Clinical Trial Protocol: MOM-M281-005

Study Title:	An Open-label Extension Study of MOM-M281-004 to Evaluate the Safety, Tolerability, and Efficacy of M281 Administered to Patients with Generalized Myasthenia Gravis
Study Number:	MOM-M281-005
Study Phase:	2
Product Name:	M281
IND Number:	138975
EudraCT Number:	2018-003618-41
Indication:	Generalized myasthenia gravis
Investigators:	Multicenter

Sponsor:	Momenta Pharmaceuticals, Inc. 301 Binney Street Cambridge, MA 02142 USA PPD
Sponsor Contact:	Santiago Arroyo, MD Chief Medical Officer PPD

	Date
Original Protocol:	01 Oct 2018
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Amendment 2:	01 August 2019

SYNOPSIS

Sponsor:

Momenta Pharmaceuticals, Inc.

Name of Finished Product:
M281

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

Study Number:
MOM-M281-005

Study Phase: 2

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the long-term safety and tolerability of M281 in patients with generalized myasthenia gravis (gMG)	• Incidence and severity of adverse events (AEs; including serious AEs [SAEs], and AEs of special interest [AESIs]), vital signs, physical examinations, clinical laboratory testing (including chemistry, hematology, coagulation, and urinalysis), electrocardiograms (ECGs), and the Columbia-Suicide Severity Rating Scale (C-SSRS)
Secondary	
• To evaluate the long-term efficacy of M281	• Change from baseline in the total Myasthenia Gravis – Activities of Daily Living (MG-ADL) score over time • Number of patients with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥8-point improvement in total MG-ADL score over time • Change from baseline in total Quantitative Myasthenia Gravis (QMG) score over time • Change from baseline in total Revised Myasthenia Gravis Quality of Life – 15 Scale (MG-QoL15r) score over time • Change from baseline in Clinical Global Impression of Severity (CGI-S) over time and Clinical Global Impression of Improvement (CGI-I) ratings • Change from baseline in Myasthenia Gravis Foundation of America (MGFA) classification over time
• To evaluate the long-term immunogenicity of M281 • To evaluate the long-term pharmacodynamic (PD) activity of M281	• Incidence of anti-drug antibody (ADA) and neutralizing ADA (nADA) seroconversion over time • Total serum immunoglobulin (Ig)G concentrations over time and change from baseline

Objectives	Endpoints
Exploratory	
• To evaluate the effect of M281 on fatigue and level of physical activity	• Change from baseline in Neuro-QOL Fatigue scores over time • Quantitative level of physical activity over time and changes from baseline
• To evaluate the long-term PD activity of M281 on serum concentrations of IgA, IgM, and IgE • To evaluate the long-term PD activity of M281 on serum titers of pathogenic autoantibodies associated with gMG (anti-acetylcholine receptor [anti-AChR] and/or anti-muscle-specific kinase [anti-MuSK])	• Serum concentrations of IgA, IgM, and IgE over time and changes from baseline • Titers of serum anti-AChR or anti-MuSK antibodies over time and change from baseline
• To evaluate the long-term response to treatment with M281 in relation to other treatment(s) and/or clinical status	• Changes in dose/regimen of standard-of-care concomitant medications for gMG over time • Number of patients who discontinued immunosuppressive medications over time • Need for rescue therapy over time • Number of patients with clinical deterioration • Number of episodes of myasthenic exacerbation requiring hospitalization/intensive care unit admission, and length of stay • Proportion of patients with minimal manifestations, and change in status per the Myasthenia Gravis Foundation of America Post-intervention Status (MGFA-PIS) over time, and proportion of patients with pharmacologic remission
• To evaluate the potential relationship between change in MG-ADL score and change in anti-AChR antibody levels	• A model-based analysis of MG-ADL score change from Baseline in relationship to total serum IgG and anti-AChR titer (the latter is only for patients with anti-AChR antibodies)

Study Design:
This is a long-term, open-label extension (OLE) study of patients who completed the proof-of-concept (POC) study (MOM-M281-004) without discontinuing study drug during the POC study for reasons other than the need for rescue therapy (eg, glucocorticosteroids, intravenous immunoglobulin [IVIG], plasmapheresis) as specified in the POC protocol, and who completed the protocol-specified 8 weeks of follow-up after the last dose of study drug in the POC study. If the patient received rescue therapy during the POC, the Medical Monitor should be consulted before the patient is enrolled in the OLE study.

The Screening Period for the OLE study begins (at the earliest) at the Day 85 POC Visit

(ie, 4 weeks after the last dose of study drug in the POC study) and ends upon enrollment in the OLE study. The screening procedures consist of signing the informed consent form for the OLE study and initiation of continuous physical activity monitoring via a medical device (Embrace device, Empatica, Inc., Cambridge, MA) worn on the wrist. Any screening procedure for the OLE study must not be done until after completion of all the assessments and procedures required by the POC protocol for the Day 85 POC Visit.

Eligibility for the OLE study will be assessed and enrollment into the OLE study will occur (at the earliest) at the patient's last follow-up visit in the POC study (Day 113 POC Visit). After completion of all Day 113 POC Visit assessments, the patient will be assessed for eligibility for enrollment into the OLE study per the OLE inclusion and exclusion criteria. Any OLE assessment or procedure designated on the Day 113 POC Visit must not be performed until after completion of all the assessments and procedures required by the POC protocol for the Day 113 POC Visit. Eligibility for the OLE study will be determined based on results of safety laboratory testing from the patient's Day 85 POC Visit, the assessments from the patient's Day 113 POC Visit, and additional procedures to be performed predose on OLE Day 1. Patients meeting all eligibility criteria will be enrolled into the OLE study and may receive the first infusion of M281 under this protocol (day of first infusion is considered OLE Day 1). Patients not meeting all OLE eligibility criteria will be considered screening failures for the OLE study and will not be enrolled or receive treatment under this protocol.

If it is not feasible to complete any/all designated OLE assessments/procedures on the same day as the Day 113 POC Visit, or if there is a valid reason to delay enrollment of the patient in the OLE study, the Investigator can confirm the patient's eligibility and enroll the patient at a later date as agreed between the Investigator and Medical Monitor; however, depending on the length of the delay the patient may need to have an additional unscheduled blood draw for safety laboratory testing to confirm eligibility for the OLE study.

Patients who are enrolled in the OLE study will initially receive M281 30 mg/kg every 4 weeks (Q4W) by intravenous (IV) infusion. This dose (M281 30 mg/kg Q4W) is one of the doses evaluated in the POC study. This starting dose and dosing frequency may be revised if available results from the POC study reveal a different optimal dose for development. However, the revised dose and dosing frequency in the OLE study will not exceed 60 mg/kg every 2 weeks (Q2W), which is the highest dose and most frequent dosing interval evaluated in the POC study.

Patients should be maintained on a stable M281 dose and dosing frequency for at least the first 8 weeks of the OLE study. If the starting dose and dosing frequency for the study is revised after the patient started receiving the dose of 30 mg/kg Q4W, it is recommended that the patient receives the revised dose for at least 8 weeks regardless of the length of time the patient received the 30 mg/kg Q4W treatment.

After at least 8 weeks of treatment on a stable dose of M281, the dose and/or dosing frequency of M281 may be individually adjusted for a given patient at the discretion of the Investigator and previous consultation with the Medical Monitor, based on the patient's tolerability to M281 and the patient's MG status. The individually adjusted dose will not exceed 60 mg/kg and the dosing frequency will not exceed Q2W.

Each patient will be observed for safety after their first 2 infusions in the study; if no clinically relevant AEs or abnormal vital signs related to the infusion are observed in these

first 2 infusions, the post-infusion observation period is no longer needed unless the M281 dose level is later increased. A post-infusion observation period is also required for the patient's first infusion at the higher M281 dose level. All patients must attend clinic visits at 2, 4, and 8 weeks after the first infusion (on OLE Day 1) to undergo safety, tolerability, efficacy, PD, and immunogenicity assessments. Serum biomarkers will also be explored. After Week 8, patients will receive an infusion of M281 on a Q2W or Q4W basis, depending on the dosing frequency established for the patient. All infusions may be administered at the site, or every other infusion (except those that fall every 12 weeks [Q12W]) may be administered in the home or at another location per the Infusion Manual, at the discretion of the Investigator and if this option is made available to the site. As an example, for patients continuing on a Q4W regimen at Week 8, the schedule for optional home infusions would be as follows: Weeks 16, 28, and 40 (assuming no M281 dose increase and assuming end of treatment at Week 52). As an example, for patients switching to a Q2W regimen at Week 8, the schedule for optional home infusions would be as follows: Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50 (assuming no M281 dose increase and assuming end of treatment at Week 52).

Each infusion will be administered per the Infusion Manual. On each infusion day predose vital signs will be measured. For infusions administered in the clinic, ECGs will also be measured, and AEs and concomitant medication/therapy since the previous clinical visit will be recorded. If the M281 dose and/or dosing frequency is adjusted, the first infusion at the new dose/frequency must occur at a clinic visit; for increases in the M281 dose level (but not for change in dosing frequency), the patient will undergo a post-infusion observation period following the first infusion at the higher dose level per the Infusion Manual. In the event of either a dose increase and/or dosing frequency increase, the patient's next scheduled infusion must be conducted in the clinic because a blood sample for safety laboratory testing must be obtained and a physical examination must be performed within 2 to 4 weeks after the first infusion at the new dose/dosing frequency. Regardless of the patient's dosing frequency, the full schedule of safety, tolerability, efficacy, PD, and immunogenicity assessments will be done at Week 12 and Q12W thereafter. The duration of each patient's participation in the study is planned to be approximately 1 year or until the study is terminated by the Sponsor. Patients will return to the clinic approximately 8 weeks after their last infusion for follow-up assessments.

Patients should continue their stable therapeutic regimen (standard of care) for gMG and should maintain the same dose and regimen for at least the first 8 weeks of the OLE study (unless toxicity or safety/tolerability issues mandate a change). In the event the starting dose of M281 (30 mg/kg Q4W) is revised to a different dose and/or dosing frequency, it is recommended that the dose and regimen of concomitant treatment not be changed until the patient's M281 dose has been stable for at least 8 weeks. A consultation with the Medical Monitor regarding changes to the patient's standard-of-care therapy is recommended.

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

Study Population:
The sample size for the OLE study will depend on the enrollment in the POC study, which plans for approximately 60 patients with possible expansion up to 90 patients.

Test Product, Dose, and Mode of Administration:
M281 for IV infusion, initially at a dose of 30 mg/kg (Q4W); the starting dose and/or dosing frequency may be revised depending on available results from the POC study. After at least 8 weeks of treatment on a stable dose of M281, the dose/regimen may be individually adjusted for a given patient upon agreement between the Investigator and Medical Monitor. The revised dose and dosing frequency or any individually adjusted dose or dosing frequency will not exceed 60 mg/kg Q2W, which is the highest dose and most frequent dosing interval evaluated in the POC study.

Duration of Treatment:
Patients will receive IV administration of M281 for approximately 1 year or until the study is terminated by the Sponsor.

Efficacy Assessments:
Efficacy will be assessed at designated site visits prior to start of M281 infusion (ie, predose), using these measures in the following preferred order: MG-ADL, QMG, MG-QoL15r, applicable elements of the MGFA-PIS, physician-rated CGI scales, patient-reported Neuro-QOL Fatigue, and MGFA classification. If possible, these efficacy assessments throughout the study should be done at approximately the same time of day as performed on Day 1.

In addition, the level of physical activity will be monitored via the Embrace device worn continuously on the wrist during the Screening Period (to establish a baseline) and for the first 6 months of the treatment period during of the study.

Safety Assessments:
Safety assessments include collection of AEs (including serious AEs, AESIs, and device-related AEs), vital signs, physical examinations, clinical laboratory testing (including chemistry, hematology, coagulation, and urinalysis), ECGs, and the C-SSRS. Severe infections and events of hypoalbuminemia (Grade 3 or higher according to the Common Terminology Criteria for Adverse Events [CTCAE] v5.0) will be considered AESIs.

Reporting of device-related AEs in the OLE study will start following the patient signing the OLE informed consent form. AEs from the POC study that are ongoing at the Day 113 POC Visit will be recorded as medical history for the OLE study. Recording of new AEs (ie, any new clinically relevant finding or worsening of a pre-existing condition, such as an ongoing AE from the POC study) will start at the time of enrollment into the OLE study.

Assessments of Pharmacodynamics and Biomarkers:
Blood samples will be drawn for analysis of the following PD parameters: concentrations of total serum IgG; serum concentrations of IgA, IgM, and IgE; and titers of anti-AChR and anti-MuSK autoantibodies.

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

Statistical Methods:

Baseline is defined as the assessment obtained at the time of enrollment into the OLE study (Day 1) for all assessments except physical activity; baseline for physical activity will be established during the Screening Period.

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 to study drug/device will also be provided. Concomitant medications will be coded by the World Health Organization Drug Dictionary Enhanced and will be summarized. Medical history (to include AEs from the POC study that are ongoing at OLE Day 1) 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, and C-SSRS. For vital signs and ECGs, descriptive statistics at each visit and change from baseline to each subsequent visit will be provided. Physical examinations will be summarized as shift tables.

All efficacy data will be analyzed using descriptive summary statistics.

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.

Date of Protocol Amendment 2: 01 August 2019

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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
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CK	creatine kinase
CK-MB	creatine kinase MB isoenzyme
CK-MM	creatine kinase MM isoenzyme
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
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IRB	Institutional Review Board
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
MuSK	muscle-specific kinase
nADA	neutralizing anti-drug antibody
NCS	not clinically significant
OLE	open-label extension
PD	pharmacodynamics
POC	proof of concept
Q2W	every 2 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
QMG	Quantitative Myasthenia Gravis
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SAP	statistical analysis plan
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 and Antozzi 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 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. In patients with gMG, M281 is expected to reduce circulating levels of IgG antibodies by blocking IgG recycling, including the pathogenic autoantibodies that cause MG, potentially leading to improvement of the disease manifestations. Administration of M281 is not expected to reduce levels of other immunoglobulins, including IgA, IgM, or IgE, or impact other aspects of immune system response to infection, considering FcRn blockage only affects IgG half-life.

A completed Phase 1 study of M281 in healthy volunteers (MOM-M281-001) showed that M281 was well tolerated in single infusions of doses up to 60 mg/kg (the highest single dose tested) and in up to 4 weekly infusions of doses up to 30 mg/kg (the highest repeat dose tested). Self-limited, recoverable decreases in total serum IgG concentrations to a mean of approximately 15% to 20% of baseline values (an 80% to 85% decrease from baseline) were observed, confirming the drug's mechanism of action. Further details are provided in the Investigator Brochure.

The Phase 2, placebo-controlled, proof-of-concept (POC) study (MOM-M281-004, hereafter referred to as the POC study) in patients with gMG is evaluating the therapeutic potential of single (60 mg/kg) and repeat doses of M281 (5 mg/kg every 4 weeks [Q4W], 30 mg/kg Q4W, and 60 mg/kg every 2 weeks [Q2W]) for the treatment of patients with gMG who have an insufficient clinical response to ongoing, stable standard-of-care therapy. Safety, tolerability, efficacy, pharmacodynamics (PD), and immunogenicity of M281 compared with placebo are being evaluated in the Phase 2 study over an 8-week Treatment Period and an 8-week Follow-up Period after the last infusion of study drug. Upon completion of the placebo-controlled POC study, patients have the option to enroll in this open-label extension (OLE) study to receive treatment with M281.

The purpose of this OLE study is to collect long-term safety, tolerability, efficacy, PD, and immunogenicity data for M281 in patients who completed the POC study (MOM-M281-004).

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. 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 6.6.1 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 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, except in the case of stable CK ≥2×ULN, but <5×ULN in a patient with no CK related disease and CK level is believed to be the result of non-pathologic factors. Serum CK levels will be monitored during the study and CK-related AE stopping rules are included in Section 6.6.1 of this protocol.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate:

- The long-term safety and tolerability of M281 in patients with gMG.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate:

- The long-term efficacy of M281,
- The long-term immunogenicity of M281, and
- The long-term PD activity of M281.

2.3 Exploratory Objectives

The exploratory objectives are to evaluate:

- The effect of M281 on fatigue and level of physical activity,
- The long-term PD activity of M281 on serum concentrations of IgA, IgM, and IgE,
- The long-term PD activity of M281 on serum titers of pathogenic autoantibodies associated with gMG (anti-AChR and/or anti-MuSK),
- The long-term response to treatment with M281 in in relation to other treatment(s) and/or clinical status, and
- The potential relationship between change in Myasthenia Gravis – Activities of Daily Living (MG-ADL) score and change in anti-AChR antibody levels.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a long-term, OLE study of patients who completed the POC study (MOM-M281-004) without discontinuing study drug during the POC study for reasons other than the need for rescue therapy (eg, glucocorticosteroids, IVIG, plasmapheresis) as specified in the POC protocol, and who completed the protocol-specified 8 weeks of follow-up after the last dose of study drug in the POC study.

The Screening Period for the OLE study begins (at the earliest) at the Day 85 POC Visit (ie, 4 weeks after the last dose of study drug in the POC study) and ends upon enrollment in the OLE study. The screening procedures consist of signing the informed consent form for the OLE study and initiation of continuous physical activity monitoring via a medical device (Embrace device, Empatica, Inc., Cambridge, MA) worn on the wrist.

Eligibility for the OLE study will be assessed and enrollment into the OLE study will occur (at the earliest) after completion of assessments at the patient's last follow-up visit in the POC study (Day 113 POC Visit). Thus, the Day 113 POC Visit can be Day 1 for the OLE; patients who meet the eligibility criteria for the OLE study can receive their first open-label infusion of M281 on the same day.

Patients who are enrolled in the OLE study will initially receive M281 30 mg/kg Q4W by intravenous (IV) infusion. This dose (M281 30 mg/kg Q4W) is one of the doses evaluated in the POC study. This starting dose and dosing frequency may be revised if available results from the POC study reveal a different optimal dose for development. However, the revised dose and dosing frequency in the OLE study will not exceed 60 mg/kg Q2W, which is the highest dose and most frequent dosing interval evaluated in the POC study.

After at least 8 weeks of treatment on a stable dose of M281, the dose and/or dosing frequency of M281 may be individually adjusted for a given patient at the discretion of the Investigator and previous consultation with the Medical Monitor, based on the patient's tolerability to M281 and the patient's MG status. The individually adjusted dose will not exceed 60 mg/kg and the dosing frequency will not exceed Q2W.

Each patient will be observed for safety after their first 2 infusions in the study; if no clinically relevant AEs or abnormal vital signs related to the infusion are observed in these first 2 infusions, the post-infusion observation period is no longer needed unless the M281 dose level is later increased. A post-infusion observation period is also required for the patient's first infusion at the higher M281 dose level. All patients must attend clinic visits at 2, 4, and 8 weeks after the first infusion (on OLE Day 1) to undergo safety, tolerability, efficacy, PD, and immunogenicity assessments. Serum biomarkers will also be explored. After Week 8, patients will receive an infusion of M281 on a Q2W or Q4W basis depending on the dosing frequency established for the patient. All infusions may be administered at the site, or every other infusion (except those that fall every 12 weeks [Q12W]) may be administered in the home or at another location per the Infusion Manual, at the discretion of

the Investigator and if this option is made available to the site. As an example, for patients continuing on a Q4W regimen at Week 8, the schedule for optional home infusions would be as follows: Weeks 16, 28, and 40 (assuming no M281 dose increase and assuming end of treatment at Week 52). As an example, for patients switching to a Q2W regimen at Week 8, the schedule for the optional home infusions would be as follows: Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50 (assuming no M281 dose increase and assuming end of treatment at Week 52).

Each infusion will be administered per the Infusion Manual. On each infusion day predose vital signs will be measured. For infusions administered in the clinic, electrocardiograms (ECGs) will also be measured, and AEs and concomitant medication/therapy since the previous clinical visit will be recorded. If the M281 dose and/or dosing frequency is adjusted, the first infusion at the new dose/frequency must occur at a clinic visit; for increases in the M281 dose level (but not for change in dosing frequency), the patient will undergo a post-infusion observation period following the first infusion at the higher dose level per the Infusion Manual. In the event of either a dose increase and/or dosing frequency increase, the patient's next scheduled infusion must be conducted in the clinic because a blood sample for safety laboratory testing must be obtained and a physical examination must be performed within 2 to 4 weeks after the first infusion at the new dose/dosing frequency. Regardless of the patient's dosing frequency, the full schedule of safety, tolerability, efficacy, PD, and immunogenicity assessments will be done at Week 12 and Q12W thereafter. The duration of each patient's participation in the study is planned to be approximately 1 year or until the study is terminated by the Sponsor. Patients will return to the clinic approximately 8 weeks after their last infusion for follow-up assessments.

Patients should continue their stable therapeutic regimen (standard of care) for gMG and should maintain the same dose and regimen for at least the first 8 weeks of the OLE study (unless toxicity or safety/tolerability issues mandate a change). In the event the starting dose of M281 (30 mg/kg Q4W) is revised to a different dose and/or dosing frequency, it is recommended that the dose and regimen of concomitant treatment not be changed until the patient's M281 dose has been stable for at least 8 weeks. A consultation with the Medical Monitor regarding changes to the patient's standard-of-care therapy is recommended.

The Schedule of Study Assessments is provided in Section 6.

3.2 Rationale for Study Design

The study will enroll patients with gMG who completed the POC study (MOM-M281-004) without discontinuing study drug during the POC study for reasons other than the need for rescue therapy as specified in the POC protocol, and who completed the protocol-specified 8 weeks of follow-up after the last dose of study drug in the POC study. Such patients may have been exposed to one or more doses of M281 or may have received placebo in the POC study. Therefore, the safety, tolerability, efficacy, PD, and immunogenicity assessments for first 8 weeks of this OLE study are similar to those for the POC study. PK sampling is not being done for this study because PK is being characterized in the POC study.

Using data derived from nonclinical studies in nonhuman primates and data from the completed Phase 1 study of M281 in healthy volunteers (MOM-M281-001), the M281 dose that will initially be used at the start of the OLE study is 30 mg/kg given Q4W. This dose (M281 30 mg/kg Q4W) is one of the doses evaluated in the POC study. The dose regimen of 30 mg/kg Q4W was selected to achieve significant IgG lowering while not fully saturating the FcRn receptor for the dosing interval. The top dose allowed for adjustment (60 mg/kg Q2W) is expected to achieve maximum IgG reduction over the treatment period. The starting dose and dosing frequency may be revised based on available results from the POC study. Unlike the POC study, dose adjustment of M281 and of gMG standard-of-care therapy is allowed for individual patients after at least 8 weeks on a stable M281 dose to reflect real-world practice of tailoring the medication regimen based on tolerability and/or gMG status. The dose and dosing frequency in the OLE study will not exceed 60 mg/kg Q2W, which is the highest dose and most frequent dosing interval evaluated in the POC study.

The approximate 1-year duration of the study will be sufficient to characterize the long-term safety and tolerability, and to further evaluate efficacy, PD, and immunogenicity of M281.

3.3 Study Duration

Following a Screening Period, the duration of each patient's participation in the study is planned to be approximately 1 year or until the study is terminated by the Sponsor.

4 STUDY POPULATION SELECTION

4.1 Study Population

The sample size for the OLE study will depend on the enrollment in the POC study, which plans for approximately 60 patients with possible expansion up to 90 patients.

4.2 Screening Period

The Screening Period for the OLE study begins (at the earliest) at the Day 85 POC Visit and ends upon enrollment in the OLE study. The screening procedures consist of signing the informed consent form for the OLE study and initiation of continuous physical activity monitoring via the Embrace device. Any screening procedure for the OLE study must not be done until after completion of all the assessments and procedures required by the POC protocol for the Day 85 POC Visit.

If the patient received rescue therapy during the POC study, the Medical Monitor should be consulted before the patient is enrolled in the OLE study.

As specified in the POC protocol, patients who receive rescue therapy in the POC study are discontinued from study drug infusions but are to continue assessments in the POC study. The follow-up visits in the POC study are the Day 85 POC Visit and the Day 113 POC Visit. Thus, for patients who receive rescue therapy during the Treatment Period of the POC study, the Day 85 POC Visit translates to 4 weeks after their last dose of study drug in the POC

study regardless of the study day of their last dose in the POC study. Likewise, the Day 113 POC Visit translates to 8 weeks after their last dose of study drug in the POC study regardless of the study day of their last dose in the POC study.

4.3 Enrollment

Eligibility for the OLE study will be assessed and enrollment into the OLE study will occur (at the earliest) on the same day as the patient's last follow-up visit in the POC study (Day 113 POC Visit). Any OLE assessment or procedure designated on the Day 113 POC Visit must not be performed until after completion of all the assessments and procedures required by the POC protocol for the Day 113 POC Visit. After completion of all Day 113 POC Visit assessments, the patient will be assessed for eligibility for enrollment into the OLE study per the OLE inclusion and exclusion criteria. Eligibility for the OLE study will be determined based on results of safety laboratory testing from the patient's Day 85 POC Visit, the assessments from the patient's Day 113 POC Visit, and additional procedures to be performed predose on OLE Day 1. Patients meeting all eligibility criteria will be enrolled into the OLE study and may receive the first infusion of M281 under this protocol (day of first infusion is considered OLE Day 1). Patients not meeting all OLE eligibility criteria will be considered screening failures for the OLE study and will not be enrolled or receive treatment under this protocol.

If it is not feasible to complete any/all designated OLE assessments/procedures on the same day as the Day 113 POC Visit, or if there is a valid reason to delay enrollment of the patient in the OLE study, the Investigator can confirm the patient's eligibility and enroll the patient at a later date as agreed between the Investigator and Medical Monitor; however, depending on the length of the delay the patient may need to have an additional unscheduled blood draw for safety laboratory testing to confirm eligibility for the OLE study.

4.4 Inclusion Criteria

1. Has completed the M281 POC study (ie, participated in the POC study without discontinuing study drug for reasons other than the need for rescue therapy as specified in the POC protocol, and completed the protocol-specified 8 weeks of follow-up after the last dose of study drug) and had no major eligibility deviations or other major protocol deviations in the POC study. If the patient received rescue therapy during the POC, the Medical Monitor should be consulted before the patient is enrolled in the OLE study.
2. Has sufficient venous access to allow drug administration by infusion and blood sampling as per this OLE protocol.
3. Is up to date on all age-appropriate vaccinations as per routine local medical guidelines.
4. Women of childbearing potential, defined as women physiologically capable of becoming pregnant, must have a negative urine pregnancy test predose on OLE study Day 1. Menopausal women who did not have elevated follicle-stimulating hormone (FSH) at the time of enrollment in the POC study must also have a negative urine pregnancy test predose on OLE study Day 1.
5. Women of childbearing potential (including menopausal women who did not have elevated FSH at the time of enrollment in the POC study) 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 OLE study and for 30 days after the last M281 infusion.
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.

6. 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 OLE study and for 100 days following the last M281 infusion, unless the patient provides documentation of a vasectomy at least 6 months prior to OLE study enrollment. Male patients must also abstain from sperm donation during the OLE study and for 100 days following the last M281 infusion.
   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.
7. 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 should be at a stable dose and regimen using the same preparation since enrollment in the POC study.
8. Is able to understand and voluntarily provide written informed consent to participate in the long-term OLE study and comply with all study procedures for duration of the OLE study.

4.5 Exclusion Criteria

1. Has Myasthenia Gravis Foundation of America (MGFA) Class IVb or V disease.
2. Met any of the study drug stopping criteria in the POC study or discontinued study drug in the POC study for any reason (eg, adverse event [AE]) other than the need for rescue therapy as specified in the POC protocol. (If the patient received rescue therapy during the POC, the Medical Monitor should be consulted before the patient is enrolled in the OLE study.)
3. 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) administered predose on OLE study Day 1.
4. Currently has a serious or clinically significant infection (eg, pneumonia, biliary tract infection, diverticulitis, *Clostridium difficile* infection) requiring parenteral anti-infectives and/or hospitalization, or currently has any infection requiring oral anti-infectives.
   Note: An uncomplicated, presumably viral, upper respiratory tract infection (eg, 'the common cold') is not an exclusion.

5. Has current alcohol/substance abuse/dependence, or in the Investigator's opinion, shows evidence of ongoing alcohol/substance abuse/dependence.
6. Has donated or had significant loss of whole blood (480 mL or more) within 30 days, or plasma within 14 days prior to OLE study Day 1.
7. Has a hypersensitivity to M281 or any constituent of the study drug solution.
8. Has had a prior severe drug reaction that included shock or severe hypersensitivity.
9. Has liver impairment with Child-Pugh Class B or C.
10. 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 before OLE study Day 1 for conditions other than MG (inhalational, intra-articular, topical or ocular glucocorticosteroids are not exclusionary), or taking any immunosuppressive agents not being used to treat MG.
11. Is receiving a systemic biologic antibody for any concurrent disease.
12. Has a QT interval corrected for heart rate (QTc) at OLE study Day 1 of >450 msec for males or >470 msec for females; or QTc >480 msec in patients with Bundle Branch Block, by the Fridericia formula.
13. Had any of the following abnormal laboratory values based on the safety laboratory tests done at the Day 85 POC Visit: aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase ≥2× upper limit of normal (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).
14. Had elevated CK ≥2×ULN based on the safety laboratory tests done at the Day 85 POC Visit.
    Note: If the CK value is ≥2×ULN at the Day 85 POC visit, the value from the Day 113 POC Visit can be used to assess eligibility. If the value from the Day 113 POC Visit is also ≥2×ULN, but <5×ULN, and in the opinion of the investigator the patient has no CK-related disease and CK level is believed to be the result of non-pathologic factors, the CK may be repeated once within 28 days and if stable/improved the patient can be enrolled.

5 STUDY TREATMENT

5.1 Description of Treatment

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.

5.2 Treatment Administered

M281 will be diluted with D5W and administered by IV infusion. The starting dose of M281 will be 30 mg/kg Q4W based on body weight at the time of enrollment into the OLE study.

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

Patients who are enrolled in the OLE study will initially receive M281 30 mg/kg Q4W. After at least 8 weeks of treatment on a stable dose of M281, the dose and/or dosing frequency of M281 may be individually adjusted for a given patient at the discretion of the Investigator and previous consultation with the Medical Monitor, based on the patient's tolerability to M281 and the patient's MG status. If the M281 dose and/or dosing frequency is adjusted, the first infusion at the new dose/frequency must occur at a clinic visit (not at a home infusion). The individually adjusted dose will not exceed 60 mg/kg and the dosing frequency will not exceed Q2W.

The M281 infusions will be administered without regard to mealtimes or time of day. Guidelines for management of infusion site reactions are provided in the study manual. Each patient will be observed for safety after their first 2 infusions in the study; if no clinically relevant AEs or abnormal vital signs related to the infusion are observed in these first 2 infusions, the post-infusion observation period is no longer needed unless the M281 dose level is later increased. A post-infusion observation period is also required for the patient's first infusion at the higher M281 dose level.

The date of infusion, start and end times, the volume administered, and the time of the infusion rate change (if applicable) for all doses are to be recorded. The infusion time is noted in the Infusion Manual.

5.4 Method of Assigning Patients to Treatment Groups

No comparator arm is included in the OLE study. All patients will receive M281.

5.5 Blinding

Not applicable.

5.6 Concomitant Therapy

Patients should continue their stable therapeutic regimen (standard of care) for gMG and must maintain the same dose and regimen for at least the first 8 weeks of the OLE study (unless toxicity or safety issues mandate a change), after which the dose/regimen can be changed at the Investigator's discretion, as appropriate based on the patient's gMG status. It is recommended that the dose and regimen of concomitant treatment is not changed until the

patient's M281 dose has been stable for at least 8 weeks. A consultation with the Medical Monitor regarding changes to the patient's standard-of-care therapy is recommended.

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 enrollment and the use of these medications is acceptable to the Investigator. The patient should maintain the same dose and regimen using the same preparation (and new preparations should not be initiated) for at least the first 8 weeks of the OLE study (unless toxicity or safety issues mandate a change).

5.7 Restrictions

5.7.1 Prior Therapy

Patients should continue their stable standard-of-care MG therapy (eg, glucocorticosteroids, acetylcholinesterase inhibitor, statins, immunosuppressants) as described in Section 5.6.

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 for the study visit and until efficacy assessments are completed.

5.7.3 Patient Activity Restrictions

Patients may continue their usual activities during the study, including exercise, but should notify their Investigator about starting any new exercise program during the study. Patients should avoid 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, or by a qualified healthcare provider for optional home infusions (at the discretion of the Investigator and if this option is made available to the site), thus ensuring treatment compliance.

5.9 Packaging and Labeling

Open-label M281 will be supplied as one container per carton. Supplies of M281 will be labeled with the local language.

5.10 Storage and Accountability

Vials of M281 must be stored at 2°C to 8°C in a secure, controlled-access location. M281 must only be used for patients who have consented to participate in this OLE study.

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 1.

Table 1. Schedule of Study Assessments

Study Week	Start of Screening for OLE Study[a]	OLE Study Enrollment (Day 1)[b]		Week 2	Week 4 and Week 8	Week 10 (only for Q2W regimen)	Week 12 and Q12W thereafter (both regimens)	Q2W or Q4W depending on regimen[c]	Last Treatment/ Early Termination	Follow-up Visit
Visit/Window	**After completion of Day 85 POC Visit**	**Day 113 POC Visit (ie, 8 weeks after last infusion in POC)**	**Additional OLE procedures[b]**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**NA**	**8 weeks (±7 days) after last infusion**
Vital Signs[d]		X	X[d]	X	X[d]	X	X	X	X	X
Weight		X					X		X	X
Physical Examination[e]		X[e]		X	X	X	X	X[f]	X[e]	X
12-Lead ECG[d]		X	X[d]	X	X	X	X	X	X[d]	X
Efficacy Assessments[g]										
MG-ADL		X			X		X		X	X
QMG		X			X		X		X	X
MG-QoL15r		X			X		X		X	X
MGFA-PIS – applicable elements		X					X		X	X
Blood sample for anti-AChR and anti-MuSK autoantibody levels (as applicable for the patient)[h]		X			X		X		X	X
Safety Laboratory Testing[h]		X		X	X	X	X	X[f]	X	X
Blood sample for total and neutralizing anti-M281 antibodies[h]		X			X		X		X	X
Blood sample for levels of total IgG[h]		X		X	X		X		X	X
Blood sample for IgA, IgM, and IgE levels[h]		X					X		X	

Table 1. Schedule of Study Assessments

Study Week	Start of Screening for OLE Study[a]	OLE Study Enrollment (Day 1)[b]		Week 2	Week 4 and Week 8	Week 10 (only for Q2W regimen)	Week 12 and Q12W thereafter (both regimens)	Q2W or Q4W depending on regimen[c]	Last Treatment/ Early Termination	Follow-up Visit
Visit/Window	**After completion of Day 85 POC Visit**	**Day 113 POC Visit (ie, 8 weeks after last infusion in POC)**	**Additional OLE procedures[b]**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**±7 days**	**NA**	**8 weeks (±7 days) after last infusion**
Informed Consent for OLE	X									
Review Incl/Excl criteria for OLE and confirm patient eligibility			X[i]							
Medical History, Demographics, and Height			X							
Urine pregnancy test[j]			X							
C-SSRS			X	X	X		X		X	
AEs / Concomitant Medications/Rescue Therapy[k]		X	X	Monitored throughout the study						
CGI-S			X		X		X		X	X
CGI-I					X		X		X	X
Neuro-QOL Fatigue assessment			X		X		X		X	X
MGFA clinical classification		X			Week 8 only		Every 24 Weeks		X	
Monitor physical activity (Embrace device)	Continuous from screening through 6 months after first OLE M281 dose									
Study Drug Infusion[l]			X		X	X	X	X	X[m]	

Abbreviations: AE = adverse event; anti-AChR= anti-acetylcholine receptor autoantibody; anti-MuSK = anti-muscle-specific kinase autoantibody; CGI-I = clinical global impression of improvement; CGI-S = clinical global impression of severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; Ig = immunoglobulin; 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; NA = not applicable; OLE = open-label extension; PD = pharmacodynamic; Q2W = every 2 weeks; Q4W = every 4 weeks; QMG = Quantitative Myasthenia Gravis.

[a] The Screening Period for the OLE study begins (at the earliest) at the Day 85 POC Visit (which translates to 4 weeks after the last dose of study drug in the POC study). Any screening procedure for the OLE study must not be done until after completion of all the assessments and procedures required by the POC protocol for the Day 85 POC Visit.

[b] OLE enrollment will occur (at the earliest) on the same day as the patient's last follow-up visit (Day 113 POC Visit) in the POC study. Any OLE assessment or procedure designated on the Day 113 POC Visit must not be performed until after completion of all the assessments and procedures required by the POC protocol for the Day 113 POC Visit. If it is not feasible to complete any/all designated OLE assessments/procedures on the same day as the Day 113 POC Visit, or if there is a valid reason to delay enrollment of the patient in the OLE study, the Investigator can confirm the patient's eligibility and enroll the patient at a later date as agreed between the Investigator and Medical Monitor; however, depending on the length of the delay the patient may need to have an additional unscheduled blood draw for safety laboratory testing to confirm eligibility for the OLE study.

[c] Only predose vital signs (but not physical examination, ECG, or safety laboratory testing) are required if the infusion is administered in the home. Every other infusion (except those that fall every 12 weeks [Q12W]) may be administered in the home or at another location per the Infusion Manual, at the discretion of the Investigator and if this option is made available to the site. As an example, for patients continuing on a Q4W regimen at Week 8, the schedule for optional home infusions would be as follows: Weeks 16, 28, and 40 (assuming no M281 dose increase and assuming end of treatment at Week 52). As an example, for patients switching to a Q2W regimen at Week 8, the schedule for optional home infusions would as follows: Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50 (assuming no M281 dose increase and assuming end of treatment at Week 52)

[d] 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 2 infusions in the OLE study, vital signs will also be measured after completion of the infusion as specified in the Infusion Manual. Twelve-lead ECGs will be recorded before the start of the M281 infusion. For the first infusion in the OLE study, a single 12-lead ECG will also be conducted within 10 minutes after the infusion has been completed. Predose ECGs will not be required on days when the infusion is administered in the home.

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

[f] If the M281 dose and/or dosing frequency is increased (which must occur at a clinic visit, not at a home infusion), the patient's next infusion must be conducted in the clinic because a blood sample for safety laboratory testing must be obtained and a physical examination must be done within 2 to 4 weeks after the first infusion at the new dose/dosing frequency.

[g] All MG assessments must be done starting at approximately the same time of day, and prior to study drug administration on infusion days. It is preferable to perform the applicable MG assessments in the order shown in this Schedule of Study Assessments.

[h] Blood samples must be collected before the start of the M281 infusion. Safety laboratory testing includes chemistry, hematology, coagulation function (including prothrombin time), and urinalysis.

[i] The assessment of patient eligibility for the OLE study includes review of the safety laboratory testing results from the patient's Day 85 POC Visit.

[j] Women of childbearing potential must have a negative urine pregnancy test at study enrollment prior to the first M281 infusion in the OLE study. Menopausal women who did not have elevated FSH at the time of enrollment in the POC study must also have a negative urine pregnancy test prior to the first M281 infusion in the OLE study.

[k] All medications/therapies are to be recorded from the time of enrollment into OLE study (ie, Day 1) throughout the patient's participation in the study, including administration of rescue therapy during the study for worsening of MG-related symptoms. Reporting of device-related AEs in the OLE study will start following the patient signing the OLE informed consent form. AEs from the POC study that are ongoing at the Day 113 POC Visit will be recorded as medical history for the OLE study. Recording of new AEs (ie, any new clinically relevant finding or worsening of a pre-existing condition, such as an ongoing AE from the POC study) will start at the time of enrollment into the OLE study.

[l] Infusion to be administered as specified in the Infusion Manual. Each patient will be observed for safety after their first 2 infusions in the OLE study; if no clinically relevant AEs or abnormal vital signs related to the infusion are observed in these first 2 infusions, the post-infusion observation period is no longer needed unless the M281 dose level is later increased. A post-infusion observation period is also required for the patient's first infusion at the higher M281 dose level.

[m] Study drug will not be administered at an Early Termination Visit.

6.1 Safety Assessments

Safety assessments include collection of AEs, vital signs, physical examinations, clinical laboratory testing (including chemistry, hematology, coagulation, and urinalysis), ECGs, and the C-SSRS. Severe infections 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).

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.

The manufacturer of the Embrace device advises that it should only be worn on the surface of healthy skin, and to suspend or discontinue use if the skin becomes red, itchy, or if any pain is felt. Adverse events associated with wearing the Embrace device are to be recorded as device-related AEs and the use of the Embrace device should be discontinued.

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 device-related AEs in the OLE study will start following the patient signing the OLE informed consent form. Adverse events from the POC study that are ongoing at the Day 113 POC Visit will be recorded as medical history for the OLE study. Recording of new AEs (ie, any new clinically relevant finding or worsening of a pre-existing condition, such as an ongoing AE from the POC study) will start at the time of enrollment into the OLE study (Day 1).

6.1.1.3 Severity

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

The CTCAE provides specific criteria for grading AEs 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/device 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/device; 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/device, 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/device (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 (the Investigator's Brochure for M281 and the manufacturers information for the Embrace device).

6.1.1.6 Adverse Events of Special Interest

For this study, any CTCAE Grade 3 or higher severe infection or event of hypoalbuminemia will be considered an AESI. These cases will be handled similarly to a serious adverse event (SAE) for reporting purposes (see Section 6.1.1.8) and reviewed by the Drug Safety Monitoring Board (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 electronic case report form (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 via MMS Holdings, the safety group that will be processing the information, 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 during OLE study participation and at any time during the 30 days for female patients or 100 days for the female partner of a male patient after the last dose of study drug 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 of enrollment into the OLE study (ie, Day 1) 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 Day 1 only. Weight will be measured at Day 1 and every 12 weeks thereafter. A full physical examination will be performed at Day 1 and at the end of the study; 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 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 a CS change from baseline values is noted, the CS 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 baseline, 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 2.

Table 2. 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 Myglobin (if serum creatine kinase is elevated) Specific gravity Urobilinogen Urine pregnancy test (for females of childbearing potential and menopausal females if follicle-stimulating hormone was not elevated at time of enrollment in the POC study)	Serum Chemistry: Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Blood urea nitrogen Calcium Carbon dioxide Chloride Creatinine Creatine kinase (MB and MM isoenzyme fractionation 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

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 all ECG recordings except those obtained at the follow-up visit, which will be evaluated by the Investigator. 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, personnel who are C-SSRS certified). The C-SSRS Since Last Visit version will be used. When the C-SSRS is administered on an infusion day in the clinic as specified in Table 1, 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 on Day 1 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

Efficacy will be assessed at designated site visits prior to M281 infusion (ie, predose), using these measures in the following preferred order: MG-ADL, Quantitative Myasthenia Gravis (QMG), revised Myasthenia Gravis Quality of Life – 15 Scale (MG-QoL15r), applicable elements of the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS), physician-rated Clinical Global Impression (CGI) scales, patient-reported Neuro-QOL Fatigue, and MGFA classification. If possible, these efficacy assessments throughout the study should be done at approximately the same time of day as performed on Day 1.

In addition, the level of physical activity will be monitored via the Embrace device worn continuously on the wrist during the Screening Period (to establish a baseline) and for the first 6 months of the study.

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. The MG-ADL should be administered by the same healthcare professional for a given patient throughout the study, if possible. 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 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. 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 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 MGFA-PIS is a measure of the patient's MG status after treatment/intervention. For the purpose of this study, the selected elements of the MGFA-PIS as shown in Table 3 will be assessed.

Table 3. Assessments Based on the Myasthenia Gravis Foundation of America Post-intervention Status

Assessment	Definition
Investigator assessment of Minimal Manifestations	The patient has no symptoms of functional limitations from MG, but has some weakness on examination of some muscles (Yes/No)
Change in Status derived from QMG score	• 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
Investigator Assessment of Pharmacologic Remission (not applicable if the treatment duration is <1 year)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG, other than M281, 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.

Note: Baseline referred to the as the assessment obtained at the time of enrollment into the OLE study (Day 1).

6.2.5 Clinical Global Impression Scales

The CGI scales should be administered by the same clinician/physician for a given patient throughout the study, if possible.

The CGI Severity (CGI-S) scale is the clinician/physician's global assessment of the patient's illness severity, and is rated by answering the following question on an 8-point scale:

> CGI-S: Considering your total clinical experience, how do you rate the current severity of the patient's gMG?

- 0 = Not performed
- 1 = Normal, not at all ill
- 2 = Borderline illness
- 3 = Mildly ill
- 4 = Moderately ill
- 5 = Markedly ill
- 6 = Severely ill
- 7 = Among the most extremely ill patients

The CGI of Improvement (CGI-I) scale is the clinician/physician's global assessment of the change in severity of the patient's gMG since starting the OLE study, and is rated by answering the following question on an 8-point scale:

> CGI-I: Compared to the beginning of the MOM-M281-005 study, how would you rate the current severity of the patient's gMG?

- 0 = Not performed
- 1 = Very much improved
- 2 = Much improved
- 3 = Minimally improved
- 4 = No change
- 5 = Minimally worse
- 6 = Much worse
- 7 = Very much worse

6.2.6 Patient-Reported Assessment of Fatigue

Fatigue will be assessed by the patient using Neuro-QOL Fatigue.

6.2.7 Measurement of Physical Activity

The patient's physical activity will be measured during the study via the Embrace device, which is a removable digital health device worn on the wrist. The Embrace device is United States (US)-licensed for use in neurology. It provides sleep, rest, and physical activity analysis. Before using the Embrace device, patients will be trained on its use and procedures for electronic data transmission.

6.2.8 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 classification should be assessed by the same clinician/physician for a given patient throughout the study, if possible.

6.3 Assessments of Pharmacodynamics and Biomarkers

Blood samples will be drawn for analysis of the following PD parameters: concentrations of total serum IgG; serum concentrations of IgA, IgM, and IgE; and titers of anti-AChR or anti-MuSK autoantibodies, as applicable for each patient. Blood samples will be collected at the visits specified in Table 1.

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

6.4 Immunogenicity Assessments

Blood samples will be drawn to determine the presence/absence and titers of total and neutralizing anti-M281 antibodies, as applicable.

6.5 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 AE 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.

6.6 Stopping Criteria

Unless patient safety precludes doing so, the Medical Monitor should be consulted prior to stopping or interrupting the dosing schedule of M281. The DSMB will be informed about any such changes, with the reason they were initiated, and any laboratory data that were a part of the discussions. Any patient who meets the study drug stopping criteria will be withdrawn from the OLE study and followed for safety for 8 weeks after the last infusion of M281 or until the AE resolves/stabilizes, whichever is the longest.

6.6.1 Study Drug Stopping/Interruption Rules for Individual Patients

Treatment with M281 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.
- The patient requires initiation of a new MG therapy that was not already part of their standard of care.
- Any circumstance or finding that, in the clinical judgment of the Investigator, would represent undue risk to the patient.

Treatment with M281 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 M281 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 M281 will be made by the Investigator, in consultation with the Medical Monitor.
- If a patient develops elevated CK levels, CK fractionation (CK-MB isoenzyme, CK-MM isoenzyme) and troponin will be automatically tested by the laboratory. If the CK-MB 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. The 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.

6.6.2 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 (ie, enrollment in the extension study will be held), 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 considered potentially related to treatment 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 M281 (eg, accidents or other external causes) will not trigger study stopping rules.

6.7 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 3 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 judgment of the Investigator. If a patient receives rescue therapy, the Investigator and Medical Monitor will jointly determine whether to continue treatment with M281 or withdraw the patient from the study.

6.8 Appropriateness of Measurements

The efficacy scales in this study have been shown to be reliable and valid for measuring clinical status of patients with MG. The use of the wearable Embrace device for quantifying physical activity is being explored for potential use in later studies. The 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 consistency of 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 one or more study centers.

8 PLANNED STATISTICAL METHODS

8.1 General Considerations

Baseline is defined as the assessment obtained at the time of enrollment into the OLE study (Day 1) for all assessments except physical activity; baseline for physical activity will be established during OLE screening.

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.

Further details on endpoints and analyses will be provided in the Statistical Analysis Plan (SAP).

8.2 Determination of Sample Size

The sample size for the OLE study will depend on the enrollment in the POC study, which plans for enrollment of approximately 60 patients with possible expansion up to 90 patients.

8.3 Analysis Populations

The Safety Population will include all patients who received any amount of M281 in the OLE study.

The PD Population will include all patients in the Safety Population with at least one evaluable PD value in the OLE study.

8.4 Demographics and Baseline Characteristics

Descriptive summary statistics will be provided for demographic data and other baseline characteristics for the Safety Population.

8.5 Patient Disposition

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

8.6 Primary Endpoints

Safety and tolerability of M281 will be evaluated in terms of the incidence and severity of AEs (including SAEs, and AESIs), vital signs, physical examinations, clinical laboratory testing (including chemistry, hematology, coagulation, and urinalysis), ECGs, and the C-SSRS.

Analysis of all safety data will be performed using the Safety Population. 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 to study drug/device will also be provided. Concomitant medications will be coded by the World Health Organization Drug Dictionary Enhanced and will be summarized. Medical history (to include AEs from the POC study that are ongoing at OLE Day 1) 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, and C-SSRS. For vital signs and ECGs, descriptive statistics at each visit and change from baseline to each subsequent visit will be provided. Physical examinations will be summarized as shift tables. Listings will also be provided for each type of safety data.

8.7 Secondary Endpoints

Descriptive summary statistics will be provided for each endpoint.

8.7.1 Efficacy Endpoints

- Change from baseline in the total MG-ADL score over time
- Number of patients with a 2-, 3-, 4-, 5-, 6-, 7-, or ≥8-point improvement in total MG-ADL score over time
- Change from baseline in total QMG score over time
- Change from baseline in total MG-QoL15r score over time
- Change from baseline in CGI-S over time and CGI-I ratings
- Change from baseline in MGFA classification over time

8.7.2 Immunogenicity Endpoint

- The incidence of anti-drug antibody (ADA) and neutralizing ADA (nADA) seroconversion over time

8.7.3 Pharmacodynamic Endpoint

- Total serum IgG concentrations over time and change from baseline

8.8 Exploratory Endpoints

- Change from baseline in Neuro-QOL Fatigue scores over time
- Quantitative level of physical activity over time and changes from baseline
- Serum concentrations of IgA, IgM, and IgE over time and changes from baseline
- Titers of serum anti-AChR or anti-MuSK antibodies over time and change from baseline
- Changes in dose/regimen of standard-of-care concomitant medications for gMG over time
- Number of patients who discontinued immunosuppressive medications over time
- Need for rescue therapy over time
- Number of patients with clinical deterioration
- Number of episodes of myasthenic exacerbation requiring hospitalization/intensive care unit admission, and length of stay
- Proportion of patients with minimal manifestations, and change in status per the MGFA-PIS over time, and proportion of patients with pharmacologic remission
- A model-based analysis of MG-ADL score change from Baseline in relationship to total serum IgG and anti-AChR titer (the latter is only for patients with anti-AChR antibodies)

Descriptive summary statistics will be provided for each endpoint, as applicable.

8.9 Interim Analysis

No interim analysis is planned.

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

9.2 Institutional Review Board or Independent Ethics Committee Approval

The final study protocol, including the final version of the informed consent form (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 any written materials 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 Investigational New Drug application.

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, as applicable, by national or local laws/regulations or requirements, US FDA regulations or regulations of the authority having jurisdiction over the location in which the study is being conducted, 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 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 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. The eCRF Completion Guideline 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 will 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 after 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 for data retrieval 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

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Appendix 1 Sponsor Signature

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

Study Number: MOM-M281-005

Amendment 2 Date: 01 August 2019

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

Signed: PPD Date: August 2, 2019

Printed name: Santiago Arroyo, MD

Title: Chief Medical Officer

Appendix 2 Investigator's Signature

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

Study Number: MOM-M281-005

Amendment 2 Date: 01 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: _____