator deems the event to be chronic or the patient is stable. Other supporting documentation of the event may be requested by the DSMB or Sponsor and should be provided as soon as possible.

6.1.1.9 Treatment-Emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as any AE occurring during or after the initiation of the first infusion of study drug.

6.1.1.10 Pregnancy

Any pregnancy (including the pregnancy of the partner of a male study patient) occurring from the time the patient signed in the ICF until 30 days (for female patients) or 100 days (for the female partner of a male patient) after the last dose of study treatment must be reported to the Sponsor using a clinical trial pregnancy form. To ensure patient safety, each pregnancy must be reported to the Sponsor, via MMS Holdings, the safety group that will be processing the information (see Section 6.1.1.8), within 24 hours of the Investigator learning of its occurrence. The pregnancy should be followed up to determine outcome (including premature termination) and status of mother and child. The patient and/or patient's partner will be requested to provide written informed consent to enable collection of information pertaining to the outcome of the pregnancy.

While pregnancy itself is not an AE/SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE as appropriate and must be communicated by the Investigator to MMS Holdings within 24 hours of receipt of notification of an event. An abortion, whether accidental, therapeutic,

or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly birth defect in a child born to a patient exposed to the study treatment should be recorded and reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study drug must be promptly reported to MMS Holdings.

6.1.2 Concomitant Medication Assessments

From the time the patient signs the informed consent, all medications/therapies, and procedures administered to patients at any time during the study, including MG rescue medication/therapy, are to be recorded in the eCRF. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications and supplements. Other therapies and procedures (eg, immunizations) are also to be recorded.

6.1.3 Physical Examination

Height will be measured at Screening only. Weight will be measured at Screening and at all other visits. A full physical examination will be performed at Screening, Baseline, and Day 113; at all other visits, a focused physical examination will be performed to determine if there has been any change in neurologic function, upper respiratory tract (ears, nose, throat, and sinuses), eyes and lungs, abdomen, or skin.

6.1.4 Vital Signs

Vital signs measurements will include recumbent blood pressure and pulse rate, and body temperature. The patient will be resting in the recumbent position for 3 to 5 minutes before all vital signs are recorded, according to the practices of the investigative site.

The Investigator will determine if any of the vital sign measurements are clinically significant or not clinically significant. Clinical significance is defined as any variation in assessment results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from screening values is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the patient's eCRF. The Investigator will continue to monitor the patient with additional assessments until the values have reached reference range and/or the values at Screening, or until the Investigator determines that follow-up is no longer medically necessary.

6.1.5 Clinical Laboratory Tests

Patients will be in a seated or supine position during blood collection. Patients are not required to be fasting. Instructions for blood sample collection, processing, storage, and shipping are described in the Laboratory Manual.

Clinical laboratory tests will include the parameters listed in Table 3.

Table 3. List of Clinical Laboratory Tests

Hematology:

- Hematocrit
- Hemoglobin
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Platelet count
- Red blood cell count
- White blood cell count with differential

Urinalysis:

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Nitrite
- Occult blood
- pH
- Protein
- Myoglobin (if serum creatine kinase is elevated)
- Specific gravity
- Urobilinogen

Hepatitis B virus (HBV core antibody), hepatitis C virus, HIV-1 and HIV-2 (at Screening only to assess eligibility)

Serum/urine human chorionic gonadotropin (for females of childbearing potential and menopausal females if follicle-stimulating hormone is not elevated)

Serum follicle-stimulating hormone (only for menopausal females at Screening to assess eligibility)

Serum Chemistry:

- Albumin[a]
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Blood urea nitrogen
- Calcium
- Carbon dioxide
- Chloride
- Creatinine
- Creatine kinase; MB and MM subtypes if creatine kinase is elevated
- Troponin if creatine kinase is elevated
- Gamma-glutamyl transferase
- Glucose
- Lactate dehydrogenase
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

Coagulation:

- Prothrombin time
- Activated partial thromboplastin time

QuantiFERON-Gold tuberculosis test (at Screening only to assess eligibility)

[a] Knowledge of a patient's albumin level could potentially be unblinding; therefore, albumin results obtained after initiation of study drug will not be reported to the patient, Investigator, or Sponsor during study conduct.

Clinically significant changes from baseline in laboratory results must be considered an AE and recorded in the eCRF. Clinical significance is defined as any variation in a laboratory result that has medical relevance and that results in a change in medical care. The

Investigator will continue to monitor the patient until the finding is resolved, or in the judgment of the Investigator follow-up is no longer medically necessary.

6.1.6 Electrocardiograms

A single 12-lead ECG will be obtained after the patient has been in the supine position for at least 5 minutes. A central ECG service will measure and interpret the ECG recordings. Electrocardiogram reports will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T Wave, and U Wave abnormalities. In addition, the following intervals will be measured and reported: RR, PR, QRS, QT, and QTc.

The Investigator will determine if the ECG results are CS or NCS. Clinical significance is defined as any variation in assessment results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If an ECG finding is identified as CS, the patient should be assessed by the Investigator for symptoms (for example, palpitations, near syncope, syncope). Any CS finding should be documented as an AE on the AE eCRF, and the Investigator must to continue to monitor the patient until the finding is resolved, or in the judgment of the Investigator, follow-up is no longer medically necessary.

6.1.7 Columbia-Suicide Severity Rating Scale

The C-SSRS is administered by trained study personnel (ie, C-SSRS certified). The C-SSRS Baseline/Screening version will be used for the Screening Visit, and the C-SSRS Since Last Visit version will be used for subsequent visits as specified in Table 2. When the C-SSRS is administered on an infusion day, the C-SSRS must be administered before the infusion.

Any patient who answers “yes” to Questions 4 or 5 in the Suicidal Ideation section of the C-SSRS at Screening or Baseline should not be enrolled and should be referred to a mental health specialist by the Investigator. During the course of the study after initiation of study treatment, any patient who answers “yes” to Questions 4 or 5 in the Suicidal Ideation section or answers “yes” to any question in the Suicidal Behavior section of the C-SSRS will be referred by Investigators to a mental health specialist. After initiation of study treatment, affirmative answers to Questions 4 or 5 for suicidal ideation or to any question for suicidal behavior will be reported in the eCRF as an AE.

6.2 Efficacy Assessments

6.2.1 Myasthenia Gravis – Activities of Daily Living

The MG-ADL is administered by a trained qualified healthcare professional (eg, physician, physician assistant, nurse practitioner, nurse) and provides a rapid assessment of the patient’s MG symptom severity (Appendix 3). The MG-ADL should be administered by the same healthcare professional for a given patient throughout the study, if possible, and the assessment should be performed at approximately the same time of day throughout the study. Eight functions (talking, chewing, swallowing, breathing, impairment of ability to brush teeth

or comb hair, impairment of ability to arise from a chair, double vision, eyelid droop) are rated on a 4-point scale. The total score can range from 0 to 24. A higher score indicates greater symptom severity.

6.2.2 Quantitative Myasthenia Gravis

The QMG test is a standardized quantitative strength assessment comprising 13 components (Appendix 4) and is administered by a trained qualified healthcare professional (eg, physician, physician assistant, nurse practitioner, nurse). The QMG should be administered by the same healthcare professional for a given patient throughout the study, if possible, and the assessment should be performed at approximately the same time of day throughout the study. The quantitative results of each strength component are mapped to the following 4-point scale:

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

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

6.2.3 Revised Myasthenia Gravis Quality of Life – 15

The MG-QoL15r (Appendix 5) is a 15-item, health-related quality of life measure designed to assess limitations related to living with MG (Burns et al 2016). Responses to each item are rated by the patient, using a reflection period of "over the past few weeks" on the following 3-point scale:

- 0 = Not at all
- 1 = Somewhat
- 2 = Very much

The total score can range from 0 to 30. A higher score indicates more limitation.

6.2.4 Myasthenia Gravis Foundation of America Post-Intervention Status

The Myasthenia Gravis Foundation of America Post-intervention Status (MGFA-PIS) is a measure of the patient's MG status after treatment/intervention (Appendix 6). For the purpose of this study, only two elements of the MGFA-PIS will be assessed.

1. The Investigator will indicate whether or not the patient meets the following definition of Minimal Manifestations:
   - The patient has no symptoms of functional limitations from MG, but has some weakness on examination of some muscles (Yes/No).

2. The patient's change in status will be derived as follows:
   - Improved = A decrease of ≥3 in the QMG score from baseline.
   - Unchanged = No change in the QMG score over baseline.
   - Worse = Any increase in the QMG score over baseline.
   - Died of MG = The patient died of MG or of complications of MG therapy.

6.2.5 Myasthenia Gravis Foundation of America Clinical Classification

This clinical classification system was established by the MGFA for clinician/physician assessment of a patient's MG severity (Jaretzki et al 2000). The system comprises 5 classes of disease severity ranging from Class I (ocular muscle weakness only) to Class V (the patient is intubated). Classes II through IV are each further divided into 2 subclasses based on which muscle groups are primarily affected. The MGFA Clinical Classification should be assessed by the same clinician/physician for a given patient throughout the study, if possible.

6.3 Pharmacokinetic Assessments

Patients will undergo blood sampling as specified in Table 2 to determine serum M281 concentration(s). Instructions for blood collection, processing, storage and shipping are described in the Laboratory Manual.

6.4 Assessments of Pharmacodynamics and Biomarkers

Blood samples for PD analysis of total serum IgG, anti-AChR autoantibodies, and anti-MuSK autoantibodies will be collected. Blood samples will also be collected for assessment of exploratory PD biomarkers in serum (concentrations of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE). Additional blood samples will be collected to explore characteristics of pathogenic MG antibodies (anti-AChR and anti-MuSK). At Screening and Baseline, samples will be tested for both anti-AChR and anti-MuSK; thereafter, samples will only be tested for the antibody that was positive at Screening/Baseline. Blood samples will be collected at the time points specified in Table 2.

Aside from IgA, IgM, and IgE, the PD parameters could potentially be unblinding; therefore, results of PD parameters obtained after initiation of study drug will not be reported to the patient, Investigator, or Sponsor 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.

Instructions for blood sample collection, processing, storage, and shipping are described in the Laboratory Manual.

6.5 Immunogenicity Assessments

Blood samples will be drawn to determine the presence/absence and titers of total and neutralizing anti-M281 antibodies, if applicable. Knowledge of anti-drug antibody (ADA) levels could potentially be unblinding; therefore, these results after initiation of study drug will not be reported to the patient, Investigator, or Sponsor during study conduct.

6.6 Removal of Patients from the Trial or Study Drug

The investigator may withdraw a patient for any of the following reasons:

- A protocol violation occurs,
- A serious or intolerable adverse event occurs,
- A clinically significant change in a laboratory parameter occurs,
- The sponsor or investigator terminates the study, or
- The patient requests to be discontinued from the study.
- If the patient receives the first dose of M281 before the Screening results for autoantibodies (anti-AChR, anti-MuSK) are available and the results are subsequently negative, the patient may be withdrawn and replaced.

6.7 Stopping Criteria

Unless patient safety precludes doing so, the Medical Monitor should be consulted prior to stopping or modifying the dosing schedule of study drug. The DSMB will be informed about any such discussions, with the reason they were initiated, and any laboratory data that was a part of the discussions. Unblinding of study drug in the event of an emergency is the sole responsibility, and will occur at the discretion, of the Investigator; however, if possible, the Medical Monitor should be consulted before unblinding.

Discontinuation of study drug administration does not necessarily mean discontinuation from the study. Patients who discontinue treatment with study drug should be asked to continue in the study to be followed for safety and to complete all remaining study procedures as indicated by this protocol. Any new clinical finding is to be reported as an AE.

6.7.1 Study Drug Stopping/Interruption Rules for Individual Patients

Study drug administration must be stopped, and the Medical Monitor notified, if any of the following events occur:

- A patient becomes pregnant.
- A patient develops a CTCAE Grade 4 infection.
- A patient develops a CTCAE Grade 3 infection that is unresponsive or worsens while on anti-infective therapy.
- Any circumstance or finding that, in the clinical judgment of the Investigator, would represent undue risk to the patient.

Study drug administration may be interrupted after consultation with the Medical Monitor for the following events:

- If a patient develops a CTCAE Grade 3 infection, the Investigator may elect to withhold study drug until the clinical scenario clarifies whether the infection is improving or getting worse.
- If a patient develops 3+ pedal edema, ascites, or pleural or pericardial effusions, the Investigator will monitor the patient's condition. The decision to continue treatment or withhold additional doses of study drug will be made by the Investigator, in consultation with the Medical Monitor.
- If a patient develops elevated CK levels, CK fractionation (CKMB, CKMM) and troponin will be automatically tested by the laboratory. If the CKMB or troponin level is elevated, the patient will be asked to go immediately to the emergency room for further evaluation.

  For any patient with elevated CK levels, additional assessments will be as follows:

  - CK elevations <5× ULN - further assessment can be made at the discretion of the Investigator.
  - CK elevations ≥5× ULN - the Investigator will call the patient to inquire about excessive exercise, trauma, and any muscle or cardiac-related symptoms. CK will be repeated and if there is a decrease, no action will be taken. However, if the CK is of similar or higher level, the patient will be asked to return to the clinic, where further investigation will be done (in-depth clinical assessment, ECG, myoglobin in urine, repeat CK with fractionation and troponin level, ALT, and AST). The decision to continue treatment or withhold additional doses of study drug for the patient will be made by the Investigator, in consultation with the Medical Monitor.

6.7.2 Study Stopping Rules

- In the event of the death of a study patient, treatment will be held in all patients pending evaluation by the Sponsor and DSMB recommendation, and until approval is received by the applicable regulatory authority(ies) to resume.
- If a CTCAE Grade 4 event considered potentially related to treatment occurs, treatment will not be initiated in new patients, pending evaluation by the Sponsor and DSMB recommendation, and until approval is received by the applicable regulatory authority(ies) to resume.
- If a CTCAE Grade 3 or higher infection occurs in three separate patients, treatment will be temporarily held in all patients, pending evaluation by the Sponsor and DSMB recommendation, and until approval is received by the applicable regulatory authority(ies) to resume.

NOTE: Deaths that are definitely not related to study treatment (eg, accidents or other external causes) will not trigger study-stopping rules.

6.8 Other Study Procedures

Clinical Deterioration and Use of Rescue Therapy

Study sites are required to evaluate a patient's report of clinical deterioration within 48 hours of the patient notifying the Investigator of the onset or worsening of symptoms of gMG.

Clinical deterioration is defined as any of the following:

- An MG crisis, defined as MG-related weakness sufficiently severe to necessitate intubation, or requires noninvasive ventilation to avoid intubation, or would be severe enough to delay extubation following surgery (Sanders et al 2016), with the respiratory failure being due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness may accompany the respiratory muscle weakness, or may be the predominant feature in some patients.
- Significant symptomatic worsening on any MG-ADL item of three or more points, excluding double vision or eyelid droop (ie, talking, chewing, swallowing, breathing, upper and lower extremity weakness).
- Any patient whom the Investigator believes will jeopardize his/her health if MG rescue therapy is not given (eg, emergent situations).

Depending on the severity of worsening of MG-related symptoms, rescue therapy (eg, glucocorticosteroids, IVIG, plasmapheresis) will be permitted, as per the clinical judgement of the Investigator. Patients who receive rescue therapy will be discontinued from study treatment infusions and PK sampling, but will continue all other assessments designated at the Day 85 and Day 113 follow-up visits. Thus, for patients who receive rescue therapy during the Treatment Period, the Day 85 Visit translates to 4 weeks after their last dose of study drug, regardless of the study day of their last dose of study drug. Likewise, the Day 113 Visit translates to 8 weeks after their last dose of study drug, regardless of the study day of their last dose in the study.

6.9 Appropriateness of Measurements

The measures for assessing efficacy in this study have been shown to be reliable and valid scales for measuring clinical status of patients with MG. The PK and routine safety assessments included in this study are standard for Phase 2 clinical studies in patients. The PD biomarkers being studied are relevant for patients with MG based on scientific literature and clinical practice.

Although preclinical studies and the first-in-human study with M281 did not indicate any central nervous system effects, the C-SSRS will be used in this study as an additional safety assessment based on the recommendation by the United States Food and Drug Administration (US FDA) for all clinical trials involving the development of drugs or biologics for neurologic indications to assess suicide risk. The US FDA has provided guidance to prospectively assess suicidal ideation and behavior in clinical trials to ensure that patients in clinical trials who are experiencing suicidal ideation and behavior are properly

recognized and adequately treated and to ensure the collection of more timely and more complete data on suicidal ideation and behavior than have been collected in the past (US FDA, 2012).

7 QUALITY CONTROL AND ASSURANCE

To assure quality and consistent study data, procedures will only be carried out by the Principal Investigator or trained staff under the direction of the Principal Investigator. Study related procedures will be carried out in accordance with written materials (eg, study manual, Drug Handling Manual, eCRF completion guidelines, etc).

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor or a Sponsor's designee may conduct a quality assurance audit of the study center(s).

8 PLANNED STATISTICAL METHODS

8.1 General Considerations

Descriptive summary statistics will be provided for demographic, disposition, and exposure data. The number and percentage of patients who discontinued from the study, along with reasons for discontinuations, will be tabulated and described in listings.

Continuous data will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) and, where appropriate, coefficient of variation (CV%) and graphic representation. Categorical data will be summarized by sample size and proportions. Graphs of actual values and changes over time may also be created as appropriate.

8.2 Determination of 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 sample size may be increased by up to 30 additional patients based on the results of the interim analysis (Section 8.8).

8.3 Analysis Populations

The Intent-to-Treat (ITT) Population will include all randomized patients.

The Safety Population will include all patients who received any amount of M281 or placebo.

The PK Population will include all randomized patients in the Safety Population with at least one evaluable serum 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.

8.4 Demographics and Baseline Characteristics

Descriptive summary statistics will be provided for demographic data and other baseline characteristics for the Safety population overall and by treatment group.

8.5 Primary Endpoints

8.5.1 Primary Safety Endpoint

M281 safety and tolerability will be evaluated in terms of the incidence of AEs (including SAEs and 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 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.

8.5.2 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 of use may be explored since MG diagnosis may be added to the model along with different variance-covariance structures. Further details on the statistical analyses for the primary efficacy endpoint will be in the statistical analysis plan (SAP).

8.6 Secondary Endpoints

8.6.1 Secondary Efficacy Endpoints

- A model-based analysis of total MG-ADL score change from Baseline and difference from placebo in relationship to total serum IgG percent of Baseline and treatment frequency. All five study arms will be included in a simultaneous analysis of total MG-ADL score as a function of total serum IgG (Baseline to Day 57).
- A model-based analysis of total MG-ADL score change from Baseline and difference from placebo during the study as a response to percent change in total serum IgG (Baseline to Day 57), for patients positive for anti-AChR antibodies only
- 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
- Change in total QMG score from Baseline to Day 57
- Change in total MG-QoL15r score from Baseline to Day 57
- Shift in MGFA classification from Baseline to Day 57 for each treatment group
- Change in total serum IgG from Baseline to Day 57 for each treatment group
- Change in total MG-ADL, QMG, and MG-QoL15r scores over time after the last dose
- Responder analysis: number of patients with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥8-point improvement in total QMG score over time after the last dose
- Shift in MGFA classification over time after the last dose
- Change in total serum IgG over time after the last dose

The model-based analysis of total MG-ADL score change from Baseline, change from placebo will assess a set of monotonic models to define the effect of IgG lowering on MG-ADL changes from baseline. The models will be averaged (weighting by Akaike information criterion), and the effects will be summarized by median IgG lowering for each of the treatment groups. A second analysis will perform the same model-based assessment including only patients positive for anti-AChR antibodies. Full details for the model-based analyses will be provided in the SAP.

The statistical methods for other secondary efficacy endpoints will be similar to that for the primary endpoint. Details on the statistical methods for the secondary endpoints will be in the SAP.

8.6.2 Other Secondary Endpoint(s)

Serum 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.

8.7 Exploratory Endpoints

- Change in serum concentration of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE over time
- Change in gMG-related serum autoantibody titers over time
- Potency and other characteristics of pathogenic MG antibodies may be assayed and possible relationship with clinical status may be explored
- The incidence of ADA and neutralizing ADA (nADA) seroconversion over time
- Need for increase (rescue) in glucocorticosteroid use before Day 57 and before Day 113
- Need for rescue therapy before Day 57 and before Day 113
- Number of patients with clinical deterioration before Day 57 and before Day 113
- Number of episodes of myasthenic exacerbation (hospitalizations, ICU admissions, and length of stay)
- Number of patients with a durable response, defined as ≥4 consecutive weeks with improvement ≥2 on MG-ADL
- Duration of response, defined as the first week that the patient has an improvement ≥2 on MG-ADL and the response was sustained to the next study visit
- Number of patients with change in MGFA classification status at Day 57 and over time
- 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
- A simultaneous model of all score-based measurements (QMG, MG-ADL) over time by IgG change from Baseline
- Proportion of patients with minimal manifestations, and change in status at Day 57 and Day 113 per the MGFA-PIS
- 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

Details on the statistical methods for the exploratory endpoints will be in the SAP.

8.8 Interim Analysis

An interim analysis will be performed when approximately 30 patients have completed the Day 57 assessments. The results will be used to adjust the sample size, if necessary, and to guide future development activities. If the model-adjusted standard deviation of MG-ADL change from baseline is >4.0, up to 30 additional patients may be recruited.

The interim analysis will be conducted by an independent unblinded team. The study team (including the investigator, site personnel, Sponsor, and Sponsor's designee) will remain blinded. A detailed unblinding plan will be included in the SAP.

9 ADMINISTRATIVE CONSIDERATIONS

9.1 Investigators and Study Administrative Structure

A Coordinating Investigator for the study will be identified by the Sponsor or designee.

Contact information for the Medical Monitor is as follows:

PPD Pharmaceutical Product Development, Inc.	Phone (US): PPD Fax (US): PPD	Phone (EU): PPD

9.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The Investigator must submit written approval from the IRB/IEC to the Sponsor before he or she can enroll any patient into the study. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. Protocol amendments will be prepared and approved by the Sponsor or Sponsor's designee and sent to the appropriate IRB/IEC for review and approval. Documentation of IRB/IEC approval must be forwarded to the Sponsor or designee before the procedures associated with the amendment commence.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

9.3 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor, its authorized representative and Investigators abide by GCP as described in International Council for Harmonisation (ICH) guideline E6(R2), and in 21 Code of Federal Regulations (CFR) parts 11, 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the most recent revision of the Declaration of Helsinki (October 2013) that is recognized by the US FDA, the European Medicines Agency, and other regulatory agencies.

Investigators from countries who are not permitted to sign the US FDA Form 1572 must sign a statement of compliance with internationally recognized rules (ICH E6) governing conduct of clinical trials, that satisfies the US FDA regulation in 21 CFR 312 regarding foreign clinical studies not conducted under an IND.

9.4 Patient Information and Consent

A template ICF will be provided by the Sponsor or designee. The ICF must be reviewed and approved by the IRB/IEC and must contain all elements required by national or local regulations or requirements, US FDA regulations, state and federal laws, and institutional policies. If, during the approval process, the IRB/IEC makes any substantive changes to the ICF, then this altered ICF must be provided to the Sponsor or designee for review before it is implemented.

All patients will be provided with the approved written ICF for this study, which will provide sufficient information for the patient to make an informed decision about participation in this study and to facilitate comprehension of the information. Each patient will be provided adequate opportunity to ask questions and to consider whether to participate. The Investigator is responsible for obtaining the potential participant's voluntary agreement to participate, and to continue providing information as the clinical trial progresses or as the patient or situation requires.

Voluntary informed consent must be obtained from each eligible patient (and/or legally authorized representative) before any protocol-defined procedures are performed. The patient's signature on the ICF indicates his/her willingness to participate in this study. Other study personnel (eg, Principal Investigator, Study Nurse) will sign the ICF in accordance with local procedures.

9.5 Patient Confidentiality

The Investigator must assure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In the eCRFs and other documents (eg, laboratory reports) submitted to the Sponsor, patients will not be identified by name, but by a randomly assigned, patient identification number.

Personal medical information may be reviewed for the purpose of verifying data recorded in the eCRF by the study monitor, Sponsor or designee, IRB/IEC, and regulatory authorities. Personal medical information will always be treated as confidential and in compliance with applicable local laws and regulations.

9.6 Study Monitoring

Clinical research associates (CRAs) representing the Sponsor will routinely visit the study site throughout the study. The Investigator will also ensure that the monitor, or other compliance or quality assurance reviewer, is given access to all study-related documents and study related facilities (eg, pharmacy, diagnostic laboratory, medical records, etc), and has adequate space to conduct the monitoring visit. In addition to the monitoring visits, frequent communications (email, letter, telephone, and/or fax) by the CRA will ensure that the investigation is conducted according to protocol design and regulatory requirements. The Investigator, or appropriate designee, will allocate adequate time for monitoring activities and follow-up correspondences.

The CRA will review ICFs, eCRFs, and laboratory and other diagnostic reports, comparing them with source documents to verify adherence to the protocol, and to ensure complete, accurate, consistent, and timely collection of data. The CRA will record and report any protocol deviations not previously sent to the Sponsor. The CRA will also confirm that AEs and SAEs have been properly documented on eCRFs and confirm that any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC. The Investigator will be asked to provide any missing information or to clarify any discrepancies found by the CRA/monitor. It is expected that the Investigator will be present for a concluding review at the end of each monitoring visit.

9.7 Case Report Forms and Study Records

Wherever possible, all data will be entered directly into the eCRFs. In some cases, source documents will be used. A Data Management Plan will be written by the Sponsor or designee, which will be finalized prior to performing any data validation. The Data Management Plan will identify any data to be recorded directly in the eCRF (ie, no prior written or electronic record of data), and which data should be considered source data.

Source documents are all original documents, data, and records that pertain to a study patient and can be either electronic or physical in origin. Examples of source documents are: hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files and records kept at the pharmacy, at the laboratories and at technical departments involved in the study. When source document data are shared with originating files (eg, hospital records or other clinic charts), photocopies of specific components of these data can be included as source document provided that these copies are signed and dated by appropriate research site personnel.

Source data must be legible and written concurrently with the patient visit, and no data may be obliterated. If the source document contains a patient's address and phone number, it must be obliterated before it is included as a study document and the patient's name will be obliterated except for the first letters of the first, middle (if present), and last names. The completed eCRF must be reviewed and approved by an authorized Investigator before it can be considered final.

9.8 Data Monitoring Committee

An independent DSMB will be responsible for safety oversight of the patients in the study. The DSMB will meet on a regular basis and review all available data (AEs, SAEs, AESIs, and laboratory results); ad hoc meetings may be scheduled as needed. The specific responsibilities of the DSMB will be outlined in a DSMB charter.

9.9 Protocol Violations/Deviations

Except for a change intended to eliminate an immediate hazard to a participant, the protocol shall be conducted as described without any changes or deviations. Any change must be reported immediately to the Sponsor and to the IRB/IEC, as required by their regulations.

9.10 Access to Source Documentation

The Investigator will permit study related monitoring, audits, and inspections by the IRB/IEC, the Sponsor, government regulatory bodies, and compliance and quality assurance groups of all study related documents (eg, source documents, regulatory documents, data collection instruments, study data, etc). All authorized personnel, including health authority inspector(s), Sponsor and designees, CRAs, Medical Monitor(s), and auditor(s) will be given direct access to source data and documentation (eg, medical records, laboratory results, etc) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

9.11 Data Generation and Analysis

Data management and control processes specific to the study will be described in the data management plan. Details on the study's analysis methods will be provided in the SAP, which will be developed prior to study completion and database lock.

9.12 Retention of Data

The Principal Investigator shall retain all study-related documentation, including source data, source documents, eCRFs, laboratory and diagnostic results, protocol and amendments, study drug accountability records, regulatory documentation and correspondence, ICFs, patient identification lists, and correspondence. These records should be retained in the format they were originally obtained (eg, electronic or paper) unless a quality controlled and authorized complete electronic version is created for long-term storage at the end of the study. The Sponsor will provide an electronic copy of the final eCRF for each study patient within 3 months of study closeout.

The Investigator must retain an organized file with all study-related documentation that is suitable for inspection by the Sponsor and representatives of Regulatory Authorities.

The Investigator must retain essential documents until notified by the Sponsor, and at least for 15 years after study completion.

Documents should be stored in such a way that they can be accessed and data can be retrieved at a later date. Consideration should be given to security and environmental risks.

Documentation retention will generally comply with Section 8 of the ICH consolidated guideline on GCP, Essential Documents for the Conduct of a Clinical Trial.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator or the Research Site should the Investigator leave the institution. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor prior to any actions being taken.

9.13 Publication and Disclosure Policy

This trial will be registered at ClinicalTrials.gov and after study completion, results information from this trial will be posted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Publication of the results by the Investigator will be subject to mutual written agreement between the Investigator and the Sponsor or determined by the publication/steering committee.

10 REFERENCE LIST

Argenx. Phase 2 clinical proof-of-concept trial of ARGX-113 (efgartigimod) in generalized myasthenia gravis. Management call; December 11, 2017. Available from: http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9Njg1NTQzfENoaWxkSUQ9Mzk1NjcwfFR5cGU9MQ==&t=1. Accessed 18 June 2018.

Blumberg L, Humphries JE, Lasseter KC, Blumberg RS. A humanized IgG4 monoclonal antibody that disrupts the interaction of FcRn and IgG for the treatment of IgG mediated autoimmune diseases. Poster presented at American Society of Hematology (ASH) 59th Annual Meeting and Exposition; 2017 December 9-12; Atlanta, Georgia.

Burns TM, Sadjadi R, Utsugisawa K, Gwathmey KG, Joshi A, Jones S, et al. International clinimetric evaluation of the MG QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. Muscle Nerve. 2016;54:1015-22.

Gilhus NE. Myasthenia gravis. N Engl J Med. 2016;375(26):2570-81.

Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis – autoantibody characteristics and their implications for therapy. Nat Rev Neurol. 2016;12(5):259-68.

Hansen JS, Danielsen DH, Somnier FE, Frøslev T, Jakobsen J, Johnsen SP, et al. Mortality in myasthenia gravis: A nationwide population based follow up study in Denmark. Muscle Nerve. 2016;53(1):73-7.

Howard JF Jr, Barohn RJ, Cutter GR, Freimer M, Juel V, Mozaffar T, et al. A randomized, double blind, placebo controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis. Muscle Nerve. 2013;48(1):76-84.

Howard JF Jr, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double blind, placebo controlled, multicentre study. Lancet Neurol. 2017;16(12):976-86.

Jaretzki A, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, Sanders DB. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology. 2000;55:16-23.

Kiessling P, Lledo-Garcia R, Watanabe S, Langdon G, Tran D, Bari M, et al. The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study. Sci Transl Med. 2017;9(419). Erratum in: Sci Transl Med. 2017;9(419).

Liu L, Garcia AM, Santoro H, Zhang Y, McDonnell K, Dumont J, et al. Amelioration of experimental autoimmune myasthenia gravis in rats by neonatal FcR blockade. J Immunol. 2007;178:5390-8.

Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. Ther Adv Neurol Disord. 2018;11:1756285617749134. Erratum in: Ther Adv Neurol Disord 2018;11:1756286418765591.

Meriggioli MN, Sanders DB. Muscle autoantibodies in myasthenia gravis: beyond diagnosis? Expert Rev Clin Immunol. 2012;8(5):427-38.

Nixon AE, Chen J, Sexton DJ, Muruganandam A, Bitonti AJ, et al. Fully human monoclonal antibody inhibitors of the neonatal fc receptor reduce circulating IgG in non-human primates. Front Immunol. 2015;6:176. doi: 10.3389/fimmu.2015.00176. eCollection 2015.

Robak T, Jarque I, Musteata V, Kiessling P, Massow U, Higginson J, et al. Phase II, multiple-dose study of anti-FcRn antibody, rozanolixizumab (UCB7665), in patients with primary immune thrombocytopenia: Interim analysis. Blood. 2017;Dec;130(Suppl 1):15.

Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis. Neurology. 2016;87:419-25.

Sathasivam S. Diagnosis and management of myasthenia gravis. Progress in Neurology and Psychiatry. 2014. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/pnp.315. Accessed 21 May 2018.

Silvestri N, Wolfe G. Treatment refractory myasthenia gravis. J Clin Neuromuscul Dis. 2014;15(4):167-78.

US FDA. Guidance for Industry. Suicidal ideation and behavior: Prospective assessment of occurrence in clinical trials, Draft Guidance. August 2012. Revision 1. Available from: https://www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf. Accessed on 11 June 2018.

Zhang B, Tzartos JS, Belimezi M, Ragheb S, Bealmear B, Lewis RA, et al. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. Arch Neurol. 2012;69(4):445-51.

Appendix 1 Sponsor Signatures

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

Study Number: MOM-M281-004

Amendment 3.2 Date: 28 August 2019

This clinical study protocol was subject to critical review and has been approved by the sponsor.

Signed:_____ Date:_____

Printed name: Santiago Arroyo, MD, PhD

Title: Chief Medical Officer, Momenta Pharmaceuticals, Inc.

Appendix 2 Investigator's Signature

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

Study Number: MOM-M281-004

Amendment 3.2 Date: 28 August 2019

I have read the protocol described above. I agree to conduct the study as described in the protocol. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) and all applicable national and local laws and regulations, as well as with the requirements of the appropriate Institutional Review Board or independent Ethics Committee (IRB/IEC) and any other institutional requirements. These are stated in "Guidance for Good Clinical Practice," International Council for Harmonisation (ICH) guideline E6(R2) of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Declaration of Helsinki, and any other applicable regulatory requirements. No changes will be made to the study protocol without prior written approval of the Sponsor and the IRB/IEC.

Signed:_____ Date:_____

Printed name: _____

Title: _____

Affiliation: _____

Appendix 3 Myasthenia Gravis – Activities of Daily Living

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, 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 one of these functions	
Impairment of ability to arise 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	

Total score _____

Appendix 4 Quantitative Myasthenia Gravis

Quantitative MG score

Test item	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
Double vision on lateral gaze right or left (circle one), 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. 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	90–239	10–89	0–9	____
Left arm outstretched (90 degree sitting), seconds	240	90–239	10–89	0–9	____
Vital capacity, % predicted	≥80	65–79	50–64	<50	____
Right-hand grip, kgW					
Men	≥45	15–44	5–14	0–4	____
Women	≥30	10–29	5–9	0–4	____
Left-hand grip, kgW					
Men	≥35	15–34	5–14	0–4	____
Women	≥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	____
			Total QMG score (range, 0–39)		

Appendix 5 Revised Myasthenia Gravis Quality of Life – 15

Please indicate how true each statement has been (over the past few weeks).	Not at all 0	Somewhat 1	Very much 2
1. I am frustrated by my MG			
2. I have trouble with my eyes because of my MG (e.g. double vision)			
3. I have trouble eating because of MG			
4. I have limited my social activity because of my MG			
5. My MG limits my ability to enjoy hobbies and fun activities			
6. I have trouble meeting the needs of my family because of my MG			
7. I have to make plans around my MG			
8. I am bothered by limitations in performing my work (include work at home) because of my MG.			
9. I have difficulty speaking due to MG			
10. I have lost some personal independence because of my MG (e.g. driving, shopping, running errands)			
11. I am depressed about my MG			
12. I have trouble walking due to MG			
13. I have trouble getting around public places because of my MG			
14. I feel overwhelmed by my MG			
15. I have trouble performing my personal grooming needs due to MG			

Total MGQOL-R score

Appendix 6 Myasthenia Gravis Foundation of America Post-Intervention Status

MGFA Post-intervention Status (MGFA-PIS)

Complete Stable Remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic Remission (PR)	The same criteria as for CSR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal Manifestations (MM)	The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.
Change in Status	
Improved (I)	A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.
Unchanged (U)	No substantial change in pretreatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.
Worse (W)	A substantial increase in pretreatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score.
Exacerbation (E)	Patients who have fulfilled criteria of CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria.
Died of MG (D of MG)	Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy. List the cause (see Morbidity and Mortality table).